EGEA

THIRD EDITION

Rome – Italy – May 18th - 21st , 2005

International Conference on Health Benefits of Mediterranean Diet

From scientific evidence to health prevention actions

Preface

This is the third edition of EGEA, the International Conference on the Health Benefits of a Mediterranean Style Diet. Progressively, this Conference is taking an important place at the crossroads of scientific evidence and health prevention actions. The aim is to establish a consensus on an effective strategy to prevent and control chronic diseases such as obesity, diabetes, cardiovascular diseases and cancer, which are becoming, according to the World Health Organization, leading causes of morbidity and mortality around the world. Like infectious diseases, these chronic diseases could be, and should be, prevented and controlled on a mass scale by the preservation or creation of healthy environments, including healthy food systems.
Such prevention, however, faces difficulties stemming from the diversity and economic consequences of the environmental factors involved, including the changing nature and quality of food supplies, food advertising, marketing, promotion and food pricing. With the increasing number of meals taken away from home, time limitations of consumers, the food industry has responded by increasing the number of convenience foods and the availability of prepared meals, together with an increase in portion sizes and per capita availability of fat and added sugar.
EGEA constitutes a unique and valuable opportunity for the convergence of multidisciplinary approaches, from basic science, health, agriculture, communication, to global prevention politicies. Two round tables are being organized to share experiences on various strategies available and to define guidelines for health nutrition policies which could be implemented at the general population level. With the participation of the best world specialists on these issues, the support of the French and Italian Ministries of Health and IARC-WHO, this conference is fully in line with the global strategy of the World Health Organization concerning nutrition, physical activity and health.
It is my sound conviction that this conference will again be a success story!

Pr. Ambroise MARTIN
Professor of Nutrition, University of Lyon,
member of the steering committee of the French national nutrition health policy (PNNS)

An official opening talk was held prior to the scientific lectures on Wednesday, May 18th , 2005, featuring Mr Laurent Damiens, Director of Aprifel and Dr Saida Barnat, Head of the Scientific Department of Aprifel, who welcomed their distinguished guests.

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Romano MARABELLI
Director General, Directorate General for Veterinary Health and Food, Ministry of Health, Rome, Italy

It is an honor for us to host this conference, as well as an honor for the Italian Health Ministry to take an active part in the event, as part of its great interest for key aspects of the obesity issue such as lifestyle, diet and food security.

Let me introduce the matter that will later be discussed by my colleague Pr. Greco: I would like to remind you of the goals that were set in 2004 by the World Health Organization towards the implementation of a global strategy for healthy diets and lifestyles worldwide, as the WHO acknowledged the social and economic role and possible benefits of traditional diets and lifestyles.

During the 2004 Assembly of the WHO, some of the most urgent issues were raised before Member States such as: the need for national goals to be set, and for an implementation schedule to be determined, as well as national guidelines for diet and physical activity and specific indicators for the monitoring and evaluation of actions undertaken. And most of all need to find appropriate measures in order to maintain and promote traditional food and lifestyles.

I would also like to underline, as a food security expert, that, when talking about traditional food, we refer exclusively to the foods that live up to our modern security standards. It would definitely be dangerous to imagine less safe processes for these products.

The issue of overweight and obesity is a growing problem in Europe, and has increased by 25% between 1994 and 1999 in Italy, according to available data for the year 1999. The most important consequences of the phenomenon in terms of non-contagious diseases include cardiovascular diseases, type II diabetes, some cancers, osteoporosis and dental caries. All of these are linked with unhealthy diets. Eating disorders in women aged 12-25 include anorexia (0.3% to 0.5%) bulimia (1 to 3%) and others (6%).

Italy has tackled this issue through national health plans, specifically the 2003-2005 plan that aims at a better lifestyle, and more prevention and communication around health issues (point 9). Awareness campaigns were also led in schools through actions targeting children and through physicians. National awareness campaigns have also been launched in the country.

In 2002, in coordination with the Ministry of Education, we focused on prevention of children's eating disorders. In 2003, the goal was to encourage people to maintain a healthy diet. Awareness campaigns were conducted through television and other media in order to promote lower caloric intake, higher physical activity and healthy diets such as the Mediterranean diet.

The 2004 campaign specified what healthy diet and physical activity really mean thanks to a press campaign which promoted healthy lifestyles. This year, in 2005, we have started a campaign that offers a 5-points programme for a healthy lifestyle: more fruit, vegetables and water, less fat, a greater diversity, a less sedentary lifestyle and smaller servings.

This is the work that has been achieved to date by the Italian Health Ministry and the Italian government through its various services and ministries. It certainly is an ambitious project, as it aims at very sensitive targets such as the youth and demands therefore strong, positive and significant commitment.

In this context, this Roman Conference is a great opportunity for us to evaluate together during the next three days the possible common strategies to be implemented in Italy and the rest of Europe.

Thank you.

Ferdinando ROMANO
President of the National Institute for Research on Food and Nutrition (INRAN), Italy

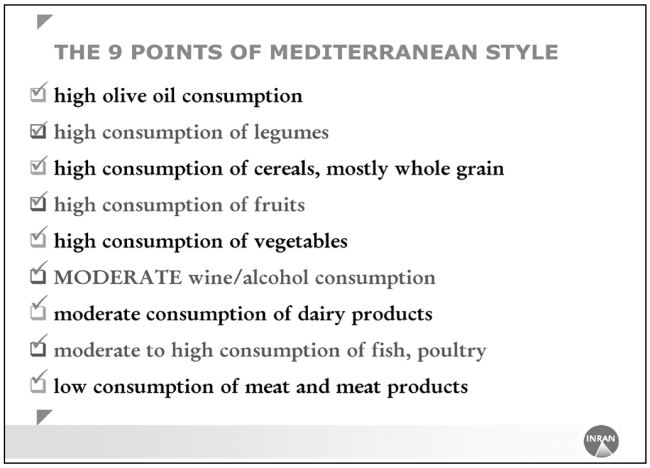
Thank you for this invitation. It is an honour to be here at this meeting in Rome.

I would like to begin with something that I believe is extremely important regarding the issue we are discussing today. This is a mission statement from the incredible recognition and information of chronic diseases conducted for the FAO in 2003. It says that the cost to the world of the current and projected epidemic of chronic disease related to diet and physical inactivity dwarfs all other health costs. Let us take into account that the situation regarding diet is a major emergency today. To give a rough estimate of the cost of obesity in the United States, I am told that obesity costs about 1.7% of the gross national product in the United States. The estimate is much lower in Italy because we have a much lower rate of obesity: it is about 0.24% of the gross national product. We are talking only about the health costs of obesity.

Everybody knows how important nutrition is in the development of these types of diseases: we have 41% of the main diseases with nutrition as a major determinant, and another 38% for whom nutrition plays a role. Consensual literature data reported that dietary factors account for 30% of cancers in industrialised countries.

The concept of Mediterranean dietetic style became famous after 1986 Time Magazine appearance and since that time it has been deeply investigated. This slide is another example of pyramid graphical representation showing the comparison between Mediterranean diet and northern Europe and the United States dietetic style. The latter is practically reverse than the former, according to this comparison.

Numerous and solid scientific evidence demonstrating that the major nutrients that characterise the Mediterranean diet have a beneficial effect on health exist. For example, convincing evidences exist on health benefits of fish and fish oils. A good overview of the scientific evidence of the protective effects of fruit and vegetable is provided by WHO. Actually these data should be updated but the results are still valid.



There are some clear evidences of the beneficial effect of the Mediterranean diet. This is the recently published Epic study, and some scientists participating in the study are attending this meeting This study explored the effect of the Mediterranean diet on survival among older people demonstrating how the Mediterranean diet as a whole was associated with a lower death rate.

I would like to mention other few papers. This last year paper considers the Mediterranean diet together with healthy lifestyle habits – moderate alcohol use, no smoking, and physical activity. All these factors lowered the mortality rate for all causes of about 50%.

Another effect of the Mediterranean diet is on circulating homocysteine concentration. The Mediterranean diet is able to lower the homocysteine concentration in blood in heterozygous and homozygous genotypes that having high homocysteine level.

In this other study published in 1998, a randomised clinical trial showed that the Mediterranean diet has been able to prolong survival and protect against cancer.

At this point, we have a lot of evidence on the health benefits of Mediterranean diet. The major question arising now is what is going on today? Professor Marabelli has told us that obesity is a major problem, in our country too. For example, recent data showed that 9% of Italians are obese and more than 50% of older Italians are overweight. Obesity is more and more a paediatric problem regarding one third of Italian children (36%) that resulted overweight with 11% of them clearly obese.

The Mediterranean areas are still Mediterranean, so what is happening? Are we still following a Mediterranean diet?

This is an Italian study assessing the so-called Mediterranean score. The Mediterranean score is a score between 0 and 8. When the score is between 4 and 8, the diet is Mediterranean. With a score between 0 and 3, there is no Mediterranean-style diet. The figures show that the score has gradually been decreasing since 1961. Presently, the score is 3 meaning that we are no longer following a Mediterranean diet in Italy.

There has been a lot of educational campaigning and a lot of efforts to reposition the Mediterranean diet as the central diet for our nutritional lifestyle. It might be that all the efforts made up to now have not been as effective as we would have expected.

The current situation regarding the Mediterranean diet should induce us to think hard about what should be done in terms of an effective educational campaign. We still have some insights on the WHO/FAO report. First of all, the public health action to prevent the adverse consequences of inappropriate dietary patterns and physical inactivity is now urgently needed.

The second point is applied research. This is an important issue because the most challenging task now is to match the demand from the general population and the results of the research. The applied research should provide convincing evidence and useful tools to guide effective interventions.

The third point is how to induce changes in nutritional habits, how to move back to a Mediterranean dietetic style. Changes can only be initiated through effective communication. What does effective communication mean? This is a crucial point because

we, as scientists, must address and reach the general population. Effective communication means bridging the gap between technical experts, policymakers and the general public. At the moment with our educational campaigns, we are producing a strong awareness among the general public on the problems of how to have a healthy lifestyle in terms of nutrition. What, in our opinion, is still lacking is an adequate production of tools for the general public to put into practice the correct information. For example, we know the benefits of antioxidants, but in which way consumers could monitor their antioxidant intake? What means more fruit and vegetables? Compared to what? We should think about how the general public can put all this information into practice in their daily lives. This is a crucial point leading us able to transform our educational campaign in intervention strategies with production of practical tools to put the information into practice in daily lives.

The fourth point is related to the fact that as scientists, we are generally used to communicate in terms of science and our information is often given to people from a scientific point of view, which could be not easily understandable. The point is to give simple and clear messages.

The last point has been covered before, and is related to the level of involvement of different stakeholders. Governments need to work together with the private sector, official health bodies, consumer groups, academics, the religious community and other non-governmental bodies in order to obtain the best results. It is necessary as a moral imperative, that concerted actions will be structured between all the stakeholders to be effective in modifying the current lifestyle in terms of nutrition and to go back to a real Mediterranean diet.
Thank you.

Donato GRECO
Director General of Health Prevention, Ministry of Health, Rome, Italy

I come from Naples, the capital of the Italian Mediterranean diet. I would like to take this opportunity to remind you that within the original campaign origin, one of the most relevant studies ever made on the health effects of the Mediterranean diet was launched, and many scientists from the US and Italy helped in the study.
As I think we are going to be overwhelmed with the 'dietary story' over the next few days, I thought I would use the next five minutes to tell you some other news about what Italy is trying to do.

After 29 years in science, I moved to implementation because I felt strongly about this enormous gap between what we know should be done and what is done.

We have seen that there is a gap in this country, in your country, as everywhere. We have known for a long time that we should eat more fruit, that we should not smoke, and that we should walk for an hour a day, but in fact there is little evidence that the population is moving, rather a lot of evidence that the population is going the other way. So we have to do something about this impact gap. Of course, I do not have a solution – otherwise I would not be here.

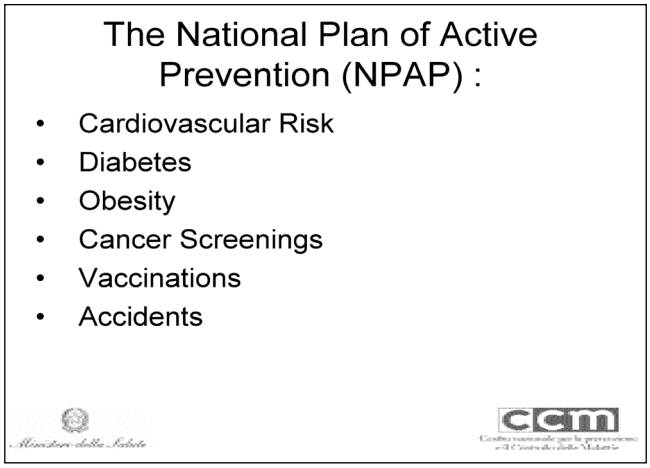
We are trying to create a new programme with a new institution to try to get science messages through to the population. This is why our parliament approved through a new law last year the Italian CCM, Il Centro nazionale per la prevenzione e il Controllo delle Malattie [The national centre for prevention and control of diseases]. It is a network between the regions and the many institutions to build our capacity to work together in a network. Our mission is to help attain assessment, surveillance and response in coordination with the regions. Each of the 21 independent health authorities of the country are becoming more and more independent. They have their own ministers, parliament and funds (funds are not managed in Rome anymore, but remain where they are collected.)

So we have training to do, presentation, networking, and information feedback. It is a very heavy mission. To start with, we have been given 6 tasks: infectious diseases, health promotion, environment and climate, vaccines and vaccination, road and domestic accidents, and bio-terrorism. This covers the country's major health problems.

We have a small additional budget on top of our main budget which allows us and the network to function. This fund is granted every year and is protected against any cuts by the government or treasury minister.

We have a national plan for active prevention, the word 'active' being a message we would like each citizen to hear; we want to reach them in their homes.

Of course, when we speak about these diseases, we are speaking about the major causes of disease: 250,000 deaths caused by cardiovascular disease and more than 1 million sick people every year at any given moment. Diabetes is now our great challenge: according to our treasury calculations, our entire health budget in the next ten years will be barely sufficient to pay for diabetes only – let alone the rest!



Our actions must include cancer screening. I have just come from the World Health Assembly in Geneva in which cancer control was one of the items discussed, and again, diet is crucial, as one third of cancers are associated with diet.

What are our main points? Smoking: I am proud and pleased to say that we are now one of the leading countries in the world for combating smoking because we have approved a quite stringent and effective law that forbids smoking in all public places. Believe it or not, despite our 'illegal' attitude – we do not usually like to respect red lights – the Italian population is accepting this law very happily. We have figures showing a minor drop in consumption of cigarette sales of about 10% a month, and out of the many tens of thousands of police inspections of restaurants and bars, less than 3% were fined for irregularities. The population is happy about the restriction of smoking in public places. However, we are not forbidding smoking: this is not a law against smokers; it is a law against passive smoking to protect the non-smokers. Things are going very well.

Physical activity: over the next few days you will hear in different presentations how people are not inclined to move and walk.

Nutrition, of course, is a major issue, as has already been mentioned by other colleagues.

As in many other European countries, alcohol is our problem, but I am pleased to say that our total alcohol consumption over the last ten years has decreased by more than 20%. We are drinking better and drinking less, and we are not much fond of spirits. Although alcohol consumption is going down, Italy, like most countries, do have a huge problem with alcohol and smoking among the young – youngsters love beer and there are many new pubs springing up, even in Rome.

There is good news, however. In general, all programmes are applied to Rome and nothing happens in other regions. However a few months ago the 21 regions signed a pact with the State to engage in this national active prevention plan for three years from 2005 to 2007. (The plan is the one I showed you earlier). What is also important is that 1,320 million euros have been set aside for these five items, including nutrition and physical activity. Historically, this has never happened. This is part of Italy's 90-billion-euros health budget, not an enormous amount, but significant enough so that there is no longer any justification for the 250 local authorities or the 21 regions not to act in accordance with the national guidelines which aggressively address the risk-factors we will be speaking of over the next few days. For once, the money is directed at the target – which sounds very simple, but that never happens in this country! The regions have to start implementing this action next month – otherwise they do not receive the funds.

Finally, there is a mechanism to assist regions as well as a verification mechanism whereby each region has to be periodically certified on the active prevention plan within its own territory to get its quota of money. I am quite hopeful and believe that this mechanism will make it difficult to deny or divert the money to pay for other things.

This is a heavy task and I strongly hope that over the next few days of this meeting, we will go in the direction that Italy is ultimately trying to take to fill the gap between science and the benefits to the citizen. Thank you.

Elio RIBOLI
Head of the Nutrition and Hormones Group, International Agency for Research on Cancer (IARC-WHO), Lyon, France

Thank you. It is a great pleasure being with you for the third edition of EGEA. I would like to give special thanks to my Italian colleagues for their excellent collaboration and support for the organisation of this conference in Rome.
Professor Greco raised a very important point in his talk: we need to find points of contact between what is known and the application of what is known. The carcinogenesis of tobacco was clearly demonstrated by 1955 and it has taken half a century to implement laws to limit the use of tobacco. When I say 'limit the use', I mean to forbid the use of tobacco. So if what we know about nutrition is not immediately translated into public health, we should look at the history of tobacco and understand that it takes time to change people's minds and to stand against economic interests.

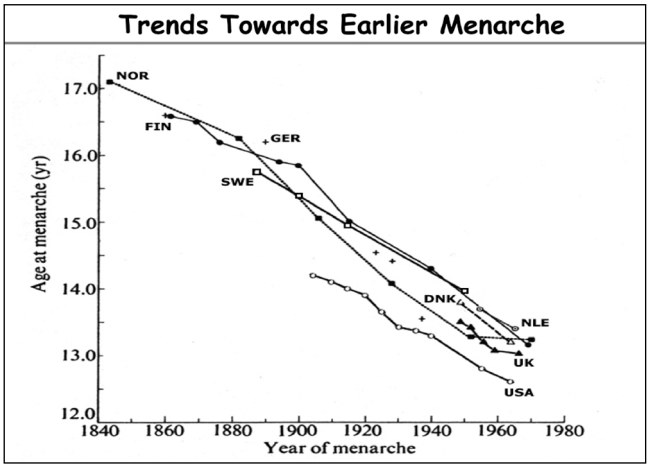
Coming from cancer research, why are we interested in nutrition? When I started working on cancer research in the late '70s in Milan at the National Cancer Institute, the idea was that cancer was basically due to chemicals in the environment. The main task of cancer researchers was to identify chemical and physical carcinogens. However, epidemiologic studies came in and started bringing evidence that chemical carcinogens did not explain the huge differences that we see around the world in the incidences of some cancers. These differences are clearly not due to chemical carcinogens in human beings. For example, colorectal cancer is much more frequent in North America, Europe and Australia than, for example, in Africa or Southeast Asia, and there is no evidence whatsoever that colorectal cancer is due to chemical carcinogens in human beings.

On the other hand, incidence rates of stomach cancer have the opposite image of colorectal cancer. The incidence of stomach cancer is very low in North America – where it is actually the lowest in the world, and in North-African countries, (two regions that have very little in common) – and it is also very low in Australia. This is exactly where colorectal cancer is most frequent.

Cancer is not a single disease, and this has to be considered to articulate our efforts for prevention. Cancer is a very large family of different diseases with completely different causes, and therefore should be addressed with different prevention strategies. For example, let us take as example the two most common cancers in women around the world. Breast cancer is very common in North America in more or less the same regions where colorectal cancer is very common. However, the incidence of cervical cancer, or cancer of the uterine cervix, is just the opposite: the incidence is very low in North America, Australia and China, but very high in some regions like Central America, the east coast of Africa and India.

In addition there are major changes in risk occurring around the world, both in the positive and in the negative direction. Let us take India and Western Europe as example. There are now very good population-based cancer registries some regions of India, which provide very good measure of the incidence of cancer in that population.
The incidence rate of colon cancer in Western Europe is 44 new cases per 100,000 people per year. There is 1 case per 100,000 people per year in this region of India. Rates of breast cancer are 78 and 14 100,000 women per year respectively– that means 780 new cases per 1 million women, as compared to 140. The incidence of cervical cancer is much higher in India – 67 cases in India versus 10 cases per 100 000 women in Western Europe. However, the year 2000 was the first year with more breast cancer than cervical cancer cases in Bombay. So the more the economic situation evolves and the hygienic condition improves, the more cervical cancer (which is a sexually transmitted cancer – 100% are due to the papilloma virus) goes down, but the incidence of the cancers that are typical of the western life style (breast cancer, colon cancer) increases. Differences in incidence rates clearly indicate that lifestyle and environment are extremely important in determining the risk of cancer, and I draw your attention to colon cancer. Basically, that means that with an Indian diet and the Indian physical expenditure characteristics, colon cancer is almost non-existent. That gives some clues for the identification of the causes of colon cancer.

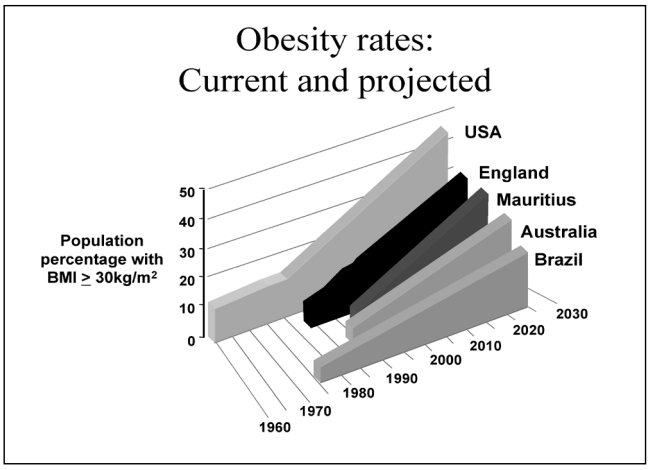
We are used to thinking that the environment changes– and this is absolutely true – but we are less used to think how the environment has changed the human race. This figure shows the height of young men (18 to 19 years old) on their entry into the army in the Netherlands, Denmark, Sweden and Norway in 1860, while the average height of men in the EPIC-Netherlands study is 187 cm. That means that in 150 years, the average height of men has increased by 22 cm in the Netherlands. This is a major change in the anthropometric, metabolic and hormonal characteristics of human beings – higher than the changes occurred in the previous 20,000 years based on the characteristics of skeletons found in fossil places.



Another impressive change is the age at the menarche. This figure shows the man age at menarche as recorded in Norway, Finland, Germany, Sweden, Denmark, the Netherlands, the UK and the United States. Until the middle of the last century, it was absolutely normal and physiologic for a girl to have the first menses at around age 17: now it is considered normal to have the first menses at around age 12. However, what is normal is not physiological, because normality means frequency. The fact that it happens frequently does not necessarily mean that it is physiologically normal. What is common is not necessarily good, because another difference between these women is that the women now have a 200% increase in their risk of breast cancer compared with women 50 years ago. The 4-year difference in anticipation of sexual maturation is totally non-physiological. The causes of this are well known – excessive weight increase, lack of physical activity and high protein consumption. We are very concerned about the hole in the ozone

layer, but relatively little attention has been paid to the huge changes body growth, and that 'taller is better' is not true in medicine.

The third point I would like to touch is obesity. In addition of being taller we are becoming heavier. The prevalence of obesity in different regions of the United States in 1991 was 12%. In 1998, over 20% of the population is obese in the United States. That is a dramatic epidemic. It is progressing a little more slowly in Europe but the increase in obesity in the UK is approaching what was observed in the United States.



Obesity was thought to be a problem of rich countries but obesity is increasing also in developing countries. Brazil is one of the countries with the largest proportion of obese people, particularly in the poor rural areas.

These are the results of a European Commission study. The aim was to determine the proportion of subjects that practiced some kind of regular physical activity, including walking, in different countries. A very high proportion of the study population does not practice any type of physical activity in southern Europe. That matches the figures presented about the high prevalence of obesity in children in southern Europe.

It has been estimated that this obesity epidemic will increase by millions the number of people living with diabetes. It is expected that the prevalence will be multiplied by 5, or even more.

Obesity is a big problem, together with overweight, and it is increasing globally. It affects developed and developing countries. Some colleagues wrote in "Living with our genes" this very interesting statement: 'If obesity were an infectious disease, like tuberculosis or AIDS, it would be declared a national emergency and would become the target of a medical war. Instead, doctors treat the various diseases caused by obesity, but not the underlying cause – that is, the obesity.' All the attention is focused on the diseases due to obesity and the metabolic syndrome, but it is very important to put together research on aetiology and research on intervention.

We have the opportunity over the next few days to be together, to exchange, to go from science to public health and vice versa, and to have an interesting discussion. I look forward to a very interesting conference, and thank you again for being here with us.

Dietary energy density as a guide to food choices and weight management

Barbara ROLLS
Department of Nutritional Sciences, The Pennsylvania State University, USA

I have divided my talk into the three stages of weight change: weight gain, weight loss, and weight maintenance. I am going to begin by speaking about whether we can find diets which promote satiety and prevent weight gain.

In the field of study of food intake, most of the focus in the past has been on macro-nutrients. We all hear talk of high-protein and low-carbohydrate diets: Dr Astrup is going to expand on this theme later during his presentation.

There are many food properties that can affect satiety and satiation, including sensory properties, physical-chemical properties, and viscosity. Today, I shall concentrate on energy density, or the calories or joules per gram. We all know how the different nutrients can be divided in terms of energy density, with fat being the most energy dense at 9 calories per gram, followed by carbohydrates and protein at 4 calories per gram, and fibre at between 1 ½ and 2 ½ calories per gram. However, relatively little attention has been paid to the water which has 0 calories per gram.

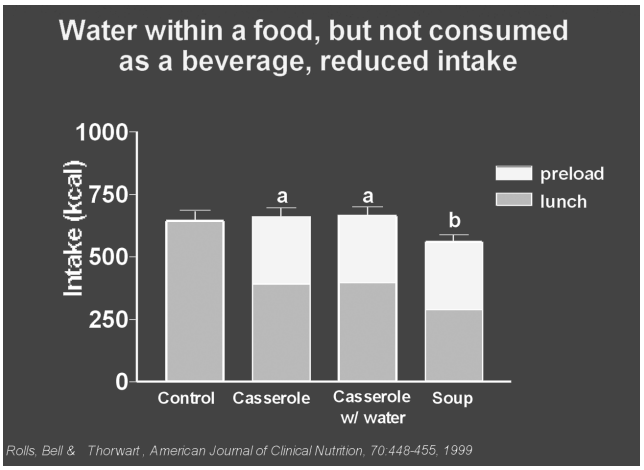
Water is the largest component of food and as a result, water has the greatest impact on how much food we eat. This leads to some interesting suggestions in terms of satiety and satiation.

As a simple example of the power of water to influence the amount of food that one can eat, we can compare grapes and raisins, essentially the same foods: a grape is dehydrated to produce a raisin. If we compare 100 calorie portions, we see that the grape portion is eight times heavier in weight than the raisin portion. This does not mean that you should not eat raisins; it simply means that they represent a far smaller portion for the same number of calories, and, furthermore, it is probably easier to overeat raisins than grapes.

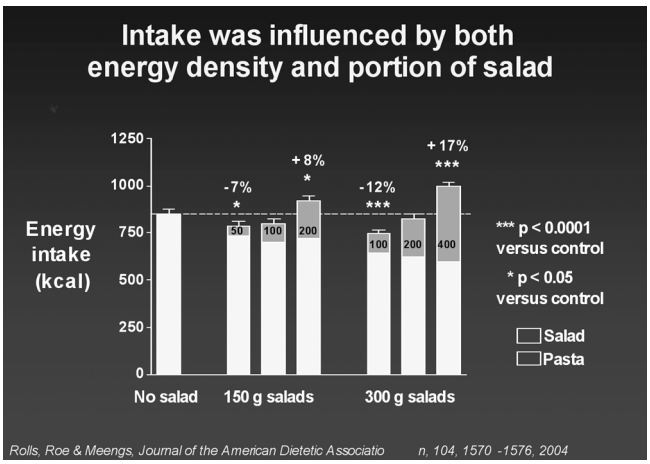
This is relatively easy to understand, but it becomes more complicated and requires greater care to explain that water also has the power to reduce the energy density of high-fat foods. Therefore, if, for example, we take one gram of fat and one gram of water and add them together, we halve the energy density. This is why a food like cheese, in which one third of the calories derive from fat, has the same energy density as a food like pretzels which is just made up of carbohydrates: the pretzels are dry, the cheese has a higher water content.

In order to study satiety, we give a preload – a first course. After a given interval during which we can track hunger and fullness, we study the impact of that preload on the types and amounts of food eaten during an ad libitum test meal.

I am going to share with you information about a few of the studies that we have carried out on satiety. In one study, we looked at the effects of water either in a food or consumed as a beverage on subsequent food intake. People came to our laboratory on three different occasions and they consumed a preload. Each preload had 270 calories, and consisted of a chicken and rice casserole. On one occasion they were given the chicken and rice casserole alone, on another occasion they drank a 10 oz. glass of water with the casserole, and on another occasion we gave them the casserole and the water cooked together as a soup. Therefore, the second and third preloads contained the same ingredients. They were also tested with no first course at all, which constituted our base-line control condition. Fifteen minutes after they had started to eat, we gave them a second course. In this graph, we see the calories from the preloads and what they ate at lunch. It can be seen that drinking water together with the casserole had no additional impact on intake at lunch, but that when the water was cooked into the food, it had an additional impact in reducing intake by around 100 calories – the people felt just as full and satisfied and did not eat more later in the day to compensate for that calorie difference. Therefore, water in food enhances satiety.



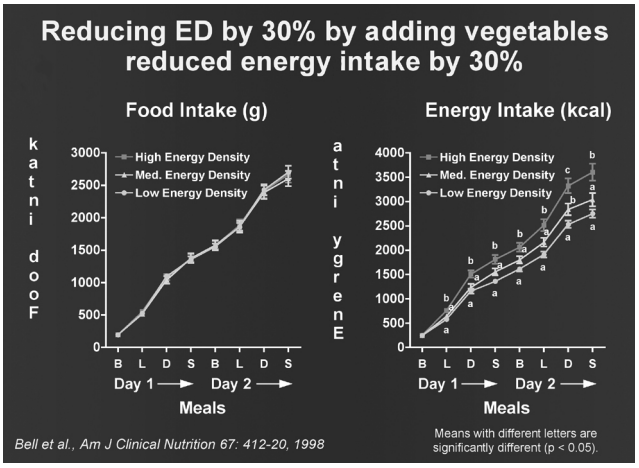
We conducted another study using salad as a first course. We were interested in using two different portions of salad, three different energy densities, and three different calorie levels. We could also compare portion size with the same number of calories using a small salad and a large salad which contained 100 or 200 calories respectively. We reduced the calories and energy density by using lower fat dressings and cheeses; it is therefore primarily achieved through fat reduction. People were allowed to eat as much pasta as they wanted in the subsequent test meal. Our findings are shown on this graph. It can be seen that the portion size, the energy density, and the calories in the salad had a significant impact on how much was consumed in total during the meal. A person consuming a large portion of a low-calorie salad ate 12% less during the total meal compared to a person consuming no first course at all: therefore, they gained an extra course in the meal and consumed fewer calories. On the other hand, a person consuming a high-calorie large salad consumed 17% more.



The basic conclusion to be drawn in this case is that 'bigger is better' if it is low calorie: the 100 calorie salads that were bigger reduced intake more. Therefore 'eat less' is not always the best message: sometimes, if a food is low calorie, it is better to eat more as it displaces the higher calorie options later in the meal.

The other method we use to study intake is to test satiation. We let people eat as much as they want. This is more difficult than other methodologies as we have to ensure that the palatability and sensory properties between the foods being compared are the same, as people eat more of one food if they like it more, regardless of our manipulation.

In this study, we gave people all their meals in the laboratory over two days. We had three different levels of energy density: low, medium and high. We used mixed dishes such as pasta and casseroles so that we could lower the energy density by adding more vegetables. The weight of food consumed over the two days is shown and the results are self-evident. What people tend to do in this kind of situation where they can eat as much or little as they wish, and where the foods are matched for palatability, is to eat the same amount. Therefore, if the energy density is lowered, people spontaneously consume fewer calories. When we reduced the energy density by circa 30% by adding more vegetables, people spontaneously ate 30% fewer calories over the two days and they felt equally full and satisfied. Therefore, adding water- and fibre-rich vegetables to meals spontaneously reduces energy intake without any change in levels of hunger or satisfaction.



We have been talking about energy density, but yesterday we heard that we should also consider portion size. We have carried out a series of studies on the effects of portion size on energy intake. In one study, we varied the portion size of all of the foods available to our subjects over three periods of two days each. Once again, study participants ate all of their meals in the laboratory. During one two day test there were standard portions which were based on what people should typically eat, and on recommendations on food packaging, and so on. Then during the other two day tests there were two bigger portion conditions in which all available foods were either 50% or 100% greater than the standard portions. The subjects did not see the portions side by side and surprisingly, most people are unaware of the fact that we were varying the portion size. What we found when we increased the portion size by 100% was that women ate 500 calories more on day 1 and 500 calories more on day 2 than when they had the standard portions. Men ate 800 calories more on day 1 and 800 calories more on day 2. Therefore, portion size has an important effect on energy intake.

However, it is not just portion size that is important: it is the combination of portion size and energy density which influences our food intake. We have carried out several studies to examine how energy density and portion size interact to influence energy intake. In one such study completed only recently, we asked people to eat all of their meals in the laboratory over a two day period. There was enough food to ensure that their intake was not limited simply because we were giving them small portions. We carried out this test over four different weeks, two days at a time under the following conditions:

- Standard energy density, standard portion size;
- Portion size reduced by 25%, standard energy density;
- Energy density reduced by 25%, standard portion size;
- Reduced portion size by 25% and reduced energy density by 25%.

We used foods that are commonly available. One aim of this study was to send a message to the food industry that small changes can have an impact on intake, so we used foods like pizza, pasta, sandwiches and so on. The energy density of the foods was varied, for example, by decreasing the cheese and increasing the vegetables on pizza. The differences in portion size and energy density were subtle, and the subjects never saw the portions side by side.

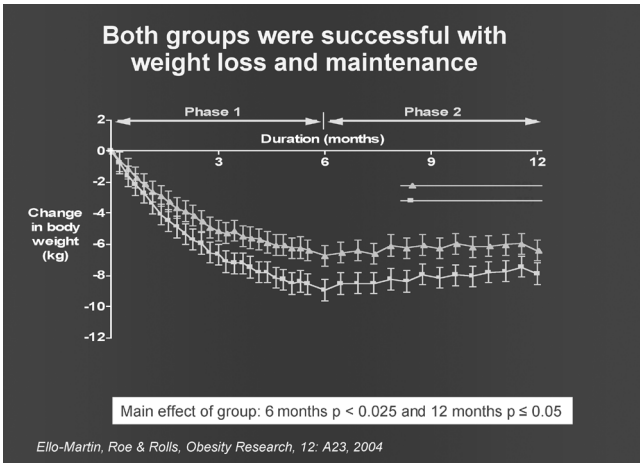
Reducing both portion size and energy density of all foods led to significant and independent decreases in energy intake over two days. A 25% decrease in portion size led to a 10% decrease in energy intake, and a 25% decrease in energy density led to a 24% decrease in energy intake. The effects on energy intake were additive and sustained over the two days. Thus, when portion size and energy density were reduced together over the two days, people ate 800 calories less on day 1 and 800 calories less on day 2, spontaneously eating 1 600 calories less over a two-day period. There were no differences in levels of hunger or fullness. Therefore, this is a strategy that could be used to reduce food intake and that would be acceptable to consumers, as long as palatability and cost were not affected.

I would like to talk about the strategies that can be used to enhance satiety and reduce energy density. Reducing fat intake does reduce energy density, but I think that it is important to emphasise that people should not reduce fat intake to such an extent that they do not enjoy their food; the message of 'healthy fat' should be emphasized. Intake of high-water and high-fibre foods does need to be increased, and these are the types of foods that we recommended in the Mediterranean diet. Portion control needs to be emphasized in the case of energy-dense foods – for higher fat foods and foods with low moisture content. We have also carried out a number of studies that demonstrate that calories from beverages add to food calories. It is also important to eat adequate amounts of lean protein: Dr Arne Astrup will tell you that protein helps to enhance the satiety of foods.

We have been discussing how to enhance satiety and weight gain. What about weight loss? We have recently completed a clinical trial where we compared two different strategies for reducing the energy density of the diet over a one-year period. We randomly selected 97 women. One half of the group was told to reduce fat intake and to restrict portions – typical of the kind of advice that has been given for years. The other group, the energy density group, was given a more positive message: to eat more fruit and vegetables, soups and wholegrain foods, and to eat as much as they wanted of foods very low in energy density. This group was taught the principles of energy density and to use portion control for energy dense foods. Neither group counted calories or fat grams; they were only given instructions as to what foods they should eat.

These are the results for weight loss over the year for those who completed the study. We can see that the number of completers was similar in both groups. After six months the low-fat group

had lost circa 15 pounds of weight, and the low-energy-density group had lost circa 20 pounds. Both groups regained circa $1^{1/2}$ pounds over the remaining six months. The groups remain statistically different over this time period. We have just finished our analysis of the diet records that we asked everyone to keep. Both groups showed a similar reduction in fat intake – which is logical, as both groups were given the same information regarding fat. However, the low-energy-density group ate more fruit and vegetables, which meant that the energy density was different between the groups, as we had hoped, and the low-energy-density group did eat a low-energy-density diet. The very interesting and positive message resulting from this study is that the low-energy-density group lost more weight, but they were eating more food in terms of food weight. Clearly, this can help people to avoid the sense of hunger and deprivation that often comes with weight management.



There have been very few studies that have focused on maintenance. Obviously, this formed a part of our studies over the last six months, but it is clear that there is a real need for far more long-term studies on weight maintenance. One of the main problems in studying weight maintenance is that of establishing adherence. Dr. Roland L. Weinsier pioneered the low energy density approach at the University of Alabama, and they are still analysing results and running a weight loss clinic there. Their approach is to recommend unlimited fruit and vegetables with fat restriction. They have reported that people following this advice were successful in not regaining weight in the long term, and they have reported more recent studies with similar results. Therefore, these studies are promising, but we clearly need more data.

We are working with the CDC examining nationally representative data from CSFII, which consists of self-reported intake data from 7 500 Americans. Dr Jenny H. Ledikwe, a post-doctoral fellow, is going to present these data here. She has looked at people who eat more than 30% of their diet as fat, or less than 30% of their diet in the form of fat. She has then divided these two groups in accordance with their intake of fruit and vegetables to look at the energy density of their diets. The results show a significant impact of fruit and vegetables on energy density of the diet. It is possible to eat a higher fat diet and have a lower energy density diet if you eat enough fruit and vegetables. This may help to explain the Mediterranean diet and how people can manage their weight eating slightly higher fat: they eat a lot of fruit and vegetables. Indeed we find that the higher fat groups eating large amounts of fruit and vegetables have a lower percentage of obesity than the lower fat diet groups who are not eating large amounts of fruit and vegetables.

In conclusion, it is starting to become clear, and the policy-making organisations, such as the World Health Organisation (WHO) with their dietary guidelines, are starting to take note of this, that energy density can have a powerful impact on our intake and on body weight. I think that the data clearly demonstrate that combining increased intake of low-energy dense foods, such as fruit and vegetables, with moderate reductions in fat intake is an effective strategy for weight loss. Furthermore, we now know that reducing energy density by eating more fruit and vegetables can affect a variety of dietary patterns, even those that are relatively high in fat, and whilst we have not been able to show all of this data, Dr. Ledikwe has also shown that a low-energy-density diet is better in terms of diet quality.

Questions

Member of the audience
I found the range for low, medium and high energy density very limited. Am I correct in thinking that a ratio greater than 1 calorie per gram is considered to be high energy density?

Barbara ROLLS
We consider very low-energy-density foods to be less than 0.6 calories per gram, and low-energy-density foods to be 0.6 to 1.5 calories per gram. Dr Jenny H. Ledikwe and colleagues published a paper recently in the Journal of Nutrition on how to look at energy densities of national data sets. It is complicated because beverages have to be considered in a different way because they have a disproportionate impact on energy density; therefore, we exclude beverages when determining the typical energy density of diets. We find that even a small difference in energy density can have a significant impact on daily energy intake. Therefore, it is important to think about small changes and to start eating at least slightly more fruit and vegetables.

Optimal dietary strategies for weight management

Arne ASTRUP
Department of Human Nutrition, Royal Veterinary and Agricultural University, Frederiksberg, Denmark

Thank you very much for inviting me to this beautiful place. I am enjoying my visit to Rome and also hope to do a little tourism whilst I am here.

The background to this presentation and to these discussions is the global epidemic of obesity. This can be seen by the differences between body shapes in Paris and New York, which are immediately apparent. Even last night, we saw that there are major differences in the prevalence of obesity between countries, and I think that Denmark and the Netherlands are amongst the countries with the lowest rates of obesity. However, we see from records that obesity did not really exist in Denmark sixty years ago and now we have a prevalence rate of 7.4%. It can be seen all over the world, and even though we are some years behind the United States and the United Kingdom, where we would prefer the problem to remain, we see that there is an upwards trend, and we are beginning to witness substantial problems ourselves in this respect.

Today, we are talking about diets, but I think the problem is also caused by our inactivity and low levels of daily physical activity. Sixty years ago, we could probably eat approximately 500 calories more every day without gaining weight due to high energy expenditure, but today, because energy expenditure is so low, it is difficult to consume the same amount of food as before. I think that this is an important part of the problem and needs to be acknowledged

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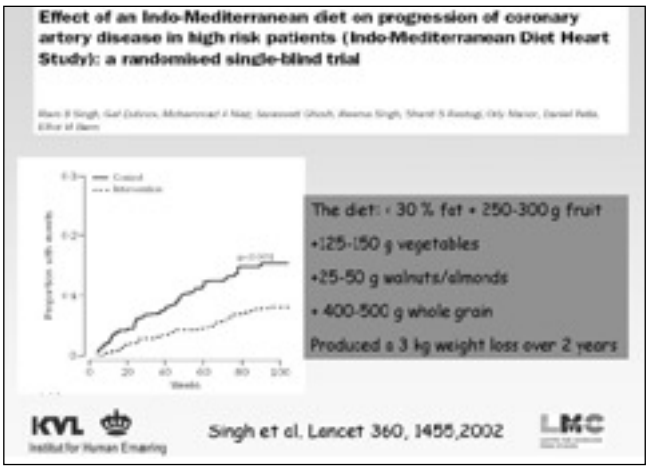
I shall not focus on portion size today as we have already heard about that and also about energy density, which are two of the very important aspects to consider. The problem that remains is how to use these findings to prevent further weight gain and obesity.

Some years ago, we carried out some meta-analyses on the randomised trials looking at fat reduction, which is reduction of energy density, even though we did not focus on energy restriction. There was strong evidence to suggest that, in the short term at least, there was spontaneous reduction in caloric intake and a slight weight reduction in normal weight to overweight subjects, and a significant weight reduction in obese subjects if they reduced energy density by reducing the fat content of the diet. There has been some controversy about the long term effects, but I believe this is because there are very few good studies on this and, more importantly, very few studies with active intervention.

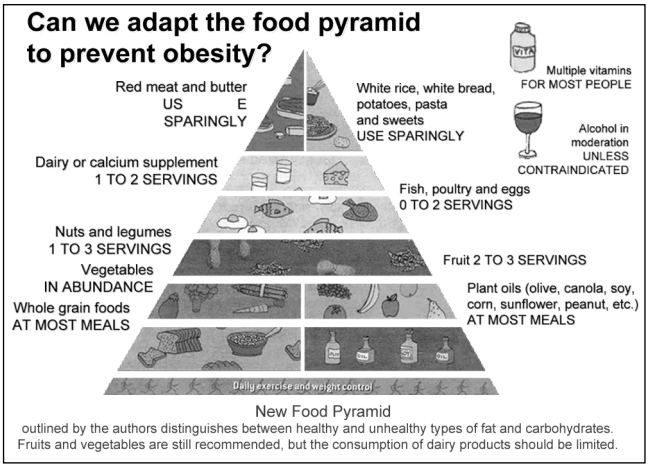
Dr Boyd Swinburn's study in New Zealand included active intervention over a period of one year with a control group using low fat food. The group lost circa 3 ½ kilo, which is what we would expect given the meta-analyses that we had carried out, but what is also apparent is that once the active intervention ended, people started to regain weight and within five years, they had regained all of the weight that they had lost. Some people have interpreted this data to mean that this low fat, low energy density approach does not work in the long term and that there has to be some adaptation. I think it is obvious that this is not the case because, as for every treatment, be it drug treatment, dietary change or lifestyle change, it does not work beyond the time that it is being carried out: therefore, as soon as the intervention ends, people resume their old habits that made them fat. Therefore, the real problem is how to make people sustain dietary change and increased levels of daily physical activity: this is the real challenge.

Another study has shown that this Indo-Mediterranean diet seems not only to produce spontaneous weight loss but also to reduce cardiovascular mortality amongst high-risk groups. When I showed this slide during a meeting recently, I was told that this study does not really exist and when someone asked for the data, they were told that all the records were eaten by termites. Therefore, I am not sure whether it actually did take place, but I like the data and I liked the study.



I think that it is also important, when talking about low fat diets, to emphasize that the non-fat component of the diet is extremely important. For example, if the fat reduction was made up by an increased consumption of sugar from soft drinks, it would probably be a problem. There are quite good epidemiological observational studies which demonstrate that those consuming high levels of sugar-rich soft drinks are at a higher risk of gaining weight and developing obesity and type 2 diabetes in the long term. When we carried out small randomised trials on this, where we compared sugar-rich with artificially sweetened soft drinks, we were surprised to see that even over a relatively short time period of ten weeks, there was a dramatic weight change. It seems that calories from sugar-rich soft drinks were simply added to the daily energy intake: there was no compensation at all. Therefore, it appears that the body did not recognize the calories entering the body through sugar-rich drinks, which seems to be different from the case of sugar in solid foods. I do not have all of the data with me here, but blood pressure also went up by between 6 and 8 mm of mercury and the amount of C-reactive Protein in the sugar group was doubled. It could not all be explained by the differences in weight loss, so it would seem that there is some adverse effect, not only on body weight but also on the inflammatory process and diabetes amongst those with high levels of soft drink consumption. By analogy, a low fat diet including a lot of soft drinks might be fattening and also have many other adverse effects on health.

One of the latest developments is this new food pyramid, which includes many 'good' foods such as fruit and vegetables and wholegrain foods. I have to admit being concerned that the potato is placed towards the top and by the recommendation to increase levels of 'healthy' fat consumption. I think that this would be the perfect diet for a very active person who has never had any weight problems. However, this would increase the energy density in a sedentary person who is having weight problems, and I am uncertain as to what would happen.



New Food Pyramid
outlined by the authors distinguishes between healthy and unhealthy types of fat and carbohydrates. Fruits and vegetables are still recommended, but the consumption of dairy products should be limited.

We are currently implementing a large-scale study in Copenhagen in collaboration with the food pyramid inventor, Dr Walter Willet, over a one-year period, to see which of the two pyramids is the most successful in maintaining weight loss. The results will be published at the beginning of next year. One of my personal concerns is that if potatoes are held to be fattening and we are told that it is better to eat avocadoes and nuts and so on, what about the energy density? I have seen no evidence to support the claim that it is better for the appetite and satiety to eat the much higher energy dense avocadoes and nuts. As Barbara Rolls told us, the volume and weight of food seem to be extremely important determinants of body weight control, so I believe that it is important that we see some randomised trials first. I cannot exclude the possibility that there is some magic in almonds and olives and avocadoes, and there is some evidence to suggest that it may be more complex than we believe today, but we need to have more concrete evidence before recommending that people change their diets; otherwise, we may exercise more harm than good.

Another one of the latest trends is the glycaemic index in dieting. It was originally invented to assist type 2 diabetics as a means of improving glycaemic control, but now it is increasingly used for weight control. It is heavily promoted for weight control, and I am convinced that it is good to choose low glycaemic index foods, but I am not certain that it can contribute towards weight maintenance and weight loss in people. There are many other problems: as soon as carbohydrates are mixed with fats and protein, something strange that we used to do in most of our meals, the effect on the glycaemic index of the carbohydrates seems to be eliminated, whereas the effect of the fats and the protein remains far more significant.

We recently carried out a study where we examined forty different European typical breakfast meals. We used this table to predict the glycaemic index and then measured it in twenty subjects each time – not a substantial number, but sufficient for our purposes. Our greatest concern was that there was really no relationship between the predicted and the measured glycaemic index, and when we tried to correlate the two, no significant correlation could be found. Therefore, it would seem to be of little use to advise consumers to keep a glycaemic bible in their bag and to check all their foods before buying them, because as soon as they are mixed with fat and protein, the values change completely. I am rather sceptical with regard to the use of glycaemic indexes in this respect.

Another part of the idea for using the glycaemic index is that a significant rise in insulin adversely affects metabolism and appetite control. However, this is not substantiated by most studies, and I can show you the meta-analysis that we have not yet published, measuring postprandial glucose and insulin, where we have compared glucose and insulin response with the postprandial satiety feeding. It is interesting to note that there is quite a strong positive correlation between insulin and satiety, so that means that a substantial increase in insulin response postprandially would lead to a sense of satiation. We know from many other studies that insulin is a central satiety hormone, so it is not logical to think that it is dangerous and that a potato should have an adverse effect because it stimulates insulin.

We did not carry out the meta-analysis in order to address this issue, but because we have seen in smaller studies that this association seems to be disrupted in obese subjects so they do not have the same relationship. This may be due to central insulin resistance, but we should not necessarily consider insulin increase as an abnormal or adverse phenomenon: we should view it in a more positive light as simply being a part of the physiological response. However, it is quite a complex issue.

I promised to talk about some of these low carbohydrate diets. In reality, if one examines them carefully – with the exception of the Atkin's diet, which consists of carbohydrate elimination – most of the books combine a reduction of carbohydrates and usually an increase in proteins, and the Palaeolithic diet recommends cutting out all potatoes and grains. My personal opinion is that these diets are extremely boring, and most dieters would not be able to sustain such a diet on a long term basis, even though they may be of interest scientifically. However, returning to the Atkin's diet trials again, there is no doubt that the low carbohydrate diets are quite effective in inducing weight loss. This weight loss is a fat loss, and there is no real adverse cardiovascular or diabetes effect, at least in the short term whilst the weight loss is occurring. However, it does not really seem to work on a long term basis, and when we carried out our analysis, which we have published during the last six months, one of the problems was that there seemed to be adverse effects such as cramps, headache, diarrhoea, weakness and so on, and it would seem that this is due to the lack of carbohydrates: when the brain has to use ketone bodies instead of glucose, this leads to headaches and the like.

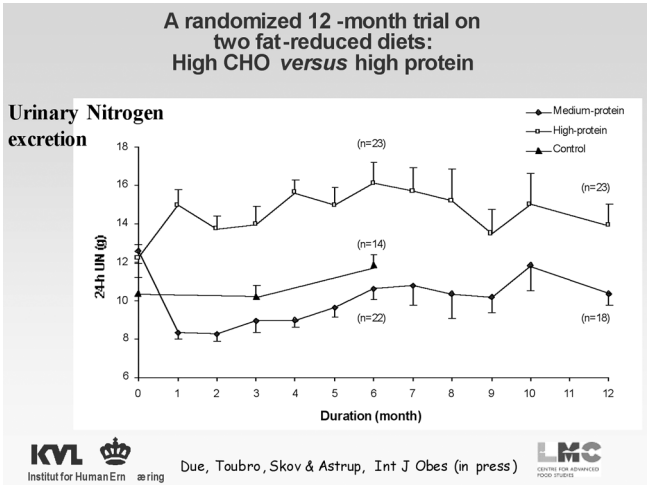
Ultimately, my main concern is that the long term impact of these diets will lead to very low consumption of fruit and vegetables which may increase the risk of cancer and other such diseases, but we would never be able to see this from short term trials and would require biological studies.

However, the real denominator of these diets is the very high level of protein, specifically between 30 and 50% of food intake, and it would seem that protein is far more satiating than carbohydrates and fat. To conclude on low carbohydrate diets, risk factors are improved but long term studies do not show that they are better than 'low-fat' diets. There are the adverse effects that we have discussed and also the predicted long term adverse effects of cardiovascular risk factors and cancers because as soon as weight loss stops, we would expect to see the adverse effects of the high saturated fat intake and the very low intake of fruit and vegetables and wholegrain foods on cardiovascular risk factors. However, perhaps it would be possible to use less extreme variations of these diets by increasing protein intake slightly at the expense of foods with low wholegrain content, such as white bread.

A paper that has recently been published in obesity reviews is an epidemiological study looking at the changes in different cultures in obesity prevalence and also in the macronutrient composition of the diet. What can be seen with changes in energy density is that with increased fat content, there is a slight increase in obesity prevalence; with a change in carbohydrate levels, there is a slight decrease; and there is an inverse association between

changes in protein content in the diet and obesity prevalence. This suggests that a slight increase in protein content is beneficial and would seem to reduce obesity prevalence. The slide that I am showing now suggests that additional studies demonstrate that protein is more satiating than carbohydrates and fat, and that even with the same energy density and calories, there is a slightly higher sensation of satiety and fullness after high protein meals. This could be of interest for weight and obesity management.

We carried out a one-year trial on this subject, where we studied high protein diets – although when I use the term 'high-protein', I am referring to a diet where 25% of the calories are derived from protein, which is far lower than what is recommended by many of the low carbohydrate diet books. Our control group was on a high carbohydrate diet where 12% of the diet was constituted by protein, which is a 'normal' level. We used a supermarket model with 1 500 different food items. The most effective system to ensure adherence to a diet is to provide the subjects with all foods free of charge and to use the bar codes to control the nutrient composition of the diet. I will not enter into too much detail but it was an effective system. A good biological marker of different protein intakes was that urinary-nitrogen excretion increased on the high protein diet, and that it decreased on the low protein diet.



We can see that there was extremely good compliance during this six-month period, but as soon as the free of charge food system was ended, compliance began to decrease. In any case, the results show that the high protein diet lead to far better weight loss, even though there was no real control of these diets and no calorie control, and people ate until they felt satiated. Our only instruction was that they adhere to the protein ratios. During the first six months this group lost significantly more weight and they really did lose fat: almost twice as much as the normal protein diet. Subsequently, between the sixth and twelfth month, when there was no control through the supermarket system, they tended to regain weight, but there was far better weight loss compared to the control group. Therefore, it would seem to have some relevance.

Of secondary importance during the study was the intra-abdominal fat, and we were quite surprised to see that a high protein diet seemed to reduce the visceral fat of the subjects. In the beginning, we were unsure as to whether we could trust that this was a real finding and wondered whether it was just a coincidence, but the result seems to be correct. I have just seen an American study which suggests that there seems to be something in dairy protein which seems to reduce visceral fat, and this is very intriguing. There is another aspect to dairy protein that I would like to discuss: calcium intake.

There is talk of how calcium seems to reduce body weight and this theory is mostly based on epidemiological and animal studies and a few human intervention trials by an American group. We are trying to carry out some control studies to understand how calcium produces weight loss, if indeed it does, and how it affects energy balance. We have been unable to see any effect on energy expenditure and fat oxidation. However, there was an effect – and I asked my laboratory technician to carry out a specific analysis to verify this – which measures the faecal fat and energy outputs in both high and low dairy protein and calcium. We can see that with an increase in calcium intake of dairy products from 500 mg to 1,500 mg per day, there is an increase in fat excretion from 5% to 18% of intake, which is sufficient to play a role in body weight regulation on a long term basis. This is approximately 100 calories that are lost spontaneously, and now we are carrying out further studies to understand its interaction with the fat content of the diet, and other calcium-related tests, although so far we have not been able to ascertain whether calcium has any effect on appetite and on energy expenditure. We can see in this graph that there does not seem to be a dramatic effect but there is an effect. We had a symposium about this in Copenhagen and there were articles about it in newspapers, and I think that this is a positive message for young girls who are afraid of milk because they think that it is fattening; if it is the low fat version, it seems that it may have the opposite effect. We have been unable to find any adverse effects of this protein diet on the bones, kidneys and so on after twelve months.

Of course, this does not mean that we would recommend that everyone increases the meat intake as it probably would not be a good idea, but in terms of assisting in the control of body weight, I think that it could be something for us to consider if ensuring more fruit and vegetables, a reduction in energy density of the diet and of the portion size at the same time. Obviously, we are all concerned about whether there might be a higher risk of cancer if we recommended this.

However, I note that the Institute of Medicine has recently increased the upper safe range for protein intake in adults to 35%, and it has also increased dramatically for children compared to what we considered to be safe in the Scandinavian countries. Only one or two months ago, the Harvard Medical School in Boston also increased their recommendations for type 2 diabetics, as well as for overweight and the obese with impaired glucose, from an allowance of 20 to 30% protein. Therefore, there definitely seems to be a tendency to accept and recommend more protein in the diet, and of course, this makes it all the more important that we consider if this presents any adverse effects.

Personally, I would like to see more long term control studies. Together with partners in Europe and the United States, we will probably conduct a large-scale intervention study in whole families with obese parents and their overweight children, and there will probably be three centres in the United States running the same protocol. The study will consist of five different levels, including normal protein and high protein in type 2 diabetes subjects, and will also include the use of the glycaemic index to try to understand what the roles of protein and the glycaemic index are for body weight control. This study will investigate weight regain principally and we hope to gain more information. Also, the epidemiological part of the diagnosis will address some of the above issues in terms of the glycaemic index and protein. I hope that this will contribute to our understanding of the optimal diet for weight control. Thank you for your attention.

Questions

Member of the audience
Thank you for this extremely interesting speech. I would like to ask you about these high protein diet results. Did you also measure the energy expenditure? Maybe the subjects began to exercise more. Did you measure energy output as well as input?

Arne ASTRUP
Yes, we have done some 24-hour energy expenditure studies in this area. Our findings were that protein increases body weight by 3 to 4% on a daily basis, but we were unable to see any change in physical activity and it seems to be more a case of the body weight increasing. This is only information gathered on a short term basis and we do not have any long term studies addressing this issue. Hopefully, this study will allow us to examine this issue in more detail.

Obesity, socio-economic status and food intake in children

Marion HETHERINGTON
School of Psychology, University of Liverpool, UK

I would like to speak to you about obesity, socio-economic status and food intake in children. Arne Astrup has set the scene for global epidemic of obesity admirably, and what I would like to do is to discuss recent evidence gathered in Scotland on socio-economic status and food intake in young children. I would also like to introduce and consider some intervention work that we have carried out previously in a school setting.

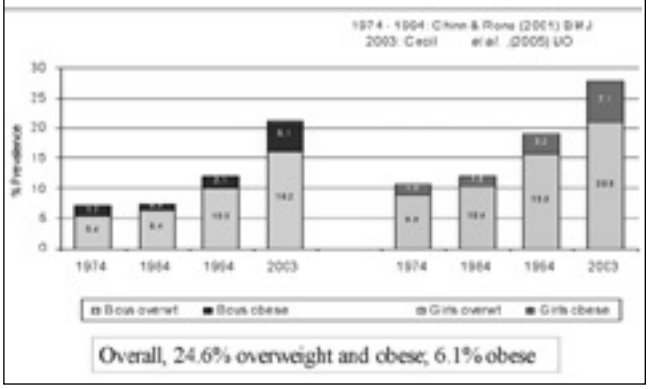
My speech is divided into four sections. I would first like to consider socio-economic status and obesity as a worldwide problem. Then I specifically wish to address the issue of obesity prevalence and the role of the socio-economic status in Scottish school children. I would like to continue from this theme to discuss some of the differences in food choices that children from high and low socio-economic status make. Finally, I would like to describe a whole-school intervention that was carried out a few years ago in an attempt to increase the consumption of fruit and vegetables amongst Scottish children, who could benefit from following a more Mediterranean diet.

Data from Dr Tim Lobstein and colleagues from the International Obesity Taskforce show very clearly that approximately 10% of the world's children are carrying excess body fat. These data demonstrate very well that this is no longer an issue which concerns Western and industrialised societies alone, but that childhood obesity is on the increase worldwide and is now recorded increasingly in developing countries. Moreover, there is an increase in overweight prevalence globally, including countries such as China, and, of course, increasing prevalence in the United Kingdom and the United States continues unabated.

In the case of the United Kingdom, childhood obesity and overweight prevalence has almost tripled in the last decade. Overweight prevalence according to family income levels presents quite an interesting and complicated relationship because it seems – and data from Jane Wardle supports this idea – that higher socio-economic status in Western industrialised countries protects against overweight and obesity, whereas the opposite is the case in developing countries such as Brazil. Therefore, it would seem that in developing countries, a higher socio-economic status is a risk factor for obesity, whereas in the United States and the United Kingdom, higher socio-economic status actually confers a protective benefit against obesity and overweight.

My interest in examining socio-economic status in children arose from a larger collaborative study on genotyping of children in Scotland (see Cecil et al., references). Essentially, the purpose of this study was to examine PPAR-γ, which is a protein involved in fat cell differentiation. We studied 2 454 children from Northeast Scotland and we characterised their genotype with respect to variants of PPAR-γ. Having genotyped the children, we then carried out energy expenditure studies on 100 children who were enriched for 3 PPAR-γ variants. In the beginning, we only considered socio-economic status incidentally as a part of the whole picture and we looked at BMI in relation to their socio-economic status. The average age of the child was 7.4 years old, and the majority of the children were of normal weight. However, when we plot the data gathered on a chart, it can be seen that there is an extremely significant increase in prevalence of obesity and overweight compared to the National Survey data of 1994. We have also found that this is a conservative estimate because most of the parents of the heaviest and most overweight children would not give permission for their children to be included in the study (Figure 1).

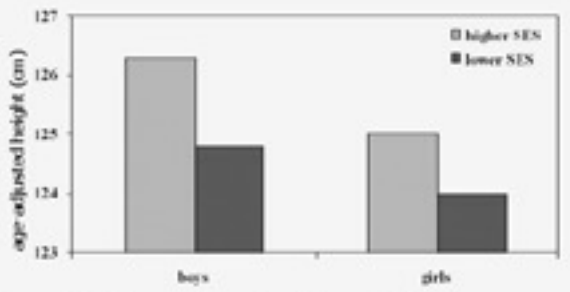
Figure 1: Prevalence of overweight and obesity Scottish cohorts



If we show this data against previous survey data taken in Scotland published in the British Medical Journal, we see that the increase in overweight and obesity prevalence is significant, and that in Scotland, childhood obesity and overweight is increasing at an exponential rate. From the original group, it can be seen that 1 in 4 children is overweight and the total percentage is 6.1 for obesity, taking boys and girls into together. In order to define the socio-economic status of the group, we used a Scottish Parliament proxy of socio-economic status by looking at free meal entitlement. The Scottish Parliament publishes details of the number of children entitled to free meals for each school and this reflects the numbers of socially-excluded and poor children. In the initial group that we examined, we found that the schools were bi-modally distributed in the group: 1 000 of the children were from low socio-economic status groups, according to above average free meal entitlement, and 1 400 of the children were of high socio-economic status, because their schools had below average free meal entitlement.

When we looked at these children in more detail, we found that having a higher socio-economic status produced a lower level of obesity In fact, the lower socio-economic status children were 65% more likely to be obese than the higher socio-economic status children. The income level was inversely related to overweight and obesity, and this is particularly true for girls: this is a finding that confirms previous work on socio-economic status and childhood obesity. Indeed, income level is a stronger predictor of childhood obesity than sex. However, when we looked at this data in more detail, we found that the children from the lower socio-economic status families were not heavier in weight. There was no difference in age and sex-adjusted weight between the groups, the difference was in height, such that there was growth limitation amongst the children from the lower socio-economic status groups (Figure 2).

Figure 2: Height and socioeconomic status (SES)



Lower SES 1.26 cm shorter than higher SES for both sexes
Height limitation (e.g. boys and girls differ by 1cm at this age)

We can see from the figure that the higher socio-economic status boys and girls were taller than their lower socio-economic status counterparts. Overall, the difference amounts to approximately 1.26 cm, which is quite significant because at this age, boys and girls tend to differ by approximately 1 cm, so the growth limitation in this group is of a greater magnitude than that expected on the basis of sex differences. The socio-economic status difference in height was quite apparent across a range of BMIs: the higher socio-economic status children were always taller, irrespective of whether they were lean or obese. In conclusion, since the height difference is observed across all levels of BMI, we can infer that growth rates were possibly similar in the children but that there was a specific influence of poverty on growth limitation, and we are able to observe from our calculations that individuals from low income families were approximately 65% more likely to be overweight than children of higher socio-economic status. These children weighed the same as the more affluent children of the same age, but were 1.26 cm shorter. Before I proceed to talk about these children in more detail, I wish to say that if the children from the low socio-economic status background are shorter, this is clearly related to the maternal diet during pregnancy. Therefore, whilst the quality of the diet may produce some differences in height during the lifetime of the child, growth limitation is determined in part by maternal diet during pregnancy.

In the second phase of this study, we were able to investigate a group of 100 children more closely. We took body composition measures, total energy expenditure, resting energy expenditure and several types of energy intake measurement. We had food frequency questionnaires completed by the children's parents – mainly by the mothers – and we also had 24 hour energy intake recorded by recall using a multiple-pass method. Of the 100 children that we studied in further detail, the boys and girls were similar in overweight and obesity status as the original cohort, and these are higher values for BMI and percentage body fat than those published previously for Scottish cohorts.

In this sample, we found that child adiposity was closely associated with maternal adiposity, but we also further investigated the dietary patterns of the children in terms of food frequency between low and high socio-economic status children. We found that there were significant differences in the number of portions of food consumed according to status. This was particularly true with pasta and rice – the high starch foods –with lower socio-economic status boys eating far fewer portions than high socio-economic status boys. Similarly, there was a significant difference in the consumption of high fibre cereals and bread. Boys in this sample never ate salads, irrespective or whether they were of high or low socio-economic status. We also found that high energy snacks were eaten more frequently amongst low socio-economic status children. Low socio-economic status children had more high fat snacks, more fizzy drinks and fewer starchy foods than the higher socio-economic status children. What was apparent was that in this cohort, all of the children were consuming fewer than the 'five-a-day' fruit and vegetable portions, and they were consuming far more high fat snacks than recommended by the United Kingdom government. The low socio-economic status children of both sexes had a higher frequency of consumption of sweets and chocolate and as a result, they were consuming fewer healthy options and more energy dense snacks (Figure 3).

Figure 3: Child Food Frequency

Food frequency (per week)	High SES		Low SES		p *
	Boys n=34	Girls n=20	Boys n=17	Girls n=29	
Pasta and rice	3.0 (2.0-5.1)	3.0 (2.0-4.8)	1.5 (0.5-2.0)	3.0 (2.2-4.1)	<0.01 b
High fibre cereals & bread	4.0 (2.8-7.4)	4.0 (1.4-7.8)	2.4 (0.6-3.4)	4.0 (2.8-7.0)	<0.05 b
Cooked green vegetables	2.0 (0-7.0)	2.0 (1.0-4.8)	0.5 (0-1.8)	2.0 (0.2-4.0)	NS
Cooked other vegetables	3.0 (0.5-3.2)	2.0 (0.5-3.0)	1.0 (0.5-1.0)	1.0 (0.4-3.0)	<0.05 b
Salads	0.0 (0-1.3)	2.0 (0.6-2.8)	0.0 (0-0.8)	0.5 (0-3.0)	<0.05 g
Sweets and chocolates	4.0 (2.0-5.8)	4.0 (3.0-7.0)	7.0 (4.5-7.0)	7.0 (4.0-7.0)	<0.05

Low SES had more HF snacks, fizzy drinks and fewer starchy foods than high SES

As some children were eating far less fruit and vegetables than recommended and as this conference concerns the health benefits of the Mediterranean diet, I thought it would be useful if I talked to you about an intervention that we carried out in order to attempt to improve the amount of fruit and vegetables being eaten in schools in Scotland with a high level of socio-economic deprivation. For this intervention, we used materials developed for us by D.C. Thomson using the 'Bash Street Kids' popular cartoon characters known to many, if not most, Scottish children. In the materials, these characters were depicted eating fruit and vegetables and these were included in curriculum materials and posters around the schools in a whole-school approach. We incorporated materials that teachers could use with the children to encourage fruit and vegetable consumption, and we limited high fat snacks from the tuck shops and offered fruit and vegetables instead. We were also able to instigate some changes into the provision of meals at school through catering by offering vegetable soups, fruit salads and fresh fruits as part of the school meals, and we gave newsletters to the parents to encourage fruit and vegetable consumption at home. Therefore, we used intervention materials across a number of different domains through newsletters, posters, curricular materials, and so on.

The materials developed for this intervention are all available on the Food Standards Agency website, and teachers in the United Kingdom can download these materials if they wish to use them in their classrooms see:
http://www.food.gov.uk/interactivetools/educational/.
We measured fruit and vegetable intake using three-day parental food diaries; we examined food preference ratings from the children and asked them to taste the foods and tell us how much they liked the foods we were using; we also looked at the success of the tuck shops by comparing control schools with intervention schools; and then we looked at fruit and vegetable consumption using parental frequency questionnaires. There were two control schools and two intervention schools which were matched for socio-economic status but in fact, all of the schools involved in the study had a higher free meal entitlement than average, and the postcode indicators of the families revealed that the majority of children came from low socio-economic status families. Sixty-four children were included in the intervention for the diary part of

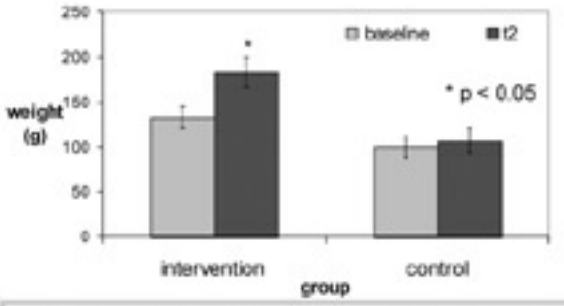
this study, and sixty-five in the control schools. As these were relatively young children, when measuring food preferences, we used facial expressions so that the children could tell us how much they liked or disliked fruit and vegetables along with other types of snack foods.

We found there was a small but significant increase in liking for foods like grapes and drinks like orange juice, and a very slight but significant decline in liking for foods like chocolate. In terms of actual food intake, the diaries showed that there was a very modest if significant increase in fruit intake in children in the intervention schools, so the mean daily weight of fruit consumed as measured by the food diaries showed a modest increase of approximately 40 grams (Figure 4). This was after 9 months of a very intensive whole-school intervention. Therefore, the effect was relatively limited (see Anderson et al., 2005 for more detail).

The whole-school approach had a modest success in increasing fruit intake, but did not have any impact on vegetable intake at all. Since this study was conducted, the Scottish Parliament has developed a programme called 'Hungry for Success', and what they have done is to completely change the culture of school meals in all Scottish schools by reducing the amount of deep-fried and high fat foods and increasing daily fresh vegetables and fruit in every part of the school meal programme. This is in line with WHO recommendations to change societal attitudes and behaviour.

In conclusion, I would like to say that socio-economic status is strongly predictive for obesity, that risk of obesity in our data derived from shorter height rather than weight measurements linked to maternal as well as childhood diet, and finally, interventions such as the one I have just described, are only moderately successful unless they are linked to larger public health solutions. It will be interesting to see whether fruit and vegetable intake has increased amongst Scottish children in five years' time to resemble the Mediterranean diet more closely as a result of the new 'Hungry for Success' programme. Thank you.

Figure 4: Fruit intake



Mean daily weight of fruit consumed as measured by 3 day food diaries in intervention (n=64) and controls (n=65); increase of 40 g after 9 months

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Questions

Barbara ROLLS
Thank you, Marion. Did the Scottish government spend a large sum of money on the 'Hungry for Success' programme?

Marion HETHERINGTON
I do not know the exact cost of the programme, although I believe that it has been quite expensive to develop. However, I think that they will see a return on this investment because more children are taking school dinners now.

Member of the audience
Thank you for your interesting speech. Could you describe in more detail the 'Hungry for Success' programme, such as the food culture change, when it started, and the kinds of things that they are changing in the culture?

Marion HETHERINGTON
I have only just returned to Scotland, so I am quite new to the programme myself. Essentially, they have completely revamped the whole school meal system. For example, there are still competitive tenders for school meals in England, and much of this is very low cost, high energy density food such as 'Turkey Twizzlers', which have been written about in the press recently in England.

What they have done in Scotland is to completely change the nutritional quality of the diet offered to children. For instance, there is a red, a blue and a green tray and the children have to choose one of these trays, or a 'grab and go', which is a packed lunch. Each day, the children have to choose one of these three trays or a 'grab and go', and each of these meals has a fruit and a vegetable content, be it salad, cooked vegetables, soup or fresh fruit. There has also been a move towards more traditional cuisines: for example, the children have home-made bread baked on the school premises. This programme is at an early stage at the moment as it was rolled out at the beginning of this year, but I have watched my own children coming home really excited about school meals. I would have thought that was impossible before but it is because there is so much choice and so much dietary variety.

Barbara ROLLS
Are they monitoring what is happening?

Marion HETHERINGTON
I hope and assume that they are.

Barbara ROLLS
It would be a great opportunity lost if they did not.

Member of the audience
I heard two weeks ago in a meeting in London that Scotland has invested £64 million into this programme, which is wonderful.

Prevention of obesity: is it ever too late to start?

Jaap SEIDELL
Free University of Amsterdam, Faculty of Earth and Life Sciences and VU University Medical Center (VUmc), Amsterdam, The Netherlands

Thank you, Dr Rolls. I would also like to thank the organisers of this wonderful symposium for inviting me to Rome. I see that it is a beautiful day outside and we are sitting inside listening to a speech on obesity prevention, when we should be outside walking, running and eating healthy Mediterranean food!

What I am going to do is to follow on from what has already been said. I am not going to discuss nutrition too extensively, but rather whether or not we are doing the right things at the right time for the right people.

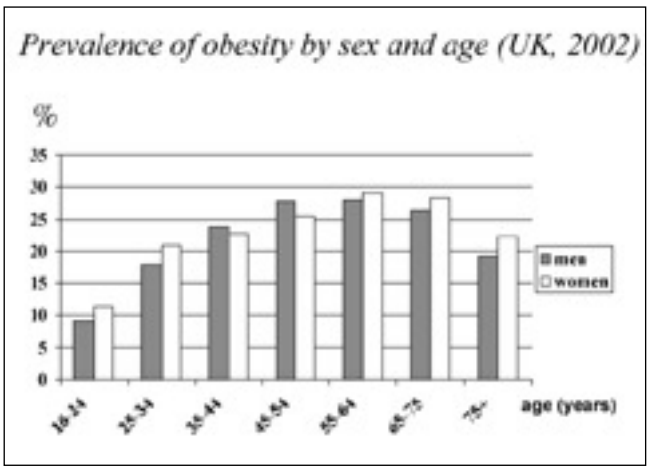
This occurred to me because we are now witnessing an explosion in interest on the part of public health officials, ministries of health and organisations such as the European Union regarding the necessity of doing something very soon about the prevalence of obesity. The trend is invariably leaning towards directing all funding towards preventing obesity in children, which is, of course, applauded by everyone. Therefore, there has been a series of studies such as those that Dr Hetherington has just discussed carried out in schools.

However, we have found that it is quite difficult to sustain the effects of these interventions over a long period of time and it has to be carried out quite intensively in order to achieve reasonable effects on body weight and health outcomes, and an even longer period of time to achieve a long term health benefit. We have noticed that due to the fact that all funding is being channelled into childhood obesity prevention programmes, there is no money left to focus on other groups. Childhood obesity prevention is very well-funded by organisations. For example, the World Health Organization (WHO), as a consequence of the obesity reports and chronic diseases strategies, is concentrating almost exclusively on children. Of course, the reason for this is that we are witnessing increases in childhood obesity which are quite dramatic and horrendous and need to be stopped, and I believe that this is a problem that deserves our attention. However, we may be missing out important categories.

The reasons we are concentrating on children are as follows: firstly, we all think that prevention should start early as habits start early and are more difficult to change later on, and if it is not started early, the benefits will not be reaped; secondly, it is assumed, especially by public health experts, that it is more difficult to change habits in adults, and that once you are an adult you are either a physically active or a sedentary person and that this cannot be changed; thirdly, that once adults have insulin resistance and risk factors for cardiovascular disease, that these factors are irreversible; and lastly, there is a strong school of thought that for middle-aged and for older people in particular, the worst thing that can happen to them is that they lose weight – this is particularly emphasised in Geriatrics and Gerontology – and also, many seem to think that it is a less important consideration for older people than for young people.

What I wish to convey to you is that there are some considerations that need to be taken into account. One of these is that obesity starts in young adults, but the prevalence of obesity is actually quite low in most populations studied across Europe, and obesity only begins to reach high proportions in adulthood. Adult weight gain is in itself an independent predictor of the weight status of an adult of most obviously related health outcomes, such as diabetes, breast cancer, cardiovascular disease, and other chronic diseases. The risk of potentially preventable non-communicable diseases increases with age; that is to say that diabetes is much more common amongst older people than amongst younger people. It is my opinion that if we wish to talk about interventions, we have to ensure that they are not only effective, but also cost-effective: they are efficient and deliver long term health improvements, rather than just costing large amounts of money without any real impact.

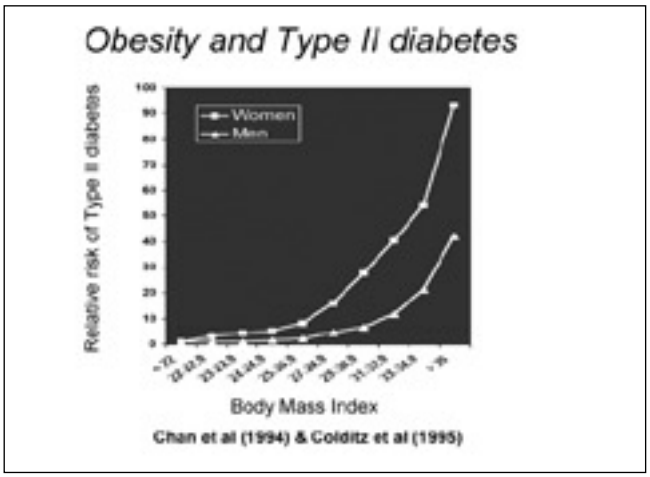
When we are talking about the prevalence of obesity, we look at the relationship of obesity with age, and we see that in the United Kingdom there is already a large amount of obesity amongst young adults at circa 5-10%, but this increases sharply until middle-age to circa 25%, and then decreases after the age of sixty or sixty-five. Many conclude from these statistics that obesity disappears with age and people lose weight and the problem is resolved. However, it has to be remembered that these figures are all based on cross-sectional data; it is a snap-shot of the population looking at the whole population and the prevalence of obesity and obesity in younger people plotted on a graph. This is done in almost every country to describe the relationship between agent and trackers. The older people included in this data were born during a completely different time in the 1930s and 1940s as these are records from the Second World War in the UK and in continental Europe: there was not much obesity, as Dr Astrup mentioned using his military conscript data.



Therefore, we are trying to develop a more sophisticated methodology to look at age, period and cohort effects. We have examined different studies over time, and following individual people over time. This slide shows that if we start with people in the 1980s at the age of twenty-five, they will gain a lot of weight. If we examine people aged thirty-five in the 1980s and follow them up the chart, they start at this level. We see that people, who are now thirty-five years of age ten years later at this point on the graph, are already six kilos heavier than the people who were thirty-five ten years earlier. It can also be seen, when looking at the association between age and body weight, that there is an increase in body weight with age and that then it seems to drop. As a result, the cross-sectional data seems to suggest that there is weight loss with age. However, if you look at people longitudinally, it can be seen that they continue to gain weight even amongst the older age-groups.

Therefore, cross-sectional data alone is misleading and needs to be examined together with longitudinal data to see the dynamics of obesity. From this, we see that the real weight gain is different from the picture shown by cross-sectional data, and thirty-five year old people are 5 or 7 kilos heavier at this point than their elders were ten years earlier. There is a continuous increase in all age groups. The rate of increase is lower, but we can also see that the major weight gain actually takes place during early adulthood, with people gaining in the order of 6 or 7 kilos over a ten year period during early adulthood. If we look at BMI, we see that there is an increase in BMI for every age group, although the starting level is higher for older age groups, of course.

Why is this important? One of the points I mentioned earlier is that if a person has a higher BMI at a young age, there is a higher risk of diabetes. However, this is really dependent on whether or not there is subsequent weight gain, because if the person maintains their weight, then, there is little knock-on effect in terms of diabetes. However, if there is a high BMI of 24 at the age of twenty-one and there is a weight gain of more than 11 kilos, which is very common in our populations, then there is a real synergy and the risk of diabetes increases exponentially. Therefore, it is not just a matter of the starting level of obesity but also what happens in adulthood that is important. It is especially important because the relationship between the body mass index and diseases such as type 2 diabetes are curvilinear and increase exponentially. As a result, middle-aged people who have a relatively high starting level of BMI and who continue to gain weight have a very high risk of developing diabetes. Dr Tuomilheto will discuss this further when he will talk about the diabetes prevention intervention study in Finland, but if the persons gain as much as 3% of their body weight, which is usually circa 2 or 3 kilos, their risk of diabetes is doubled over a period of five years. These are people who are already overweight, insulin-resistant or glucose-intolerant and a small change in bodyweight doubles their risk of diabetes.



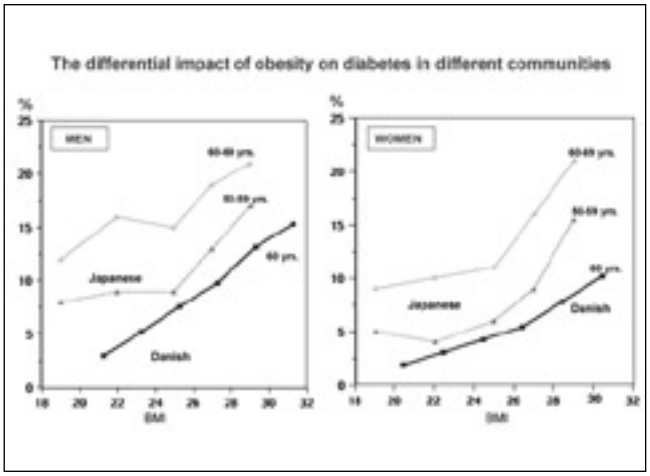
Why is so little emphasis being placed on the middle-aged and elderly groups of the population when discussing prevention? Perhaps it is because it is less attractive. Is it because we believe that adults have their own responsibility and should take care of their own lives? Or because the relative risks of disease seem to decrease with age because there is a common perception that hypertension and body weight are less of a risk factor with age? Of course, we are not thinking about this in a sophisticated way. We have to think about the different types of risk. In a paper recently published in the International Journal of Obesity, they showed that the relative risk of obesity for hypercholesterolaemia decreased with age, and the conclusion was that obesity was not a real problem in older people and that we should focus our attention on younger people. Of course, this is wrong. It occurs because clinicians and others are trained to think about relative risks in terms of how their patients can benefit from a treatment, and almost invariably papers published about public health and epidemiology present findings in terms of relative risk. However, in public health, attributable risk is far more important.

At the risk of labouring my point, I wish to present you an example. On the graph, these are two different age groups, and this is the risk of obesity or the risk of coronary heart disease with obesity. This is the age of forty-five and this is the age of seventy-five. Here, we can see that the prevalence of obesity increases sharply and the relative risk is decreasing. This is an accurate picture of what actually happens: obesity seems to be less of a problem in older people in terms of relative risk than in younger people, but the actual risk of coronary heart disease is actually much higher. If we look at the attributable risk, that is to say the number of cases of coronary heart disease that can actually be attributed to obesity in older and younger people, we can see that it is actually 20% in the older people and less than 10% in younger people. For many medical students, it is difficult to think that something that is less of a risk factor in terms of relative risk might be more important in terms of public health. Therefore, obesity in older age is actually an enormous public health problem in terms of absolute risk, attributable risk, and the number of patients who develop disease.

Estimated 10-Year Risk of Incident Coronary Heart Disease in Younger And Older Individuals with or without Obesity

Age, yrs	Obesity	Prev.	Absolute Risk	Relative Risk	Excess Risk	Attributable Risk
45	No	90%	5%	-	-	-
	Yes	10%	10%	2.0	5%	9.1%
75	No	50%	20%	-	-	-
	Yes	50%	30%	1.5	10%	20%

As a result, it is important that we do not focus only on these relative risks, which are often cited in studies to demonstrate that the relative risks of obesity in old age diminish, as it does not mean that obesity is less of a problem for society. This can be seen on this graph, which demonstrates that the absolute incidence of type 2 diabetes is actually higher at every BMI level in age groups of fifty to fifty-nine and sixty to sixty-nine.



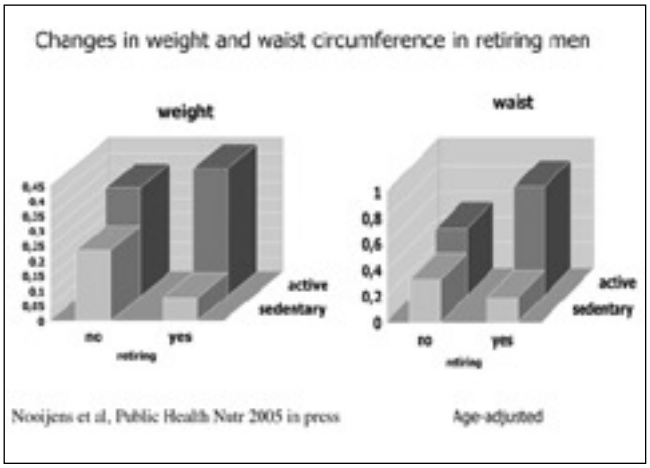
Therefore, when considering the possibility of a long-term intervention of ten years, if you would like to see that there are health benefits from the intervention and real cost-effectiveness, I would say that the potential health gain and cost-effectiveness will be far more effective if the focus is on older people rather than on younger people. If the £64 million in Scotland could be spent only once, would it be wise to invest it only in childhood programmes? I am not purporting that the school programmes should not be implemented as I believe that they are enormously important, but I am concerned that we are neglecting the rest of the population.

Rather than just concentrating on school-based interventions alone, what we are now doing is to start interventions in all of these age groups, and these are all groups that are vulnerable to incidence of obesity that is changing their lifestyles quite considerably and who have a high risk of developing obesity-related complications. We are currently implementing interventions in young adult people where there is a significant change in their lifestyle and who do not focus on physical activity and nutritional behaviour: they are also the prospective parents of our new generation of young children. This relates back to one of the problems that we noticed in our school-based interventions, that even when we were able to stimulate the interest of the children, if they went home to parents who were not interested at all, the effect is actually quite negligible. The parents have to be involved and young adults are in themselves a high risk group because it is at this time that they gain weight. Pregnancy is also very important and there is very little guidance as to how women can avoid excess weight gain and weight gain retention after pregnancy and we are currently running interventions for these women. Smoking-associated programmes are also extremely important, and I am also going talk to you about work-site programmes, as well as a group that is extremely important in numbers because of the aging of the 'baby-boomers' in our societies: people who have retired.

Let me give you a few examples. One is the work-site prevention of weight gain, where we are running different interventions situations with randomised studies in approximately a dozen different situations. This is an example of the type of studies that we are carrying out. We are carrying out randomised studies and they favour physical activity, particularly when we look at all the other lifestyle factors as well. There is a reference group which is a control group which only receives written information.

We are looking at a large variety of output measures. One of them is body fat and body mass index as cardiovascular disease risk factors. What we find is that if work-sites take up these physical activities and healthy lifestyle programmes, it does not make a difference to body mass index and moderate physical activity, but it does influence vigorous physical activity, cardio-respiratory fitness and body composition: these are the effects that we witness in intervention studies with the introduction of physical activity – no change in body mass index but an improvement in body composition. Now, if you consider how we could motivate people from companies to do these kinds of interventions, we need only look at days of sick leave. After some time, it starts to become apparent that the number of days sick leave for the intervention group is reduced by about 7 days. The cost benefit of doing this for a company is that whilst they must pay during the first year for the intervention and counselling and so on, they start to regain that investment during the second year due to improvements in absenteeism and sick leave and the like. When companies see this, they start to wake up to the benefits that this can bring to them in the long term.

Another group that I mentioned earlier is people who are retiring from their occupations. We have followed numbers of these cohorts and we divide them into two groups: there are the office workers with sedentary jobs on the one hand, and the manual workers with physical activity during work on the other. In all of these cases, there is a sharp reduction in the hours that they work upon retirement; they suddenly have thirty hours less work per week. One can imagine that in the case of a manual worker, it is a challenge to compensate for the loss of thirty hours of physical activity during the week in their leisure time in terms of energy balance and in terms of preventing obesity. When they stop working, they increase their household activity – but not significantly, according to what their wives tell you – and they do one and a half hour's of odd jobs. Instead of working between thirty and forty hours per week, they take up household activities and manual activities around the house for approximately five hours per week, but this still means that they have lost circa twenty-four hours of physical activity and this loss needs to be compensated for, either by means of a reduction in energy intake or by means of equivalent energy expenditure. Unfortunately, this rarely happens. In the case of people with sedentary jobs, when they retire their body weight decreases because they are more active physically than when they were working, and this has a favourable effect on their body weight and energy balance. However, in the case of people retiring from active jobs, there is a weight gain, and there is a sharp increase in waist circumference. To my knowledge, this was the first study that was carried out studying body composition and disease risk, and the absolute risk of type 2 diabetes and metabolic syndrome and all kinds of other diseases that will be discussed during this symposium can be seen: they are actually dramatically deteriorating and they have full metabolic syndrome within one to two years.



Do we know what kind of nutritional and behavioural factors might be important? What we have seen is that there are a number of factors that may be important. In terms of nutrition, frequency in fruit consumption is beneficial, and if they increase their sugar, sweets and soft drinks their body weight increases, if they increase their fibre intake there is less of a weight gain, and if they take up cycling and odd jobs excessive weight gain is avoided. However, these factors are marginal and do not really compensate for the total effect of retirement. The same can be seen for waist circumference, although waist circumference tends to be an even more reliable indicator than body weight in these age groups. Again, physical activity helps to prevent weight gain.

It seems that there is little interest in funding agencies and the ministries of health in different European countries, but health organisations involved with the 55+ age groups are increasingly interested in contributing in the area of physical fitness, nutrition and wellness, and I think that we need to teach people how to deal with changes in their lives and how to prevent sharp increases in obesity.

Therefore, my message is that obesity prevention is possible. However, the common perception is that it is especially possible with children because an early start is a guarantee of success for the long term, whereas we find that it is extremely difficult to sustain the effects of school-based interventions on a long term basis due to the fact that it has to be continued throughout each class in every school to be effective. However, there are some critical moments in life that make people very vulnerable and very accessible to health interventions, and they provide opportunities for obesity prevention in older age groups as well.

The message is that we need to work on obesity prevention at every stage of life. It is not sufficient to concentrate on children alone and think that once school meals are changed, they will eat healthily forever. It is necessary to work at work-sites, on retirement, on specific groups that are vulnerable to the development of type 2 diabetes and obesity. The life course approach is necessary and is being emphasised by the World Health Organization (WHO), but many public health agencies have not adopted this approach. I believe that we need to realize that obesity is an exceptionally important predictor of health in older people. Even though the relative risks of disease with increasing body mass and its decrease in ageing, the total burden of disease associated with people with moderate overweight and obesity in older people is enormous, and much higher than in younger children.

Of course, the famous Geoffrey Rose prevention paradox has not really entered into our discussion about the prevention of obesity but it needs to be reiterated: the cost-effectiveness of interventions will probably be more favourable in older ages compared to childhood obesity prevention programmes. Of course, we need more than just words, we need results. Next year, I should be able to present most of the results of the intervention studies that we have done in pregnant women, young adults, work-sites and in older people, but we really need more studies in these populations in order to understand what is happening and how we can prevent obesity and especially the associated disorders that follow on from it. Thank you for your attention.

Questions

Barbara ROLLS
Thank you for an extremely comprehensive overview. Are there any questions?

I would also like to ask the speakers to come up onto the stage during this question and we will have an open forum for five minutes after it.

Member of the audience
You emphasise the difference between the absolute risk and the relative risk and you state that the cost-effectiveness of concentrating on older people rather than on younger people would be higher, but this is only because you are taking absolute risk as your measure. However, if your measure is the number of years of life lost, the picture would be completely different. It does matter whether the same numbers of absolute risk occur at the age of thirty or at my age of seventy. I am in a good position not to argue too much in favour of everyone because otherwise you would dedicate all resources to old people as the risks increase in a never-ending circle for this group of the population.

Member of the audience
Before your answer to this comment, whilst I think that your presentation is extremely interesting, I would also like to argue this point. It is similar to working with smokers: if you want to have an immediate improvement in lung cancer rates, you only work with people who are over fifty years of age; however, if you want to prevent health damage and the number of years of life lost due to tobacco, you must concentrate on teenagers. I am sure that we both understand this point. The issue is whether we must confine ourselves with very limited resources for prevention, or whether we want to fight for there to be more resources for prevention, instead of pulling resources from the young for the old.

Jaap SEIDELL
I understand your concern. The point that I would like to make is that we should not only implement childhood obesity prevention programmes as I think that if we only concentrate on school-based intervention and stop everything else, this would not be effective. The example of smoking is a little different because the age of onset of smoking and the outcome of disease occurs many years later, whereas we see that in middle-aged people the change in weight and the occurrence is very closely linked, almost instantaneous; this is very different from the example of smoking and lung cancer. However, I do accept what you are trying to say and I am not saying that we should not carry out programmes for the prevention of obesity to prevent a large number of life years in health terms, but I think that the middle-aged are like the lost generation. Governments are investing all their money in the generation that will have the benefits from now, but what about the rest of the population? Can anything be done for them to prevent obesity-related diseases? We should also not forget old people and people going into retirement, as there are huge health benefits to be gained.

Discussion

Member of the audience
All the studies presented here report upon an increase in obesity at the beginning of the Eighties, whereas it was almost non-existent before. During these years, we witnessed the dramatic increase of hypermarkets, the modification of the supply routes and the advent of a plethora of sweetened and fatty snack bars, dairy desserts, sweetened drinks, soft drinks, and cooked dishes for which it is difficult to evaluate the energy density. These omnipresent and low-cost products promote obesity. You implement many initiatives at the consumer level – elderly persons, children, parents and pregnant women - but as long as the plethora of these foods remains the same, people will be faced with difficulties in modifying their dietary habits. Should the governments not push the food industry to put on offer more traditional products, unprocessed fresh fruit and vegetables and as well to limit the broadcast of advertisements targeting children? It would undoubtedly be more effective.

Barbara ROLLS
I think it is clear that the food industry could do more to offer foods that would help us to eat more healthily, and this is a challenge that we all need to work towards. In the United States, the subsidies programmes also present a significant problem. However, it is not going to be easy. Professor Adam Drewnowski and I sit on a panel mandated by the Food and Drug Administration and we meet with the food industry policy makers and the food industry is being very forthcoming about the challenges that they face. They find that as soon as they label a food as healthy, it makes the product unpopular and the public does not want to eat it. Therefore, it would seem that the challenge is to ensure that people eat more healthily in spite of themselves. I call it 'stealth health': we have to introduce it without people seeing us do it. We all want them to eat more fruit and vegetables and wholegrain and so on, but how can we make them want this food? This is the real challenge.

Member of the audience
Thank you for your intervention. I understand perfectly the problem in so-called wealthy European countries, but it is also present in developing countries. Obesity and diabetes concern particularly the poor within rich countries. However, the poor within developing countries will also undergo this shock in a few years. We must thus think of this now. But I will pose the problem differently. The statistical studies which were presented must be regarded as experimental data to study and correlate with others. There is enough evidence and information to enable a thorough analysis of the problem. The relation between the body mass index and diabetes is well known. However, is diabetes a consequence of weight gain? In this case, how can we explain that elderly people, generally less obese, are more sensitive to diabetes? Couldn't one say that people sensitive to weight gain are also sensitive to diabetes? In consequence, are the cardiovascular problems of coronary diseases related to obesity? Is obesity related to incipient diabetes? Don't these elements have the same origin? These questions deserve to be asked. Thank you.

Barbara ROLLS
I am sorry that none of us speak much French. Does anyone else have any comments about the food industry whilst we are waiting for a translation of this point?
Thank you for those comments. Does anyone else have any comments?

Member of the audience
I think that these are actually excellent points which deserve further discussion. Of course, this is why many of these new initiatives are actually occurring in developing countries such as Latin America, Africa and especially in Asia, where I think there is now an explosion of type 2 diabetes, heart disease and overweight. It is much more complicated than we initially thought: we are exporting our own European and Western data to third world countries and that may be totally inappropriate. How do we define obesity in Asian countries for instance? The governments there have already recognised that there is a developing public health catastrophe in terms of type 2 diabetes, and if nothing is done until everyone reaches a BMI of 30, about 80% of Indians will have type 2 diabetes: this is not a very effective way of looking at the treatment and prevention of obesity. Therefore, we must be careful about taking our data to other countries. We need to be extremely careful.

Member of the audience
My comment relates to the responsibility of the food industry. I am a researcher and I am not involved in the food industry at all. I think that we should also talk about the responsibility of research and results. What we heard this morning about protein is extremely important and maybe we are not fully aware that we are undergoing a revolution in our knowledge of the relative importance of the balance between carbohydrates, fat and protein. I studied water concentration at the end of the seventies when the dogma was that what was bad in our diets was fat and protein. The food industry, particularly in North America and some parts of Europe, reacted to this message by producing low fat foods which were high in sugar. Therefore, in a way, science gave the wrong message by saying that what was wrong with our diets was fat and protein. Some consumers followed this message and started to buy low fat, which is also low in protein, high-sugar diets. We now have clear evidence that this is the worst diet possible from the point of view of obesity, the development of diabetes, and possibly the development of cancer. Therefore, whereas our colleague and friend Donato Greco said yesterday that we need to act, I would also say that we need to obtain better scientific data because if we act on incomplete scientific data, we do more harm than good. It is very important to realise that if we need to do more, we also need to know more, rather than just proceeding in an ideological manner. Ideology does not sit comfortably with science.

Arne ASTRUP
I think that these are wise words, and it is clear that we need much more robust information before we change recommendations and issue new advice to the public. On the other hand, we need to advise people today.

As far as the low fat story is concerned, the problem was that when the recommendations on reducing fat in the diet were being made, we did not really understand the importance of energy density because what we saw was that in many of the products there was a too great reduction in fat, but the caloric content and energy density was not reduced. Therefore, these foods were not really effective because energy density was not reduced. However, we have seen beneficial changes in many countries in that people have changed their consumption to lean versions with dairy and meat products where energy density is reduced dramatically; people are choosing the lean versions. If there had not been this reduction in fat, there would have been a more dramatic increase in obesity in many countries.

However, I believe that you are right that we should be more careful in the future. I think that all low carbohydrate food is a problem as it really is not sensible, and there is no evidence to suggest that it is beneficial for the population in the long term, either in terms of body weight regulation or reducing the risk of type 2 diabetes. It is important that we tell the industry that it should not follow this advice because we do not believe that there is any evidence to support it.

Member of the audience
I would just like to say that we are now attending a new catastrophe due to incorrect information on glycaemic index, and is now being followed by the food industry as they are starting to look at fructose, because it has been said that it does not increase the glycaemic index. We know that there is fructation just as there is glycation. Fructose in fruit is not a problem but if you add large quantities of fructose, then you paralyse all the enzymatic and protein systems and I think that it would be difficult to sustain the consequences of this new movement.

Member of the audience
I think that these are extremely important points and I think that what has been said is quite clear. Whatever we do, even in the case of isolated studies, is abused by the food industry because the commercial market is misleading and the message can be misunderstood by the population. The glycaemic index is an example of this. That is why what WHO did is so important: they examined food-based dietary guidelines, food patterns and non-communicable diseases, and did not just concentrate on one isolated phenomenon. It is important that diabetes, cancer, heart disease and so on be examined in an integrated manner so that we are not promoting a type of diet that is helpful in preventing weight gain but is deleterious in terms of cancer. I think that this is the main problem with recommendations stemming from research.

For example, if we find that dairy protein is extremely beneficial in preventing weight gain and we advise people to increase their low fat milk and their dairy protein intake to high levels, this could be extremely dangerous in terms of cancer risk. What we need is someone who integrates all of this information in order to ensure that we continue to see outside the box of disease-specific nutrients and disease-specific relationships.

Barbara ROLLS
I think that we need to emphasize the consensus that we all feel. What emerges in the press is when we disagree and any outrageous remarks and things that are unexpected. As health professionals we have a responsibility to keep emphasising the points that we do agree on, and I think that it is safe for us to encourage the public to eat more fruit and vegetables, wholegrain, high fibre foods and lean proteins: many of these products form the basis of the Mediterranean diet and I think that we have to keep repeating this message as there will always be someone trying to sell snake oil to the public.

Observational studies of dietary factors and the metabolic or insulin resistance syndrome

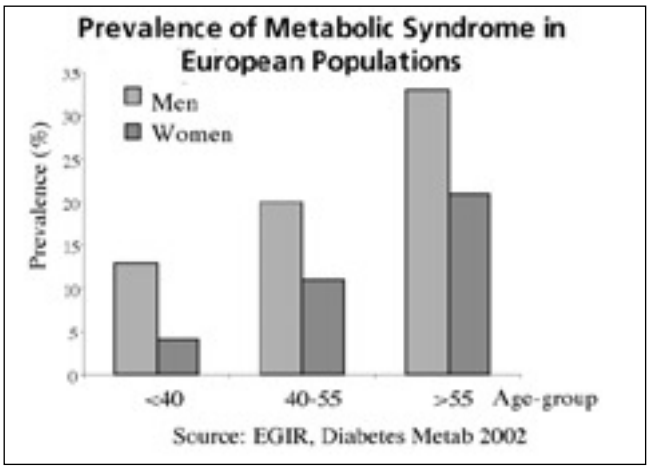
Nick WAREHAM
MRC Epidemiology Unit, Elsie Widdowson Laboratory, Cambridge, UK

It is my pleasure to introduce the second session today. My name is Nick Wareham and I am the director of the Medical Research Council Epidemiology Unit in Cambridge. This session is a small but perfectly formed session on metabolic syndrome and diabetes, which is squeezed between the expanding session on obesity and the double session on cardiovascular disease this afternoon. We have tried to structure this session slightly differently from the other sessions. We are taking an epidemiological perspective on the issues of diet, metabolic syndrome and diabetes by first concentrating on observational data for the two conditions separately, and then considering trial data.

I am going to talk about diet and the metabolic syndrome using data only from observational studies. As everyone in this audience is no doubt aware, metabolic syndrome is a loose clustering of related metabolic diseases comprising abnormal glucose regulation, insulin resistance, dyslipidaemia, principally of low HDL cholesterol and hypertriglyceridemia, hypertension and obesity: both total and central obesity.

There has been a continuing controversy in the literature about which of these features are central to the condition. We have conducted factor analysis using longitudinal data to examine how the different factors change over time. It is perfectly clear from these studies that the central determining factor of this syndrome is the degree of obesity and that drives the other factors listed on this chart. When we come to consider the dietary factors that relate to the syndrome, we cannot exclude that some of them may be mediated through obesity and some of them may be independent, and this is the main focus of our discussions today.

What ecological data do we have from studies examining the prevalence in different populations of metabolic syndrome and relating that to dietary factors, such as the proportion of the population eating a Mediterranean style diet? One of the problems that we are encountering is that we do not actually have the data to answer this question. It is only recently that we have started to obtain data about the prevalence of metabolic syndrome across European countries. Some of this originates from studies such as the DECODE study which was led in part by Jaakko Tuomilheto which was a consortium of population-based studies all performed after 1980 and all of which included both men and women and an age range of at least two decades.



One of the key prerequisites in these studies was that all of the participants had to have a two-hour 75 gram oral glucose tolerance test. Colleagues from the EGIR group reported a few years ago that the prevalence of the metabolic syndrome in European populations was greater in men than in women and that it was clearly highly age-dependent.

The EGIR group demonstrated their preference for different definitions of the syndrome as they chose the WHO definition of the syndrome, which includes a measure of insulin resistance. As the European group for studying insulin resistance, it is not surprising that they preferred that definition as opposed to others, such as the American ATP 3 definition, which focuses more on the five factors that I demonstrated previously, excluding insulin resistance. One of the difficulties here is that we have different definitions of the syndrome and indeed, only a few weeks ago another definition of the syndrome was announced by the International Diabetes Federation. This definition differs from some others in that it places obesity at the centre of the syndrome. A person is defined as having the syndrome if they have obesity plus two or more of the following factors: raised triglyceride, raised blood pressure, reduced HDL cholesterol, or abnormal glucose regulation. It is clear that the definition depends on the existence of obesity, and then the other factors are regarded as metabolic consequences of obesity. One of the difficulties is that this definition was only announced in April 2005, and there have not yet been many epidemiological studies describing prevalence. However, I know that Jaakko and his team have looked at the prevalence of metabolic syndrome in European populations using this definition and it is clear that one of the observations is that the prevalence will rise markedly if this definition is used. Indeed, using this definition, 37% of the population can be defined as having the syndrome. I think that the level of that prevalence really questions whether such a definition has clinical utility because it would be extremely difficult to treat nearly 40% of the population on an individual basis. Another issue is whether condensing this syndrome into a unitary dichotomous definition, which defines people as either having the syndrome or not, is useful when we are considering aetiology. I am convinced that it is useful to do this to make a political point about the importance of this syndrome, that it is associated with the risk of diabetes, cardiovascular disease and many other disorders. However, is it important clinically to label 40% of the population as having a syndrome? By condensing it in this manner, it is also possible that we limit our own thinking about the different aetiology of the subtypes of this syndrome.

I would like to discuss what we know about diet and metabolic syndrome in relation to specific nutrients, concentrating on fat and carbohydrate, looking at some specific foods and then moving on to dietary patterns. Then, I would like to consider whether there is any residual confounding in these observational data by key lifestyle factors, such as physical activity, alcohol consumption and smoking. Finally, I shall talk about effect modification by genes.

With regard to fat, there was a review last year conducted by Dr Riccardi, and I think some of the other groups from Italy who are here today such as Dr Rivellese. They reviewed a number of epidemiological studies, most of which were cross-sectional, and which included some by Dr Edith Feskens, who is also here

today. On the whole, they demonstrate that increased levels of saturated fat are associated with decreased insulin sensitivity. In general, total fat is positively associated with higher fasting insulin levels, a good proxy measure for insulin resistance. Increased saturated fat specifically is associated with increased insulin levels and higher polyunsaturated fat tends to be associated with lower insulin levels.

The biological mechanism is largely unknown but may well be related to altered fatty acid composition of cellular membranes which may directly affect insulin resistance. There is some suggestion in the literature of effect modification by physical activity. There have been some studies that suggest that the two factors – alteration of the composition of dietary fat and physical activity – are more than additive and the two factors may be synergistic. We examined this association ourselves in the Ely study and related fasting levels of insulin in non-glycaemic individuals who were stratified by the PS ratio in the diet and by physical activity level. We dichotomised this into high and low, but actually the measure was an objective assessment of physical activity energy expenditure by individually calibrated heart rate monitoring, so it was a careful measure of physical activity. We were able to demonstrate that there was no evidence of effect modification. This kind of study looking at the combined effects of physical effect and diet are the way forward, as we have tended to concentrate on the two factors in isolation and it is clear that from a public perspective, it is important to know how dietary and physical activity factors may combine, and whether there are any additional benefits of changing both together. There is also an important research agenda to be pursued in relation to the timing of foods and physical activity, about which we have little information at present.

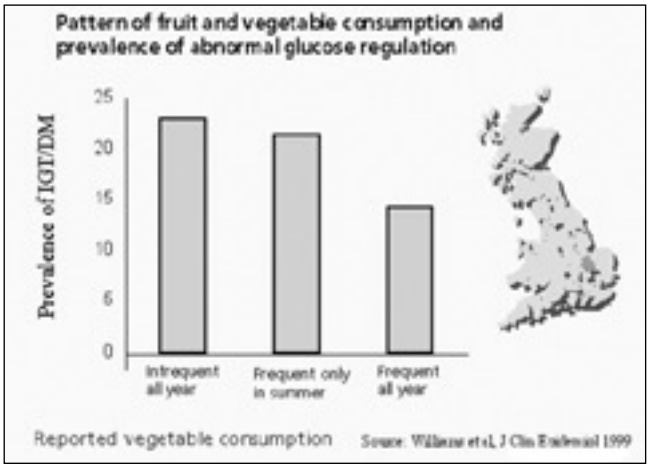
If we consider carbohydrates, it can be seen that the literature on carbohydrate intake and the prevalence of metabolic syndrome is extremely sparse and there are very few studies, even fewer which are longitudinal. However, I would like to report one study, the Framingham study that was reported by Nicola Mckeown in Diabetes Care last year. She related wholegrain intake and the prevalence of the metabolic syndrome by stratifying it by the quintiles of carbohydrate source. She showed an inverse relationship which remains statistically significant after adjustment for age and sex, smoking, total energy expenditure, alcohol, proportion of saturated fat, multivitamin use and physical activity. Therefore, there was quite extensive adjustment for possible confounding factors, although, of course, residual confounding continues to be an issue, particularly for some of these difficult but important factors, such as physical activity.

She went on to look at cereal fibre intake and the prevalence of the syndrome, and here we can see that the trend is slightly clearer and that the P value for trend is of greater statistical significance. This association survives adjustment for the same confounding factors and survives adjustment for the wholegrain intake, suggesting that the association with wholegrain intake is explained by cereal fibre. There was no association at all with total carbohydrate. This group examined the glycaemic index and the prevalence of the metabolic syndrome and demonstrated a positive association – those with the highest glycaemic index having approximately a 40% increased risk of having the metabolic syndrome after adjustment for the same factors as before. However, the confidence intervals are wide and the P value for trend is quite marginal. In this study, there was no association at all with glycaemic load rather than with glycaemic index.

I would like to move on to ask the question that I posed at the beginning of my talk, which was whether there are any disadvantages to considering studies, such as the one I have just discussed, where the outcome is condensed into a single binary condition – the metabolic syndrome. I believe that there could be instances where a food or a nutrient could be associated with one aspect of the metabolic syndrome and not with another, and that if we only conduct studies where we condense the syndrome to a binary state, we may miss those. This may be the case for salt intake, which is clearly more closely related to hypertension than the other factors but may be related in some studies to insulin sensitivity. It may also be true for fish oil intake, which would seem to have an association with lower triglyceride, but less of an association with hyperglycaemia. It is my belief that there is an argument for looking at the elements of the syndrome in isolation and then looking at the syndrome etiologically in combination, as if we only look at one or the other we may fail to include important information.

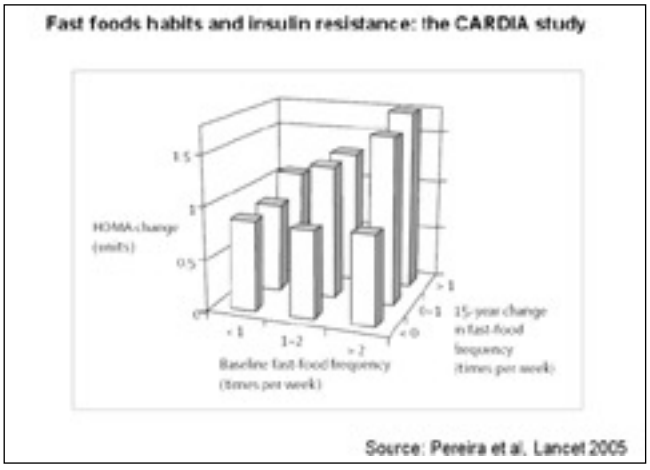
Looking at other types of foodstuff, one of the foods that has been examined is dairy intake and how it relates to dietary fibre and insulin resistance. This is one of the few longitudinal studies using more than 3 000 black and white subjects aged thirty, who have been studied for ten years in four United States' metropolitan areas. In this analysis, insulin resistance syndrome was defined as two or more of the components being abnormal: glucose homeostasis, obesity, elevated blood pressure and dyslipidaemia. What Mark Pereira and colleagues were able to demonstrate a few years ago was that compared to a reference group, who were defined as those who had high fibre intake and high dairy intake, individuals who were classified as having low fibre intake and low dairy intake had nearly a sevenfold increase in risk which survived adjustment for the factors that are listed on the right hand side of this graph. This is an intriguing observation which obviously needs to be tested in other populations. To my knowledge, there have not been any other reports of a similar nature and it may be that this is related to the calcium, magnesium or potassium intake; it could be that there is an element of alteration in satiety by the lactose, protein or fat content of diary foods; it could be that dairy foods alter the glycaemic index; it could be that there is some compound in dairy foods that has an impact on the metabolic syndrome; or, of course, it could be the result of residual confounding. Unfortunately, observational data of this type will never resolve this issue, which can only ever be resolved by trials.

What about fresh fruit and vegetable intake, a key element of the Mediterranean diet? In the EPIC Norfolk study, we used a measure of biomarker of fresh fruit and vegetable intake and the plasma vitamin C concentration and have demonstrated that this is quite strongly inversely related to glycated haemoglobin, a measure of glycaemic control. In the Ely study, we went on to look at the pattern of reported fresh fruit and vegetable consumption and the prevalence of abnormal glucose regulation,



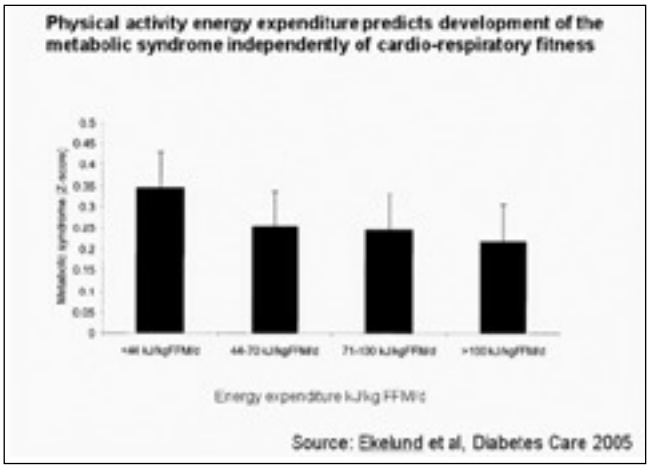
which suggested that those individuals who had frequent consumption throughout the entire year had the lowest risk of diabetes, and that there was an intermediate level of risk in those individuals who had frequent consumption only during the summer months. It may be that part of the association between the Mediterranean diet and disease risk is not just mediated by average consumption through the year but by whether or not there are periods where people eat that diet and periods when they do not. Therefore, examining the patterning of dietary intake of fresh fruit and vegetables is important because we tend to focus on averages rather than on seasonality.

It is clear that fresh fruit and vegetable intake and the other elements of the diet that I have just described are not uncorrelated, and in the same way that others have looked at the patterning of the diet and the relationship to diabetes risk, we looked at patterning of diet in relation to previously undiagnosed diabetes and features of the metabolic syndrome five years ago. One of the principle components that emerged discriminated those who had a high fruit, salad and fish consumption and those who ate lots of fried food, sausages, potatoes and fried fish. The first component was associated with a significant reduction of the risk of undiagnosed diabetes, and that was independent of age, sex and smoking, but most importantly, of body mass index. Therefore, there may be future work to be carried out looking at the patterning of the diet in relation to the metabolic syndrome, as this is still an unexplored field. One element of the pattern of the diet is, of course, the consumption of fast foods. Earlier this year, Mark Pereira and colleagues, in the CARDIA study, looked in a longitudinal way at the baseline reported frequency of consumption of fast foods, and then the change in that reported measure of fast food consumption over fifteen years. For those individuals who had a baseline consumption of under once a week and did not change over those fifteen years, there is a marked difference in the HOMA over this fifteen year period compared to those who started with a high baseline consumption and then increased and had the highest level of HOMA, which is a measure of insulin sensitivity. This is a single study which needs to be replicated in other studies.



Now the focus of this conference is on the Mediterranean diet, and so I looked through the literature for a summary paper that might describe the association between people adhering or not adhering to the Mediterranean diet and the prevalence of metabolic syndrome. I stand to be corrected but I could only find one study, which was carried out in Greece, the ATTICA study, which looked at just over 1 000 men and 1 000 women who were over eighteen years of age and were free of cardiovascular disease and diabetes. In this study, metabolic syndrome was defined using the ATP3 criteria, and the overall prevalence was 20%. The association with the Mediterranean diet in this study was 0.81 with fairly wide confidence intervals, but it was statistically significant. The authors also demonstrated a marked association with physical activity, and noted that those in the highly physically active group had a reduction of risk of 30%. This leads one to consider whether it is possible to fully remove the effects of physical activity and residual confounding in these studies because typically it is not measured particularly well in epidemiological cohorts. This is a topic of considerable interest because we carried out a systematic review at the beginning of this year on the relationship between physical activity and insulin resistance. We identified thirty-nine cross-sectional studies in adults, thirty of which demonstrated a strong inverse association and fifteen studies in children and adolescents, seven of which demonstrated an inverse association, but of those seven, six were reporting fitness rather physical activity. Therefore, there is a real need for further work to be carried out describing the relationship between physical activity and fitness and insulin resistance in children. It should also be noted that there were only four adult prospective cohort studies, so little is known about physical activity and the development of insulin resistance in adults.

Therefore, we set out to study this several years ago in the Ely study. We have just reported our findings in Diabetes Care on the relationship between physical activity, energy expenditure and the development of metabolic syndrome, independent of factors such as obesity and cardio-respiratory fitness. Energy expenditure, here, is expressed in kilojoules per kilogram fat-free mass per day, as measured by individually calibrated heart rate monitoring. We were able to demonstrate an inverse relationship with those people who had the most everyday energy expenditure progressing least in terms of a Z score computation of the metabolic syndrome. Therefore, this provides some evidence that objectively measured energy expenditure is strongly related to the risk of the progress of the metabolic syndrome.



We also reported last year in Diabetes Care the relationship between physical activity and fitness and metabolic syndrome risk in children, demonstrating that, if you stratify those on the graph in the darker grey colour as unfit and those in the white colour who are fit, those with the highest risk are those who are both inactive and unfit. The slope of the relationship between activity and the metabolic score is steeper amongst the unfit than it is amongst the fit. This is an observation that we have also demonstrated with adults. It may be that people who are naturally fit, but not particularly active, are somehow protected from the metabolic consequences of obesity due to their fitness. It suggests that those who are really most at risk are those who are unfit and inactive. This may help us to understand the aetiology and it may also help us to understand who we need to target.

Finally, what about the prospect of studying the modulation of the relationship between diet and the metabolic syndrome by

genetic factors? The clearest example of such a study is one that has been alluded to already this morning, which is PPAR-γ a gene critically involved in the process of adipocyte differentiation. This is a very good biological target for gene-nutrient interaction, because the natural ligand is a fatty acid and the degree of affinity to the receptor is affected by the length of the fatty acid and the degree of saturation. We speculated a few years ago that there would be interaction between a common variant in this gene and the ratio of polyunsaturated to saturated fat in the diet on insulin resistance, and demonstrated here that people who are the adult carriers appear to be more responsive to change diet. Obviously, I cannot really say this because this is only observational data, but this observation has now been replicated in a number of other studies and critically in a number of other trials. Therefore, perhaps the focus for the future should be not only to look more closely at the relationship between dietary factors and the metabolic syndrome, but also how those dietary factors are modified by genes, and for the moment, it seems best to concentrate on genes that are biologically plausible, such as PPAR-γ.

Of course, one would really like to move from qualitative studies, where the outcome is a measure of insulin resistance, to more clinically meaningful outcomes, such as the incidence of type 2 diabetes. However, in order to do this, it is necessary to have very large studies tested within large cohorts, and I think that it is only studies such as EPIC Europe, which have the size and the number of samples collected at baseline and the characterisation of diet, which will be able to study the interaction between genes like PPAR-γ, dietary factors like the ratio of polyunsaturated to saturated fat in the diet, and the incidence of clinical meaningful disease such as diabetes.

In summary, I think that this field has been somewhat bedevilled by difficulties with the diverse definitions of the syndrome. This has been aided with the important announcement of the International Diabetes Foundation definition, which correctly places obesity as a prerequisite for the condition, and then adds on the metabolic consequences. I think that whilst this is good for politics and descriptive epidemiology, we have to be careful that this does not obstruct etiological thinking and we may need to look at some individual components of the syndrome in addition. There is clearly limited prospective data and the studies that have been undertaken have been small. However, the associations are most consistent for the amount and type of dietary fat, there is some consistent data for wholegrain intake and there is some data on the pattern of diets, suggesting that the Mediterranean diet is indeed protective for this syndrome. Thank you.

As the chairman as well as the speaker, I can now take your questions.

Questions

Member of the audience
Thank you for that wonderful overview. I think that what is so counter-productive is the existence of the different definitions of metabolic syndrome which all emphasise different factors. Of course, we know that if a person has more risk factors, their increased risk of cardiovascular disease will increase more.
My question is that looking at these International Diabetes Foundation criteria, not only is central obesity very prominent but it has very low cut-off points. Taking our own data into consideration of people aged fifty and older, approximately 75% of them, and perhaps more, will have a waist circumference which is higher than the circumference shown on that graph. Why did they change that cut-off point?

Nick WAREHAM
I was not part of that group and I am not in a position to defend the criteria, but I believe that Jaakko Tuomilheto was. Is that correct, Jaakko? Could I suggest that you answer that question?

Jaakko TUOMILHETO
The reason for this was simply that the risks demonstrated in observational studies start at that level and this was why it was considered to be the appropriate level. Of course, many people say that this will include too many people, but the fact is that certain health risks related to diabetes start at that level and that therefore it should be considered as a cut-off point.

Nick WAREHAM
Thank you, Jaakko. Perhaps we can discuss this later but I think that it is debatable whether it is useful to define so many people as having the syndrome and I wonder whether this cut-off point should not be changed.

Member of the audience
You mentioned that the group consuming fish and fresh fruit had better health outcomes as opposed to those consuming fried foods and sugar. Do you not think that the consumption of smoked salmon and strawberries in England is a marker of social class, and that the health outcomes could be linked to financial and other resources as a result?

Nick WAREHAM
That analysis was adjusted for social class.

The previous member of the audience
It is difficult to do that because we use income and education as proxies for social class and never ask information about assets.

Nick WAREHAM
You are talking about a residual confounding by social class, which is a possibility. You are quite right.

Member of the audience
What about drugs in the treatment of the metabolic syndrome?

Nick WAREHAM
There are drugs which affect insulin sensitivity. I would have thought that one of the driving forces in having a definition of 40% of the population as having a disease is the hope of some that there may be a medical therapy for this. I personally think that this is not a very useful school of thought. It is a public health problem and we need to find public health methods of treating it, as it would be extremely difficult to medicate 40% of the population. Clearly, there is a role for drugs, but I think that we have to be very careful that the debate is not driven by the drug industry.

Member of the audience
Thank you for a wonderful presentation. If you think about the clinical aspect of this issue, it really is important for public health awareness and for politics for us to have the right numbers. The prevalence may be high, but this is not practical for clinical purposes. Is it useful to have any definition of metabolic syndrome for clinical practice?

Nick WAREHAM
I am not sure that it is very useful in clinical practice where we increasingly treat people on the basis of risk and the reduction of risk expected on the basis of therapy. We know that the relationship between many of these metabolic measures and cardiovascular risk is linear rather than curvilinear, so there is no point at which the risk is eliminated. This contrasts sharply with the risk between glycaemia and the microvascular complications of diabetes, which is flat and then increases steeply. In that instance, it is possible to identify people who are at risk and need to be treated. However, this is not the case for many of these metabolic parameters. It is not that we dichotomise into those who are and who are not at risk, some people simply are more at risk. The question is where we draw the line as to who needs treatment individually and where to say that a public health approach is needed. This is what we need to discuss and it is a question of economics.

The previous member of the audience
I have been listening to the debate so far regarding sensitivity, specificity and health economics approaches to these definitions. This needs to be done.

Nick WAREHAM
There is so little data, though. If we knew how to change the population levels of metabolic syndrome, we would not be here today.

The previous member of the audience
Of course, but if it could be done, it would reduce central obesity.

Nick WAREHAM
Yes.

Member of the audience
You mentioned that you measured fitness. What is your definition of fitness? Is it based on body mass index?

Nick WAREHAM
I should probably have mentioned earlier that the measure we used for fitness was cardio-respiratory fitness, which was assessed by sub-maximal or VO2 max test on a treadmill as a measurement of oxygen consumption. You are right that we need to be careful to be precise when using terminology.

Diet and type 2 diabetes from observational studies

Frank HU
Department of Nutrition, Harvard School of Public Health, Boston, USA

I would like to thank the organisers for inviting me to this wonderful symposium.

I would like to start my talk by introducing the three cohort studies that we are carrying out at Harvard, because much of the data that I will be presenting today derives from these studies. These cohorts (Nurses' Health Study, Nurses' Health Study II, and Health Professionals' Follow-up Study) have followed approximately 300 000 men and women, over a period of twenty to thirty years. We have collected dietary information using validated food frequency questionnaire every two to four years, and because of the prospective design, we have the ability to look at long term dietary intake in relation to risk of type 2 diabetes in these populations. This work has established that obesity is the single most important risk factor for type 2 diabetes. Therefore, the question now is whether the association between any of the dietary factors and type 2 diabetes is independent of obesity.

I am going to talk about macronutrients first. All the analyses I mention were adjusted for body mass index, as I just mentioned, to see whether the effect of dietary factors are over and above the effects of overweight and obesity. This is an analysis that we carried out several years ago looking at the association between different types of fat and the risk of type 2 diabetes in the Nurse's Health Study. In the first model, there are four different types of fat: saturated, monounsaturated, polyunsaturated, and trans-fat. The analyses were adjusted for age, family history of diabetes, BMI, alcohol, smoking and physical activity, as well as for protein and total intake. In this kind of model, the effects of dietary fat can be interpreted as the substitution of a certain percentage of fat for the equivalent percentage of carbohydrate, because total energy and protein intakes are held constant, so all that is left out is carbohydrates.

MV RRs of Type 2 Diabetes Associated with Increases in the Percentage of E from Specific Types of Fat

Model 1	RR*	(95% CI)	P-Value
Saturated fat (5% of E)	0.97	(0.86–1.10)	0.68
Monounsaturated fat (5% of E)	1.05	(0.91–1.20)	0.52
Polyunsaturated fat (5% of E)	0.63	(0.53–0.76)	<0.0001
Trans fat (2% of E)	1.39	(1.15–1.67)	0.0006
Model 2	**RR**	**(95% CI)**	**P-Value**
Animal fat (5% of E)	0.98	(0.95–1.02)	0.35
Vegetable fat (5% of E)	0.79	(0.74–0.84)	<0.0001
Model 3	**RR**	**(95% CI)**	**P-Value**
Total fat (5% of E)	0.98	(0.94–1.02)	0.24

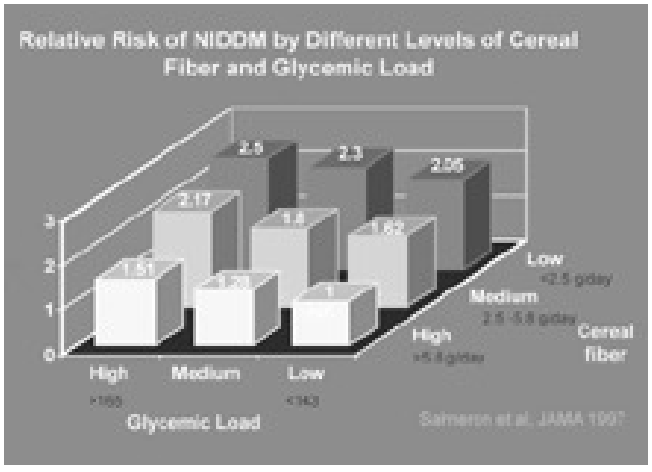
Adjusted for age, family history, BMI, alcohol, PA, protein, total energy intake

Salmeron et al. AJCN 2001

When we compared different types of fats with carbohydrates – of course, most of the carbohydrates in American diets are refined carbohydrates – saturated and monounsaturated fat were not associated with an increased risk of type 2 diabetes. This is not surprising because refined carbohydrate is a risk factor for diabetes. However, polyunsaturated fat was significantly associated with a decreased risk whereas trans-fat was associated with an increased risk. Consistent with the polyunsaturated fat results, vegetable fat is significantly associated with a lower risk of diabetes. However, when we looked at the total amount of fat in the diet, after adjusting BMI and other risk factors, there was no appreciable association between total fat and the risk of type 2 diabetes.

Now I will discuss the role of carbohydrates. The conventional wisdom based on the chemical structure of carbohydrates is that simple carbohydrates are bad and complex carbohydrates are good. However, we know that in the case of many refined carbohydrates, particularly refined starch from white bread, digestion occurs far more quickly than for some of the simple sugars. The new classification places more emphasis on the biological effects of whole food, using the glycaemic index, glycaemic load, and whole grains vs. refined grains.

As you know, the concept of glycaemic index is complex and is still controversial. Some people completely embrace the glycaemic index and use it as the only yardstick to classify good versus bad foods, which can be very misleading; there are others who completely dismiss this concept, which is also not consistent with the evidence that we have. In our cohorts, we found a strong association between the glycaemic index and the glycaemic load and a risk of type 2 diabetes and coronary heart disease. The glycaemic load represents both the quantity and quality of carbohydrates, and in this analysis we found a significant association between increase in glycaemic load and the risk of type 2 diabetes independent of cereal fibre. As expected, those who eat a very high glycaemic load diet with very small amounts of cereal fibre have the highest risk of developing diabetes.

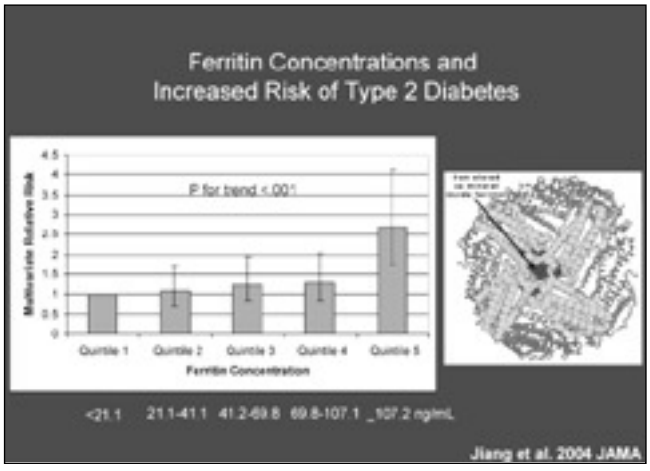


The relationship between omega-3 fatty acids and diabetes is unsettled. Animal studies have shown that long-chain omega-3 fatty acids improve insulin sensitivity, and cross-sectional studies have shown a positive association between long-chain omega-3 fatty acids in muscle cell membranes and insulin sensitivity. However, prospective epidemiological studies have not found an association between fish consumption and risk of type 2 diabetes. There was a modest inverse association between omega-3 fatty acid consumption and type 2 diabetes in the Nurses' Health Study, but after adjusting for BMI and other risk factors, this association completely disappeared.

I would like to move on to discuss micronutrients, especially chromium, magnesium and iron. In a recent study published in Diabetes Care, we looked at the mean chromium concentration in toenails for the three groups (healthy subjects, diabetic patients without cardiovascular disease, and diabetic patients with cardiovascular disease). The reason why we wanted to measure chromium concentration in toenails was that it is not possible to measure dietary chromium consumption as the variability is so great across different foods, whereas the chromium concentration in toenails could reflect long term intake of chromium. In this analysis, we found that people with diabetes had significantly reduced chromium levels compared to healthy controls and that people with diabetes and cardiovascular disease had further decreased chromium concentration. This does not prove a causal relationship, but several clinical trials have shown beneficial effects of chromium supplementation on insulin sensitivity and cardiovascular risk factors. However, I do not think that we have enough evidence to recommend regular chromium supplementation as a preventive strategy for diabetes at this point. There are several important dietary sources of chromium including whole grains, nuts, green leafy vegetables and coffee, all of which have all been associated with a decreased risk of diabetes.

There are more epidemiological studies on magnesium than on chromium in relation to the risk of type 2 diabetes. The results are generally consistent and several large studies, including ours, have found an association between increasing magnesium consumption and a reduced risk of diabetes. Like chromium, magnesium is an important co-factor for the insulin signalling pathway. People who eat large quantities of refined carbohydrate sugar need more chromium and magnesium to process the sugar. Unfortunately, the intake of these micronutrients is actually decreased during the refining process.

Iron and diabetes has become a very interesting area of research. Several years ago, a very small Finnish study found a positive association between ferritin concentration and the risk of type 2 diabetes. Last year, we published a paper with almost 800 cases and more than 1 000 controls, in which we found a positive significant association between ferritin concentration and the risk of type 2 diabetes. I would like to point out that the ferritin concentration for the vast majority of subjects was within the normal range. It is known that people hereditary haemochromatosis have extremely high ferritin levels and most of them will eventually develop diabetes. As for mechanism, iron is a catalyst for the formation of free radicals in the body, so the increased diabetes risk may be due to the increased oxidative stress.

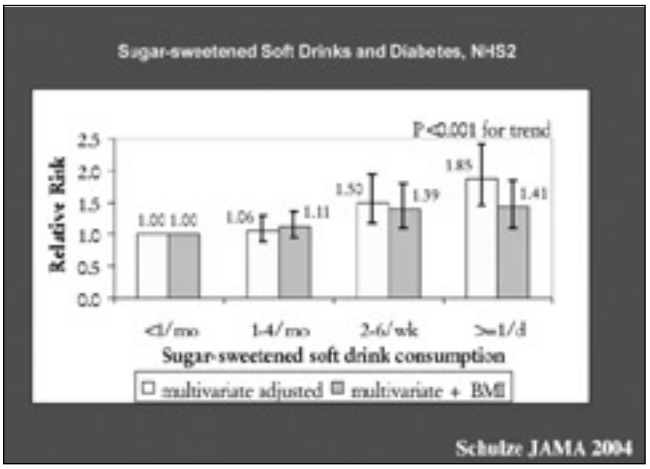


We proceeded to look at dietary intake of iron and the risk of diabetes and in these analyses, we specifically focused on heme iron, which comes from animal products, especially red and processed meat. Heme iron is a very important dietary determinant of ferritin levels. We found a very striking positive association between higher heme iron intake and the risk of diabetes, even after adjusting for red meat and processed meat, suggesting that this association is not explained by other components in those meats. What is interesting is that the association between dietary iron and diabetes may be modified by the HFE genotypes. We found that the association between heme iron and diabetes was only present among those who carry either C282Y or H63D variant genotypes, but not among those who carry the wild genotypes. This is biologically plausible because if a person eats large quantities of iron and also has the genotypes that facilitate iron absorption, the combination puts this person at a very high risk of developing diabetes.

I shall now address the subject of foods and food patterns. As many of you are aware, there has been very consistent observational data, mostly prospective studies, between nut consumption and coronary heart disease. At least five large cohort studies have found a strong inverse association between nut consumption and the risk of coronary heart disease. Metabolic trials have also found that increasing nut consumption reduced total and LDL cholesterol. In addition, we found that higher nut consumption was associated with a decreased risk of diabetes. What is interesting is that this association is actually independent of body mass index. We found an inverse association across different categories of BMI – even for those who were overweight and obese, higher nut consumption is associated with a reduced risk of type 2 diabetes. One of major concerns about increasing nut consumption is weight gain because it is a high fat food. However, we did not find increased weight gain with higher nut consumption. In fact, there seemed to be an inverse association, and several other studies have also found an inverse association between nut consumption and body mass index. We know that although nuts contain a large amount of fat, they consist mostly of good fats: monounsaturated and polyunsaturated fats. Even peanuts, whilst technically not a nut but a legume, have a similar fatty acid profile as other types of nuts, and the nutrient profile of peanut butter is no different from peanuts. These results provide further evidence that the type or quality of fat is more important than the total amount of fat in determining the risk of diabetes and coronary heart disease.

The evidence for whole grains is also very consistent. Several prospective studies over the last few years have demonstrated that a higher consumption of whole grains reduces the risk of type 2 diabetes and cardiovascular disease.

Higher consumption of sugar-sweetened soft drinks has been associated with increased obesity in children. In the study published recently in JAMA, we looked prospectively at the relationship between soft drinks and type 2 diabetes in the Nurses' Health Study II. It can be seen that those who consumed at least one can of sugar-sweetened soft drinks per day had an 80% increased risk of developing diabetes compared to those who rarely consumed soft drinks. What is interesting is that the association remained significant even after adjusting for body mass index, although it was somewhat attenuated. This result suggests that the association between soft drinks and diabetes is not entirely mediated through overweight and obesity.



There has been consistent epidemiological data on the protective effects of coffee on type 2 diabetes. The first study was conducted in a Dutch cohort, followed by at least eight cohort studies from the United States of America and Scandinavian countries. Most of these cohort studies have demonstrated that higher coffee consumption is associated with lower risk of type 2 diabetes, in both men and women. Compared to the lowest category (<2 cups/day), the risk reduction is approximately 35% in the highest category (7 to 8 cups per day in European studies, and approximately 5 to 6 cups per day in the American studies). At the moment, we still are unsure as to which components of coffee are responsible for the risk reduction; it could be caffeine or the very high amount of antioxidants, especially chlorogenic acid or, as I mentioned earlier, coffee also contains high amounts of chromium and magnesium.

The data on alcohol and type 2 diabetes has also been extremely consistent. There is a protective effect amongst moderate alcohol drinkers – consuming 5 grams to less than 3 drinks per day is associated with 30% lower risk of type 2 diabetes. However, if a person drinks more than 3 drinks per day, the risk actually increases.

There has also been consistent data on the consumption of processed meats and the risk of type 2 diabetes. Processed meats include hot dogs, bacon and hamburgers. In our cohorts and also in a few other studies, higher consumption of processed meats, once a day for example, is associated with a 40 to 50% increased risk of type 2 diabetes. Processed meats are also associated with other unhealthy diet and lifestyle factors, which could confound the results. However, when adjusted for the Western dietary pattern, the association still remains.

Recently, we found a significant decreased risk of diabetes with higher dairy consumption. Most of the protection comes from low fat and non-fat dairy products. We found no association between high fat dairy products and a risk of type 2 diabetes. As Nick Wareham has mentioned, we still do not know which component of dairy products contributes to decreased insulin resistance or type 2 diabetes. The public health implications of these findings are not clear: although dairy products may have beneficial effects on insulin resistance, hypertension, or type 2 diabetes, they may also have detrimental effects in terms of sex hormone-related cancers. Therefore, we need to be very careful in recommending high amounts of dairy to prevent diabetes.

To look at the cumulative effects of the different foods and food groups, we used principle component analysis or factor analysis, as Nick Wareham mentioned, to define the dietary patterns. In our cohorts, we have identified two major patterns: one is the 'prudent pattern', and the other is the 'Western pattern'. The prudent pattern is characterised by fruits and vegetables, legumes, fish, seafood and whole grains, whereas the Western pattern is characterized by red meat, processed meat, potatoes, French fries, butter, refined grains and high fat dairy. We created two factor scores for each individual in the cohort, and then looked at the factor scores in relation to different disease outcomes. For type 2 diabetes, we found a clear positive association between the Western dietary pattern and the risk of diabetes, and this finding is consistent with the results for individual foods and individual nutrients. For the prudent pattern, the association was not very clear: there was a slight inverse association but the trend was not statistically significant. The prudent pattern is much more protective for other outcomes such as coronary heart disease and colorectal cancer. The Western pattern also increased the risk of colorectal cancer and coronary heart disease.

To summarise our findings regarding dietary factors and type 2 diabetes, I think that we are now in a better position to understand the protective factors as well as risk factors based on the results from multiple prospective epidemiological studies. There is good evidence that higher consumption of refined carbohydrates reflected by a higher glycaemic index, glycaemic load or refined grain products, is associated with increased risk of diabetes. Trans fat is a risk factor for insulin resistance, metabolic syndrome and type 2 diabetes. Saturated fat is more complicated: if you compare saturated fat with refined carbohydrates, both are bad and as a result, it would be difficult to notice any real difference. However, a comparison of saturated and polyunsaturated fat demonstrates an increased risk of diabetes with higher consumption of saturated fat. Therefore, from a public health point of view, we need to recommend a reduction in saturated fat, replaced by unsaturated fatty acids. As I have mentioned, there is now quite strong evidence that processed meat is a risk factor for diabetes. There is also strong evidence for the so-called 'protective factors' such as polyunsaturated fat, cereal fibre and whole grains. The results for omega-3 fatty acids are less clear. The results for nuts, peanut butter and coffee are very intriguing and they need to be studied further, especially in metabolic studies. The evidence for alcohol is overwhelming so I do not wish to elaborate on that point further. I think there is a very complex public health message for dairy, but it is important doe us to understand which dairy components or substances contribute to a decreased risk in type 2 diabetes.

What do we go from here? Clearly, we need replications from other cohort studies. We already have very good replications for whole grains and for coffee, but we need more replications for dairy. These results from epidemiological studies should inspire more metabolic studies of individual dietary components and the risk of insulin sensitivity. We need to understand the mechanisms behind the association between certain dietary factors and the risk of type 2 diabetes. Ideally, we should conduct randomised trials using diabetes as end-point for all dietary components that I have just mentioned. However, this would probably not be feasible due to lack of compliance and perhaps also ethical issues, unless there were a supplement or a pill. Therefore, at this point, we probably have to rely on the consistency of the epidemiological studies and the results from metabolic studies to evaluate the casual relationships between dietary factors and type 2 diabetes. Thank you very much.

Questions

Member of the audience
Thank you for this overview. Could I ask whether you have any data on tea consumption?

Frank HU
We did look at tea consumption and the risk of diabetes but we did not find any association. The amount of caffeine and antioxidants in tea is far lower than in coffee. The reason that coffee has a very strong taste and flavour from coffee is due to the fact that there is a very high amount of antioxidants, especially chlorogenic acid.

Member of the audience
What about polyphenols, polyphenolics and antioxidants?

Frank HU
We were not able to look at individual polyphenols. It is not possible to differentiate the individual components within the products.

Edith FESKENS
In relation to alcohol, I think that you are right in concluding that moderate amounts are protective and this has been shown in many studies, but given the Mediterranean focus of this conference, were you able to look at the different types of alcoholic drinks?

Frank HU
We did look at this. The results were similar to those for coronary heart disease. The beneficial effects on diabetes are due to the alcohol itself rather than other components of the beverages. Basically, our data do not reveal any significant differences according to different types of alcoholic drinks.

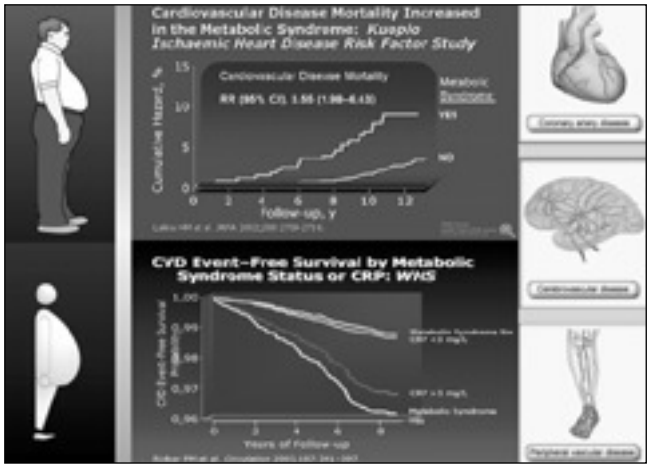
Edith FESKENS
I see. Then that would also refer to the polyphenol question. With regard to the dietary cholesterol which was on your list for risk factors and which I found myself in studies almost ten years ago, you did not explain this. I never reached a satisfactory conclusion on this point and I am interested to know what your thoughts are on this issue.

Frank HU
It is ironic that cholesterol turns out to be a stronger risk factor for diabetes than for coronary heart disease. The results are consistent across our own cohorts and several other studies in showing that higher consumption of cholesterol is a risk factor for type 2 diabetes and for insulin resistance. However, I do not know what the underlying mechanism is. There is speculation that it may work through ApoCIII, because people with underlying insulin resistance have a defect in ApoCIII so that they have compromised ability to clear cholesterol from the body.

Dietary interventions and the metabolic syndrome

Dario GIUGLIANO
Second University of Naples, Chair and Division of Metabolic Diseases, Department of Geriatrics and Metabolic Diseases, Naples, Italy

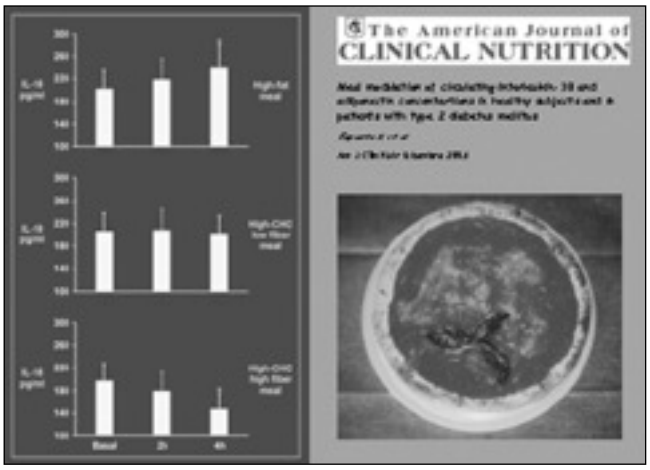
Good morning, bonjour! Thank you very much, Nick, for inviting me to attend this exciting symposium. The subject of my presentation is dietary intervention and the metabolic syndrome. First of all, I would like to begin by stating the obvious. It is obvious that during the last twenty years, there has been a decrease in coronary artery events among the population. A study from England and Wales showed a 70% decrease in coronary heart disease mortality; at the same time, there was a correlating increase in diabetes and obesity that augment the risk of coronary heart disease. This is particularly important because both obesity and diabetes are pathological conditions included in the diagnosis of the metabolic syndrome.



Prospective epidemiological studies have demonstrated that people with the metabolic syndrome have an increasing relative risk of cardiovascular disease. These observations mainly come from two studies – one Finnish and one American. They show a three times greater risk of developing cardiovascular disease mortality and a cardiovascular event. In Italy, the prevalence of the metabolic syndrome amongst adults is about 23%, very close to the prevalence of 24% reported in the U.S. applying the criteria of adults treatment panel III (ATP III). It is important to recognise that people with the metabolic syndrome have an association not only with classic risk factors, but also with emerging risk factors. For example, in 180 patients with metabolic syndrome, we found with the increase of components of metabolic syndrome, a parallel decrease in insulin sensitivity and endothelial function – and endothelial dysfunction is one of the first signs of atherosclerosis – associated with an increase of inflammatory burden. Therefore, insulin resistance, inflammation and endothelial dysfunction go hand-in-hand in these persons.

We have also shown a decrease of anti-inflammatory potential in people with the metabolic syndrome. Interleukin 10 is a cytokine which has a central anti-inflammatory activity: people with the metabolic syndrome, irrespective of whether or not they are obese, have lower circulating levels of interleukin 10. The working hypothesis we developed claims for the presence of an imbalance between pro-inflammatory cytokines (IL-6, IL-18, TNF-α), and anti-inflammatory cytokines (adiponectin and interleukin 10), the two anti-inflammatory cytokines, facilitating the generation of a pro-inflammatory milieu that, through insulin resistance and endothelial dysfunction, leads to diabetes, the metabolic syndrome and atherosclerosis. This is a working hypothesis, which is supported by several clinical and epidemiological studies.

Inflammation is now regarded as a link for many chronic diseases such as cancer, heart disease, and also for neurological diseases, such as Alzheimer's disease. However, my speech is about diet. Unhealthy diets may play an important role in increasing the incidence of chronic and metabolic diseases through the production of free radicals, oxidative stress and inflammation.



We compared two isocaloric meals, one high-fat, continental meal and one high-carbohydrate meal. Being a Neapolitan, I chose pizza. These two isocaloric meals contain approximately 750 calories. When a normal person eats pizza, there is no change in glucose and triglyceride levels, but when the same subject eats a high-fat meal, its triglycerides go on the raise. These responses are amplified in the diabetic patient who presents rapid and prolonged swings of glucose and triglyceride levels after both meals. In both normal people eating the high-fat meal, and diabetic people eating both meals, we observed circulating markers of endothelial activation, such as adhesion molecules, and inflammation, such as tumour necrosis factor, and interleukin 6, going on the raise. Depending on what one eats, endothelium does not work well during the postprandial phase, which lasts four to six hours. We also compared high-fat meals, with and without antioxidant-rich foods: the addition of natural food or antioxidant-rich foods was able to smooth the adverse effects of the high-fat meal on the endothelium.

The type of carbohydrate is also important. We compared the effects of two types of pizza: a refined-grain pizza, and a whole-grain pizza. The high carbohydrate, low-fibre meal did not change the circulating level of interleukin 18, which is involved in plaque destabilization and coronary heart events; however, increasing the amount of fibre in the meal (high-carbohydrate, high-fibre meal) was associated with reduced levels of IL-18. Thus, it is possible to modulate inflammation through appropriate foods.

It is important to recognise that the postprandial phase is important because an increase in glucose and lipids can produce a stress to our endothelia through many mechanisms, including activation of protein kinase C, protein glycation, oxidative stress, and so on. We have provided evidence that hyperglycaemic spikes may be proinflammatory. In normal people, when a hyperglycaemic clamp is introduced, i.e. when the plasma concentration of glucose is acutely increased with exogenous glucose infusions, the level of some proinflammatory cytokines, such as interleukin 6 and tumour necrosis factor-α, increased. These hyperglycaemic spikes are similar to that occurring in type 2 diabetes after a meal. Moreover, the increase in tumour necrosis factor-α and the decrease in endothelial functions are strictly correlated, providing a mechanistic explanation for the deleterious effects of foods on vessels. So, a diet rich in fat (saturated or tans-fat), and rapidly-absorbed glucose, especially when associated with the lack of natural antioxidants, may produce some mechanisms that are linked to the occurrence of atherosclerosis.

However, I wish to move on to show you the results of an intervention study with people with metabolic syndrome. We compared the effect of two different types of diet in people with metabolic syndrome. People were chosen when having at least three criteria from the adult treatment panel tree for out-patients population. The first 90 people ate a control diet containing less than 30% of energy from fat, less than 10% of energy from saturated fat, and less than 300 milligrams of cholesterol. For the intervention studies, people were recommended to increase their intake of fruits and vegetables, nuts, and whole grain. After two years of observation, there was a difference between the intervention diet and the control diet. There was an increase in fibre intake in patients of the intervention study, a decrease in saturated fat, an increase in monounsaturated fat, a decrease in omega 3 and omega 6 fatty acids ratio, an increase in consumption of fruit, vegetables, nuts and legumes, olive oil and whole grains.

Concerning the effect on the biochemical parameters, there was a decrease in triglycerides and total cholesterol, associated with an increase in HDL cholesterol. Blood pressure also decreased. C-reactive protein, which is a sensitive marker of inflammation decreased by 1 mg/dl. C-reactive protein has been considered a marker of inflammation to date. However, we have enough evidence to suggest that C-reactive protein may be a mediator of inflammation. The most important finding, at least in the clinical setting, was that the prevalence of metabolic syndrome in those patients with 3, 4 or 5 components of the syndrome was reduced by about one half by the end of the study: about 45 patients did not have the features of metabolic syndrome at the end of the experiment. Therefore, this study may be seen as a prevention of later diabetes.

To summarise, diets that favour large increases in postprandial glucose, free fatty acids and triglycerides, raise the inflammatory burden, which in turn may increase the risk of the metabolic syndrome, type 2 diabetes, and atherosclerosis. This seems particularly important if one take into account the following percentages are alarming: two-thirds of American adults are overweight; more than 30% are obese; almost 8% are diabetic; nearly 25% have metabolic syndrome; and almost 45% of women and 30% of men are seeking to lose weight each year.

Speaking about the Mediterranean diet, three scientific organisations – the American Cancer Society, the American Diabetes Association and the American Heart Association – used a few words in issuing their general prevention guidelines for adults to eat at least five servings of fruit and vegetables per day. Is this enough? The recommended six servings in Denmark may be a better goal.

In relation to the history of the Mediterranean diet, grain, oil and wine are considered to be important foods. Burned foods found in Pompeii include nuts, bread, vegetables and lentils, olives, and, as we can see from the famous fresco, wine. Finally, a last word for Ancel Keys, perhaps the father of the Mediterranean diet, who left us in 2004, as a centenarian. A living museum of the Mediterranean diet has been dedicated to his memory in Pioppi, South Italy. Thank you very much.

Questions

Member of the audience
With respect to the statistics that you gave for the American population, do you have similar data for Italians?

Dario GIUGLIANO
Prevalence of obesity and overweight is quite similar in Italy as for the United States and is rising. I used the United States data because I had more recent data and also because the quantity of people affected is greater. In Italy, the prevalence of the metabolic syndrome is circa 23% of the adult population.

Member of the audience
Often quoted, the Mediterranean diet is a healthy diet. With regard to the dairy products, it is difficult to believe that the Cretan, or the Mediterranean, do not eat milk and goat's milk cheese. The children consume a great quantity of milk. There are certainly studies on the biological and biochemical composition of various fresh milks and out of powder. Could you make a comment on this point?

Dario GIUGLIANO
The speaker was asking about goat dairy products. I do not really have any experience with relation to such products. However, the most fitting adjective I have found for the Mediterranean diet is 'frugal', because the Mediterranean diet was a frugal diet and 'frugal' comes from the Latin word frugis, which means 'product of the heart'. It is very important to recognise that the products of the heart are vegetables, fruits and grain. However, 'frugal' is not a word that is fitting with our society today.

Member of the audience
I am grateful that you put forward the inflammatory factors in obesity, metabolic syndrome and cardiovascular disease, but would you agree that it is a vicious circle in the sense that all of these processes also increase inflammation? We could say the same perhaps for the process of antioxidant status: if there is a lack of antioxidant intake, these processes are favoured, but having more fat would also trap more vitamin and soluble antioxidants, so it is an auto-aggravating situation.

Dario GIUGLIANO
In my view, inflammation is the key point. Inflammation may be a key point in our understanding of the relationship between the diet and some of the effects that you mentioned. I should like to stress that we do not know what triggers the whole process: perhaps it is the obesity; perhaps it is the diet, or the ingestion or consumption of macronutrients which may be responsible for the obesity, for insulin resistance and endothelial dysfunction, which are the precursors for type 2 diabetes, atherogenesis and so on. Therefore, the theory that I have presented claims that the macronutrients that we eat every day and the food choices that we make are important in the future of our vessels.

Member of the audience
I just wanted to try to answer the question about goat dairy products. There is some data that suggests the fatty acid content of goat's milk and cheese could be somewhat different from cow's milk and cheese, especially in the content of omega 3 fatty acid that could be higher.

Dietary interventions and risk of type 2 diabetes

Jaakko TUOMILHETO
National Public Health Institute, Diabetes and Genetic Epidemiology Unit, Department of Epidemiology and Health Promotion, Helsinki, Finland

Thank you very much, Nick. Ladies and gentlemen, I am extremely grateful to have been invited here. It is always a pleasure to come from cold Finland to the South, not only for reasons of food but also the climate.

In my presentation I will concentrate on preventive aspects of type 2 diabetes. We have heard much about the observational data, the risks and the benefits of various dietary components in relation to type 2 diabetes. Type 2 diabetes is a disease which has a very strong genetic component. Most people carry genes that permit type 2 diabetes to develop. The lifetime risk in the European population is circa 50%, and many more people have milder forms of hyperglycaemia during their lifetime. Of course, what is important is that this genetic susceptibility can be modified by lifestyle and that we can identify individuals who are in the process of developing diabetes and who have impaired glucose tolerance, which is in the middle of the process between normal glycaemia to type 2 diabetes. We have already heard about lifestyle-related risk factors and these operate in different ways: I shall talk briefly about this. Most of my presentation will focus on the data from our randomised controlled trial, 'Finnish Diabetes Prevention Study', which was published a few years ago. Today I will present not only those but also new data.

The aim of the study was to determine whether we could, using a lifestyle intervention, prevent or delay the development of type 2 diabetes in middle aged people who had impaired glucose tolerance and who were obese. We randomised individuals either to a standard reference group, which received some advice as to how to reduce health risks, or to another group, which received intensive lifestyle intervention.

Why did we carry out such a study in Finland? Finland is a country which is located in the north. Quite recently, there was a reference to the Finnish lifestyle in 'Science', and as you may read, the diet consumed by Finland in the past was certainly not a Mediterranean one.

In the study population, the selection criteria were middle-aged individuals, with an average bodyweight of 90 kilos, an average waist circumference of 100 cm or more, and elevated two hour glucose, and if we use the metabolic syndrome classification based on the previous American National Cholesterol Education Program Adult Treatment Panel III, about 75% of the individuals had metabolic syndrome.

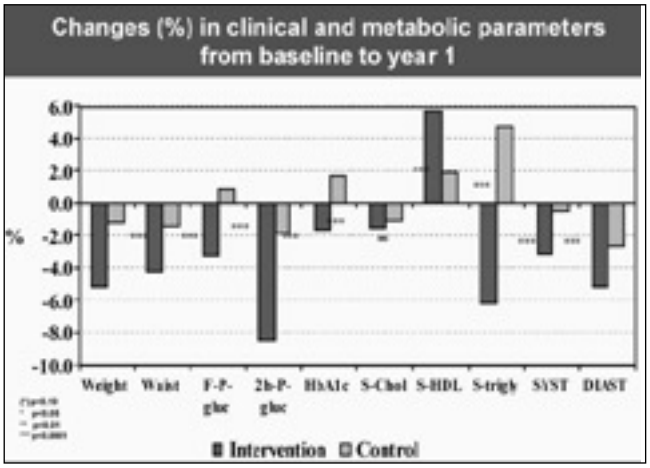
According to the baseline data regarding diet: these individuals at high risk of type 2 diabetes consumed less carbohydrates than recommended; fat intake was higher and dietary fibre intake was lower than recommended; physical activity were low, much lower than recommended for a healthy lifestyle. Therefore, it is no wonder that these individuals had impaired glucose tolerance.

The five main aims of the intervention in the intervention group of the Finnish Diabetes Prevention Study were: to reduce bodyweight, reduce fat intake, change the type of fat that people were eating, increase the dietary fibre intake to at least 15 grams per 1 000 kilocalories, and to introduce half an hour of exercise, which could be aerobic or muscle-strengthening.

How did we try to reach these intervention goals? By way of example, for the reduction of overweight, there were several strategies used in the intervention. The key people administering the intervention in five clinics that we had were dieticians or nutritionists, and there was also a study nurse and a physician meeting individuals at least once a year, but the dietician was the main interface for the intervention. With regard to the change in saturated fat intake, we tried to increase the non-fat dairy products and substitute them for the high fat products, along with the other initiatives. In relation to total fat intake, we promoted Finnish rapeseed oil, which has similar content than olive oil, but is locally made, and we also encouraged fish consumption. In terms of fibre intake, bread (mostly rye) is the most important source of dietary fibre in Finland, constituting circa 40% of dietary fibre consumption, although we also consume large quantities of oats, porridge and other similar products. We also promoted the consumption of fruit, berries and vegetables.

The physical activity programme was based on promoting everyday life physical activities which do not require extra time but which can be fitted in with peoples' lifestyles, including dancing. We also provided the opportunity to use a gymnasium with a supervised resistance-training programme for free, which was used by most people.

The intervention strategy was to achieve as much as we could during the first year, and to maintain the new habits for the following years. It can be seen that we achieved statistically significant changes in fat intake, total fat, saturated fat and in dietary fibre. The protein intake increased slightly and this was due to the fact that fat intake was reduced, so people obviously ate higher protein foods and meats. Vigorous physical activity increased more in the intervention group. It can be seen that the control group, who received health leaflets and related general information, also changed to some extent. As a result of changes in diet and physical activity, in all the components or the parameters of the metabolic syndrome improved, especially the two hour postprandial glucose level, which was reduced by 8%. Also, bodyweight decreased by circa 4 kilos and waist circumference decreased by circa 4cm. Triglycerides and HDL cholesterol also showed favourable changes. Thus all components of the metabolic syndrome improved. Changes in bodyweight resulted in expected changes in blood pressure: a loss in bodyweight of 1 kilo usually corresponds to a change by 1 mm Hg change in systolic blood pressure.



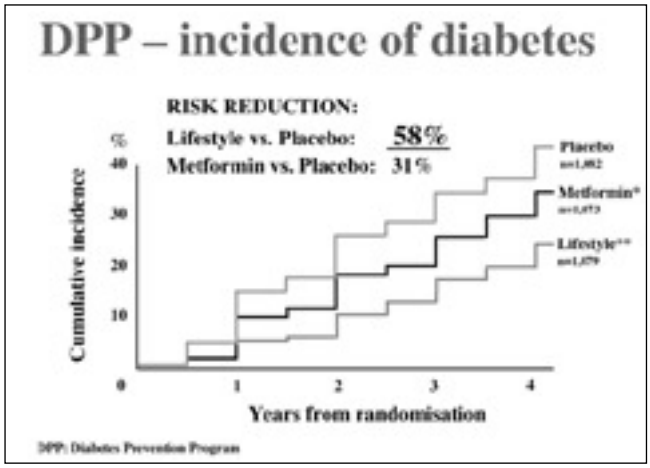
Correlations between the changes in weight and waist circumference with the metabolic parameters were not high, the highest correlations being 0.3. Therefore, lifestyle intervention comprised factors other than reduction in weight and waist circumference alone which also contributed to the changes in the glucose, lipids and blood pressure. The correlations between weight changes and dietary changes are not extremely high at circa 0.15 and 0.02, but are still statistically very significant. The risk of diabetes depended on the bodyweight change: in the individuals who gained weight by more than 1%, the risk over a three-year period was doubled compared to those whose weight did not change at all. Those who reduced bodyweight by more than 7% had a 75% to 80% lower risk of diabetes than those individuals whose weight did not change. This is in keeping with findings from earlier observational studies. Weight control is extremely powerful for the risk of diabetes and its prevention.

What about the other factors? In relation to dietary fibre, even though we only had approximately 500 individuals in the study, we were able to show that the higher the intake of dietary fibre, the more positive the outcome was, and it was highly statistically significant. Total fat intake also demonstrated a highly statistically significant increase in the risk of diabetes in those people who ate large quantities of fat, particularly saturated fat. When we combined fat and dietary fibre, it was interesting to observe that in comparison with individuals with both a low fat high fibre diet, those with a low fat diet but a low fibre intake had an increased risk of diabetes by almost 50%.

It seems that fat intake is a very important determinant of diabetes, and moreover, it seems that if we combine high fat intake with a low fibre intake, the risk of type 2 diabetes is the lowest. There is a difficulty to distinguish between the people who change their dietary fat intake from those who increase their dietary fibre intake, since usually when fat intake increases fibre intake decreases and vice versa, and therefore it is quite difficult to isolate independent effects of these dietary changes.

Baseline variables, such as body mass index, influenced the benefit of the intervention. Those with the lowest body mass index of circa 29, had a 70% benefit from the intervention, whereas there was a 40% reduction in the risk of diabetes in the most obese subjects in the intervention group compared to the control group. Therefore, the message is that it is important to begin risk modification as early as possible; the earlier a person starts, the better the benefits.

Weight change is important but when people are losing weight it is for a reason: either they are consuming more energy or they eat less. There was a clear correlation in this intervention study: the more that people exercised, the more bodyweight changed. Therefore, it is very difficult to state which component of this kind of multifactorial lifestyle intervention is producing its beneficial effects. With regard to the targets that we had for the individuals, it is important to realise that a lifestyle intervention must be a total package. Some individuals have more difficulties with certain components of these lifestyle issues than others and therefore the intervention strategies have to be modified on an individual basis. However, it was interesting to observe that amongst the individuals who achieved four or all five of the targets for lifestyle intervention, none developed diabetes: there was 100% protection where the intervention was followed properly. Therefore, we can conclude that lifestyle intervention in the prevention of diabetes is extremely powerful if carried out properly. Had we not intervened and if all five targets had not been pursued, circa 35% of high-risk individuals would have become diabetic over a three-year period.



There was a diabetes prevention programme (DPP) going on at the same time in the United States, but it started a few years later. We had similar study protocols for lifestyle because when we designed our protocols in Finland, we had a consultant from the United States (Dr. W.C. Knowler). Thus, our protocol was available to the investigators in United States and as a result, we were fortunate enough to have two studies with a similar design, although implemented differently and in different countries. The DPP revealed the same reduction in risk of diabetes as we observed in Finland: 58% relative risk reduction. In addition to lifestyle intervention the DPP also used metformin in a separate arm, a drug that lowers blood glucose; metformin resulted in a circa 30% risk reduction. In the DPP, all ethnic groups benefited similarly from the interventions, whether in the form of a drug or a lifestyle intervention.

There was also an earlier study in China, in Da Qing city, which also showed a 40-50% reduction in the risk of diabetes using lifestyle intervention. This was not an individually randomised study, although the clinics were randomised, and as a result there were some doubts as to the viability of the data. In Sweden, lifestyle intervention also seemed to work with a 50 to 60% reduction in the risk of diabetes, but there were some problems with the follow-up of these individuals and the compliance between the different individuals. There was also another Swedish intervention study, which showed a 50% reduction in the risk of diabetes with diet and exercise, but there was no individual randomisation as people could choose whether or not to join lifestyle intervention.

Let us examine the dietary changes in the US DPP, where the results were similar to ours. In general, the energy intake reduced for the intervention group. There was also a fall in body weight in the control group. Interestingly, also in the metformin group, body weight was reduced significantly. It was interesting to note that in the DPP, even though there was a significant difference in the change in dietary fibre between groups, there was hardly any increase in dietary fibre in the intervention group, but a decrease in the control group: this is quite revealing in terms of dietary patterns in America.

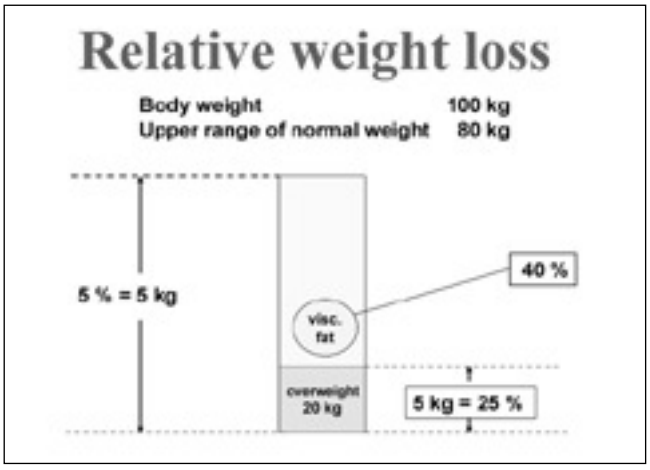
In terms of food item changes in the DPP, the main change for the lifestyle intervention group was the reduction of sweets. There was also a reduction in grains, although this may be due to the lack of non-sweet bread in the United States and the proliferation of sweet buns and rolls, which were not to be consumed in the lifestyle change intervention.

Glucose levels vary during the day. In the individuals with impaired glucose tolerance (IGT), the postprandial glucose levels were particularly elevated and fasting glucose levels were usually normal. Using continuous glucose monitoring, we tried

to evaluate the changes in glucose levels during the day using a glucose monitor which measures during three days glucose in peripheral tissue every three minutes, and then presenting it in graph form. We took the individuals from the DPS and provided them diet with a high or low glycaemic index. After the randomised trial period, we invited people to join this glucose monitoring study, and more than 70 people participated. With the high glycaemic diet in these with IGT glucose levels increased after breakfast at its highest peak to almost 11mmol/l, which is at the level of diabetes. The pattern was similar after lunch and dinner, although the typical pattern is that after lunch, the glucose levels remain at a higher level for the rest of the day and do not return to normal.

When the same individuals received the low glycaemic index diet, the curves were less variable, and during most of the day the peaks are small, unless they were given the glucose load, at which point the levels increased significantly again. Therefore, it seems that by modifying the type of carbohydrates consumed, it is possible to control glucose levels and postprandial glucose levels in people who have impaired glucose tolerance.

We now have the trial data to demonstrate convincingly that diabetes can be prevented in high-risk individuals with IGT. The lifestyle changes required are rather small, so can they be used in everyday life? We had an approximately 5% reduction in bodyweight in these individuals. The typical man had an initial bodyweight of 100 kilos at the beginning and had a 5 kilo reduction in bodyweight. Given that the upper range normal weight is 80 kilos, this 5% reduction may seem very small.



However, this should be considered in another light: if the man has 20 kilos overweight and loses 5 kilos, his overweight has reduced by 25%, not by 5%. Moreover, we already know that when weight reduction begins, initially there is more decrease in visceral fat; in this scenario it would have reduced by about 40%. Therefore, a seemingly small change in bodyweight in these individuals means a quite significant change in the fat patterning in their bodies.

There are many more questions to be answered. For instance, (i) how much does it cost to prevent a case of type 2 diabetes, (ii) whether benefits are long-lasting, and (iii) whether lifestyle intervention is cost-effective. We have shown that lifestyle intervention is feasible and produces beneficial changes in metabolic parameters, and that required lifestyle changes do not need to be extreme and could therefore be achieved by most of the people. In terms of the duration of the benefit, we have followed the individuals on a one-yearly basis and compared with the results that were originally published 4 years ago, there is no sign of disappearance of the initial effects of the intervention. In fact, the difference between the groups is becoming even more significant, even though the subjects in the intervention group were left on their own after the formal trial period was over. Thus, the intervention has long-lasting effects. In trials like the metformin arm of the DPP and other trials using anti-diabetic drugs to reduce the risk of diabetes, the effect largely disappears as soon as the drug is no longer administered. This is not surprising because the drug provides a pharmacological mechanism to control glucose, whereas in the lifestyle intervention we influenced the causal factors, and when this is done properly, the intervention provides long-term effects.

We are carrying out a cost-effective analysis of the intervention at the moment, and this has already been done by the DPP. The DPP results showed that the intervention was cost-effective even though their intervention was more labour-intensive than what is possible in real life. A very small amount of money, approximately 10-20 euros or dollars, is needed to prevent a case of diabetes with a 12 month intervention, so it is definitely cost-effective. Since the results in the Finnish DPS were similar to those in the DPP, but intervention was much less intensive, the results from the cost-effectiveness analysis will be certainly very positive.

Ladies and gentlemen, I have tried to convince you that lifestyle intervention is a very effective method for type 2 diabetes prevention in high risk individuals. Dietary advice must be combined with efforts to increase physical activity. It is important to study the importance of different dietary components and the individual effects of those components, but I think that this is more of an academic exercise. I think that we know most of the issues important for the prevention of type 2 diabetes in the population in general. Thank you.

Questions

Member of the audience
Could we have more practical information about the intensive lifestyle counselling?

Jaakko TUOMILHETO
We have published a paper in Diabetes Care which contains a full description of the intervention (Lindström J, Louheranta A, Mannelin M, Rastas M, Salminen V, Eriksson J, Uusitupa M, Tuomilehto J for the Finnish Diabetes Prevention Study Group. The Finnish Diabetes Prevention Study (DPS). Lifestyle, intervention and 3-year results on diet and physical activity. Diabetes Care. 2003;26: 3230-3236).

Member of the audience
I wonder whether it is possible to increase the body mass index and to reduce the risk of developing diabetes at the same time by converting the fat into muscle.

Jaakko TUOMILHETO
Theoretically, I believe that you could, although I am not sure how this would be done in practice. After evaluating the effect of physical activity and adjusting for bodyweight and body mass index changes, we could clearly show that physical activity independently reduced the risk of diabetes. However, in our study, there were no individuals who would have increased their body mass index and decreased their risk. I think it is rather theoretical.

Introduction

Salvatore PANICO
Dipartimento di Medicina Clinica e Sperimentale, Università di Napoli, Federico II, Naples, Italy

This afternoon, we shall talk about cardiovascular disease, which is classically related to the Mediterranean diet. The hypothesis for the diet was born on the basis of a cross-cultural investigation which included seven countries and which was the seminal work by Ancel Keys.

You will certainly be aware of Ancel Keys but may not know the details of the first steps of the Seven-country Study. The study was actually designed in Naples, the city where I live. During the last part of World War II, Ancel Keys and Paul Dudley White, the cardiologist of the US General Eisenhower, were very surprised to see so few myocardial infarction patients in hospitals there compared to Boston hospitals. Thereafter, some 15 years later the SCS started, including also Italian small villages.

Today, the issues of how much and with what components we should encourage people to eat according to the Mediterranean-type diet are still crucial.
This session is dedicated, in the first part, to the experimental evidence on the benefits of recommended dietary regimen or dietary components. Then, the reasoning on the evidence of protective effects other than trough lipids will be presented, and finally, some reflections will be provided on the preventive potential of the adherence to a Mediterranean-type diet, with special respect to Mediterranean countries.
Therefore, I offer the floor to the first speaker, Dr Marchioli, who is from the Mario Negri Sud Institute in Italy. He will present the paper 'Cardiovascular risk, n-3 PUFA, and dietary habits after myocardial infarction: the GISSI-Prevention study'.

Cardiovascular risk, n-3 PUFA, and dietary habits after myocardial infarction: the GISSI – Prevention study

Roberto MARCHIOLI
Laboratory of Clinical Epidemiology of Cardiovascular Disease, Consorzio Mario Negri Sud, Santa Maria Imbaro (CH), Italy

Mr Chairman, ladies and gentlemen, dear colleagues, I am supposed to give you a short summary of the new results of the trial, including the experimental results of the trial, and some additional information about dietary habits.

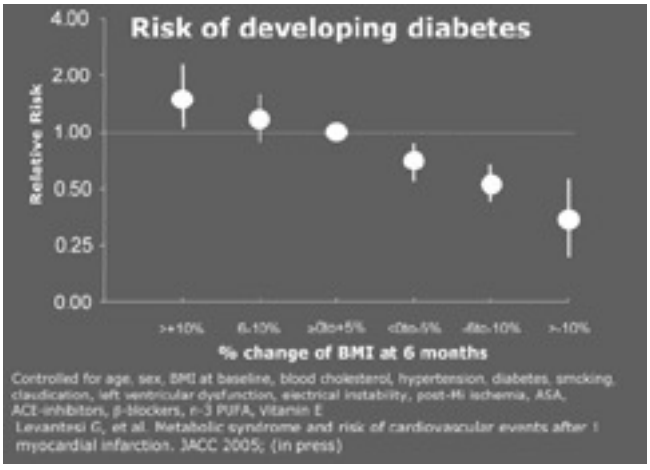
Firstly, the design of our trial was as follows: patients with a risk of myocardial infarction within three months received dietary and lifestyle counselling, drug therapy prescribed at that time, consisting mainly of aspirin and beta blocker inhibitors. They could then be randomised to one of four groups: omega-3 fatty acids, vitamin E, the combination, or no treatment at all. After six months, patients returned for their first clinical visit following randomisation, and if their blood cholesterol was higher than 200 milligrams per decilitre, they could be randomised in a nested randomised trial testing the efficacy of pravastatin in these patients. Patients were followed for 42 months following randomisation. However, the second trial was brought to a close because it duplicated other trials, such as the walk-up study and the CARE trial. When the CARE trial was published in the New England Journal of Medicine, we decided that it was not ethical to allow patients who had myocardial infarction to continue with high blood cholesterol and no cholesterol-lowering treatment at all; therefore, the trial was closed. However, when we closed the trial, we did have some results relating to pravastatin: there was a 20% reduction of LDL cholesterol and there was also some reduction of total mortality, but it was not significant because we closed the trial.

In relation to the main study on omega-3 fatty acids and vitamin E, we had interesting results. Patients were enrolled within 25 days (median value) of their myocardial infarction and none of them had a severe prognosis, as we excluded patients with malignancy or with severe congestive heart failure. They had a mean age of 60 years and a mean age at infarction of 52, and this was why we excluded patients with severe heart failure, and then we have LDL cholesterol of 136 and so on. In relation to other characteristics, 42% were smokers before myocardial infarction, 14% were diabetics and 36% had hypertension. As to pharmacological treatment, there was clearly a change in the use in the cholesterol-lowering trial between the baseline situation and at the end of the study because of the effect of the nested trial on pravastatin. However, at the end of the study, approximately 80% of patients were taking aspirin, and 40% were taking ACE inhibitors or beta blockers.

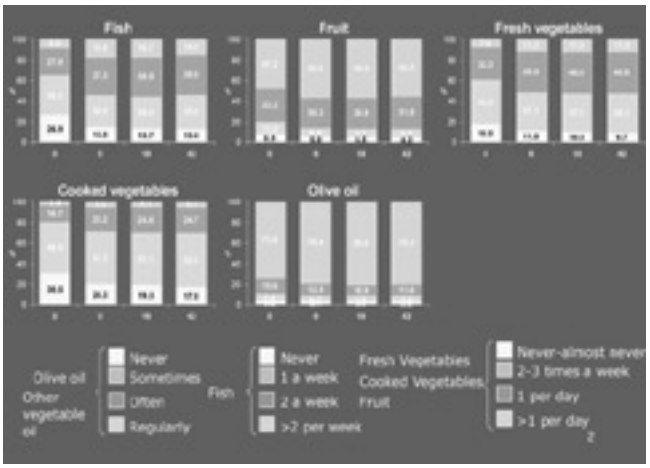
The results on omega-3 fatty acids (because vitamin E did not improve prognosis in these patients) were as follows: there was a 15% reduction of death plus non-fatal infarction or stroke, and a 20% reduction of cardiovascular death plus major non-fatal end points. These were the two main points that were established in the protocol. However, we conducted a series of additional analyses, and we realised that there was a slight, but not significant, reduction in fatal myocardial infarction and non-fatal stroke but there was an important reduction of total mortality through cardiovascular death of up to 30%, and for sudden death of up to 44%. This was associated with an early onset of this benefit within three months for total mortality, and within four months for sudden death, and this was why we thought that one of the main mechanisms through which omega-3 fatty acids could act could be through their anti-arrhythmic properties, but this has not been demonstrated yet. However, there was no change in blood lipids – there was only a 3% reduction of triglycerides, which was statistically significant but small compared to the magnitude of the benefit on total mortality.

GISSI-Prevenzione was mainly a prevention project, and patients were also given counselling about healthy lifestyles, including physical activity, diet and so on. When we look at the data relating to smoking, we can see that even after six months following myocardial infarction, 12% of patients were still smoking and this proportion had increased up to 16% by the end of the study. Therefore, we can see that it is not easy to modify lifestyle habits, as we all know. I must also emphasise that if we look at the body mass index at the beginning of the GISSI-Prevenzione study, we can see that there are a number of patients who are overweight or obese.

If we look at the modification of body mass index at six months and its relationship with the probability of developing diabetes, we can see that compared to the reference category of those not gaining weight or gaining little weight, if the patient sustains significant weight gain, there is an increase in the risk of becoming diabetic; if the patient decreases in weight, there is a clear decrease in the risk of becoming diabetic. We can see that modifying lifestyle habits has important consequences.



Unfortunately, we did not collect information about physical activity but we did collect some information about diet. Since GISSI-Prevenzione was a pragmatic trial to be conducted by cardiologists, we had to be very pragmatic about the collection of information about diet and as a result, we used a very simple food frequency questionnaire with simple markers of dietary habits regarding intake of cooked and raw vegetable, fruit and so on, and the frequency of their consumption during the week. With this approach, we collected information relating to circa 11 000 patients over 42 months.

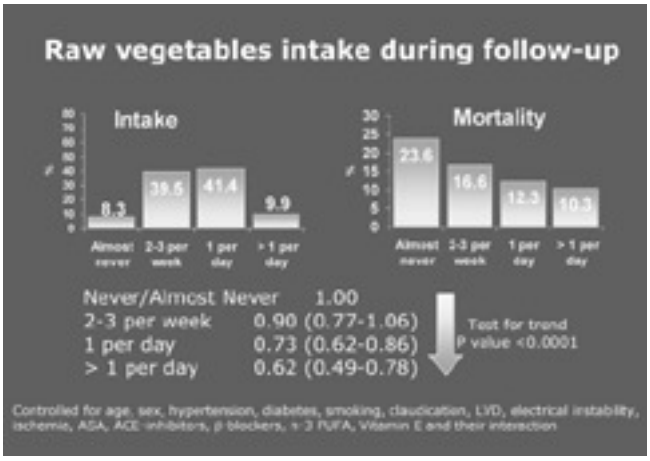


We can see on the graph, that we have the intake of fish at the baseline in this column. The green and orange parts of the column indicate those patients consuming fish once or more than twice per week respectively. We can see that if we examine the progress at six months, eighteen months and forty-two months, there is an increase in intake of fish that was maintained during follow-up. Therefore, there was an improvement of dietary health in relation to fish, but this pattern was also present for other foods such as fruit, cooked vegetables, fresh vegetables and olive oil: there was an overall improvement of dietary health. Even intake of olive oil increased after myocardial infarction, a surprising factor given that the study was performed in Italy where the level of consumption of olive oil is already high.

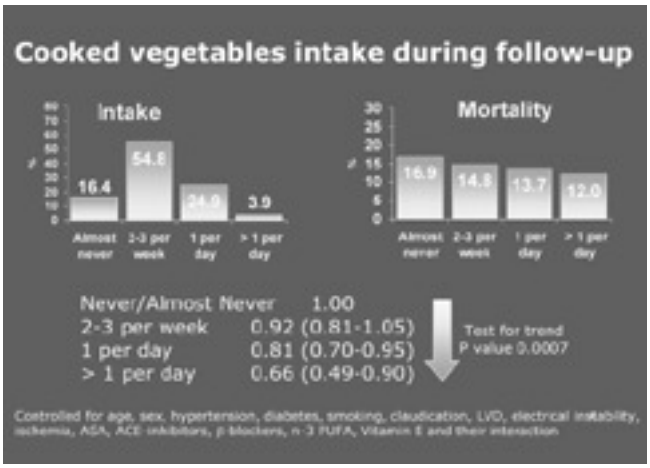
What did we do? We performed a number of multivariate analyses adjusting for main potential confounding factors, and we calculated a dietary score using the numbers that can be seen in the boxes on the graph in order to obtain higher scores for people with better dietary health. In this way, we were able to analyse the data of circa 11 000 patients and obtain information relating to total mortality for approximately 6 years of follow-up, which represents circa 60 000 person-years of follow-up.

In this graph, we can see the average food intake during follow-up or the improvement of diet during follow-up. About 80% of patients ate fruit at least once per week, and this was slightly associated in univariate analysis to a lower mortality, but on performing multivariate analysis we saw a 27% reduction in mortality for patients eating fruit more than once per day, with a highly significant P value for the trend test.

We performed the same analyses for other foods. In relation to raw vegetables, approximately 50% of patients had a high intake of raw vegetables, and this was clearly associated with lower mortality. This information was confirmed by means of multivariate analysis, with a 38% reduction in the risk of death.



In the case of cooked vegetables, 30% of patients ate cooked vegetables at least once per day. There was a slight association with a lower mortality and again, it was statistically significant with more than 30% reduction of total mortality.



In relation to fish intake, circa 50% of the patients ate fish at least twice per week and this was associated with lower mortality. This was confirmed by means of multivariate analysis with almost 30% reduction in mortality.
In relation to olive oil, many of the patients used olive oil regularly, as I mentioned before, and this was associated with a reduction in total mortality.

Interestingly, we also obtained data for other seed plant oils, as people were also regularly using other seed plant oils, and there was an inverse association with mortality, i.e. the risk increased, and this was confirmed through multivariate analysis.

Although butter intake is not high in Italy, we did obtain data for butter and we found an association with high risk of death and despite the low numbers, it was statistically significant. With regard to cheese, there was no clear association with total mortality.

For wine intake, there was an association with moderate intake of wine, that is to say that was a lower mortality in those who had a moderate intake of wine.

The results for coffee were that there was a significant increase in risk of death in patients who drunk more than 4 cups of coffee per day.

These were the results for foods individually, but as we needed to summarise the dietary patterns of these patients, we calculated the score using healthy foods alone, such as fruit, fresh vegetables, cooked vegetables, fish and olive oil. As I have already mentioned, there was an association between the score and the total mortality, that is to say that the higher the score, the better the diet and the lower the total mortality. This kind of result was also confirmed through subgroup analysis, and there was similar association for the dietary score in patients according to gender, age, drug therapy or experimental drugs like omega-3 PUFA and Vitamin E used during the trial.

In conclusion, to summarise the results of the dietary score, if we present them in terms of quartiles of the score, there was a 40% reduction in the highest quartile of patients who had the best dietary habits. Thank you for your attention.

Questions

Member of the audience
Would you exclude that those individuals adhering to the dietary recommendations more closely would also be those who took their drugs more regularly than the others?

Roberto MARCHIOLI
Yes, we did carry out an analysis looking at this point and there was such an association. However, we adjusted for the intake of drugs, such as the compliance to experimental treatment, and we obtained similar results.

Member of the audience
I would like to ask you a question relating to your results for coffee. They are not part of the score as I understand, but I am interested in coffee because as we heard earlier, we have seen an inverse association between coffee and the risk of diabetes. You have mentioned that it is associated with an increased risk of mortality. Could you tell me what causes of death could be associated with coffee? Do you have any information regarding the types or properties of coffee that are concerned? For example, we know that boiled coffee increases LDL cholesterol, and perhaps this is a part of the mechanism. Or is it related to an increase in blood pressure?

Roberto MARCHIOLI
In relation to your question, we have a problem of proxies because there were people who did not stop smoking, and people who resumed smoking during the period, and this could be associated with a higher intake of coffee. Therefore, this result is quite complex. This was what we saw. Personally, I think that the best way is to look at the whole dietary pattern rather than just concentrating on the intake of one food.

Changing dietary pattern reduces CVD risk Evidence from primary prevention trials

Edith FESKENS
National Institute of Public Health and the Environment Centre for Nutrition and Health, Bilthoven, The Netherlands

Thank you for your kind invitation to attend this conference. The task that has been set for me is extremely difficult as I was asked to talk about changing dietary patterns and how they reduce cardiovascular disease risk. The problem is that I was asked to focus specifically on the evidence from primary prevention trials and this will be difficult, as I will explain to you later. The question should really be reformulated to ask whether there is any evidence from primary prevention trials that this is the case. However, I would like to use the next 20 minutes to discuss the importance of this topic.

Firstly, I should like to pay my respects to Ancel Keys, who is no longer amongst us. Together with Paul Dudley White, he was the first to acknowledge the fact that there are so many interesting aspects to the lifestyle and diet here in the Mediterranean area. That is also why he chose to live here after his retirement after spending several periods of his life here. In collaboration with Daan Kromhout, I have been working on the Seven Countries Studies for almost fifteen years, and what Ancel Keys found was very important in saying that in Italy, Greece, Corfu, Crete, in the former Yugoslavian republics, their average saturated fat intake is quite low and the mortality rate from coronary heart disease is quite low. He was one of the first to acknowledge that the Mediterranean diet may be very important in the prevention of coronary heart disease and other cardiovascular diseases.

We analysed the data of the Cretan participants of the Seven Countries Study and looked at how they ate in 1960, and we returned to Crete to buy Cretan foods, including traditional foods that are not eaten so much now, such as the leaves and greens which are traditionally eaten in Crete. I shall not talk about this issue but Daan Kromhout may be able to expand further on this topic later when we have the data ready.

Obviously, we all know that there are many items that can be beneficial within the Mediterranean diet. We all think that there must be a healthy combination of these foods. Almost eight years ago, we published a paper on the Finnish, Italian and Netherlands' cohorts of the Seven Countries Study showing that a healthy diet, as calculated using the Healthy Diet Indicator, is associated with reduced mortality. This was especially so in the case of Italy. It was less clearly visible in the cohort in the Netherlands and this may also be the effect of the disadvantage of an observational study: in the Netherlands study, amongst the elderly men participating, the range of exposure was limited in terms of healthy diet and most of them ate an unhealthy diet. The Italians had a much higher score, which was associated with lower mortality rates.

As an epidemiologist, I can tell you that I do not spend all of my days fishing in my computer. However, we do have to acknowledge that carrying out observational research is not a fishing expedition.

The hallmark study on the benefits of a Mediterranean diet on recurrent myocardial infarctions is of course the Lyon Diet Heart Study.
Unfortunately, they did not have complete dietary information for all the participants in the experimental and control group, but the basic results indicated that they used more monounsaturated fatty acids (MUFA) and more alpha-linolenic acid and had higher fish fatty acid intake, and less linoleic acid. Looking at their data and their results on plasma acid, they say that the intake of alpha-linolenic acid is particularly important in explaining this reduced risk.

I would like to draw your attention to another more recently published study, which is the 'Indo-Mediterranean diet heart study'. This study is similar to the 'Lyon heart diet study' but was carried out in a larger population with 1 000 patients in an area in India. They used the end points fatal and non-fatal myocardial infarction and sudden cardiac death, and also obtained very convincing data on reduced risk in the patients in the intervention. They did have extensive dietary information available for their intervention group, and the intervention was aimed at eating more fruit and vegetables, nuts, whole grains, mustard and soy bean oil. It is to be remembered that this was being carried out not in a Mediterranean area but in India, and they had a higher PS ratio with this result. [Note by the speaker added in the proofs of the transcription: there are now serious doubts on the validity of this study- see the editorial 'Expression of concern: Indo-Mediterranean Diet Heart Study' by Richard Horton, The Lancet, p 354-356].

This is a secondary prevention study. We do not know, or perhaps we do not need to know, whether this would be successful in non-patients or in primary prevention. What about the possibility of using the Mediterranean diet in primary prevention of cardiovascular disease? To my knowledge, there are no studies on real events at end points, although, of course, there are many studies on markers for risk. When I looked into these studies, some of which we carried out ourselves, I found that they did not always look at the whole Mediterranean dietary pattern, even if they used the name, often simply taking elements from the diet such as using olive oil rather than saturated fat. They have often been small-scale studies. However, I think that it is worthwhile to discuss the results of these kinds of studies.

The first paper that I noticed was written by a group from Cordoba, who found some interesting results. They conducted a four-week intervention but they only used olive oil versus saturated fat and did not include other elements of the Mediterranean diet. However, they found reductions in LDL and HDL cholesterol and increased insulin sensitivity. This is an extremely good paper from Diabetologia written several years ago. In a smaller study, they found reductions in flow associated fat of dilatation, i.e. an improvement in endothelial dysfunction, and in some, but not in the biochemical, markers of endothelial dysfunction. Once again, the study was extremely interesting and well implemented, but an intervention of only four weeks and using olive oil alone.

Then, there was a group in Quebec, led by Professor Lemieux, which carried out a twelve-week intervention on 71 women, whereby the advice given was based on a Mediterranean dietary pattern with people increasing their use of olive oil alone. They found reduced LDL and reduced oxidated LDL, but they did not use a control group, which is necessary for such an intervention.

The second study on this slide was a study that I was involved in myself which was carried out in collaboration with the University of Groningen in the Netherlands. This was the Margarin Study, in which we tried to implement a small-scale Lyon diet heart study with risk factors as an end point. It was only a two-year study in 282 high risk subjects. We advised them quite intensively as to how to modify their diet into a more Mediterranean dietary pattern. Fish and fruit and vegetable intake increased, but if we looked at the risk factors such as serum lipids, hypertension or clotting factors, we could not find any associations. This was a pity. Perhaps the intervention group was small, but with 282 high risk patients, we would have expected some results. This was also a good study, because within this design we also randomised within linoleic acid margarine versus alpha linolenic acid margarine, but that is another story.

Professor Lairon will be happy today as I mentioned to him this morning that I shall also talk about the Medi-RIVAGE study, for which some results were published two years ago. They carried out an intervention in Marseille on 212 subjects. It was a randomised parallel trial and the outcome was the risk factors that have been published. They really did use a Mediterranean diet intervention, changing the fatty acid profile, increasing fish, fruit and vegetables and fibre, and the control diet was a low fat, low cholesterol diet. When we compare the results, they demonstrated larger reductions in total LDL cholesterol, larger reductions in fasting insulin and fasting glucose, triglycerides and postprandial triglycerides, and they also showed a reduction in the intervention group in body mass index.

Therefore, we have seen some developments in the field and some improvements can be seen. There is a study that has already been discussed by Dario Giugliano this morning that I would just like to mention again. It was a very good study. It concerned patients with metabolic syndrome and introduced the whole Mediterranean diet in their approach. They carried out a two-year follow-up for markers of endothelial dysfunction and vascular inflammation. They increased whole grains, fruits, vegetables, walnuts and olive oil with very interesting results, as we heard this morning. Therefore, I do not need to repeat the results but would like to point out that, once again, the Mediterranean diet group lost weight, as was the case in the Medi-RIVAGE study, sustained improvements in risk factors and improvements in the prevalence of metabolic syndrome.

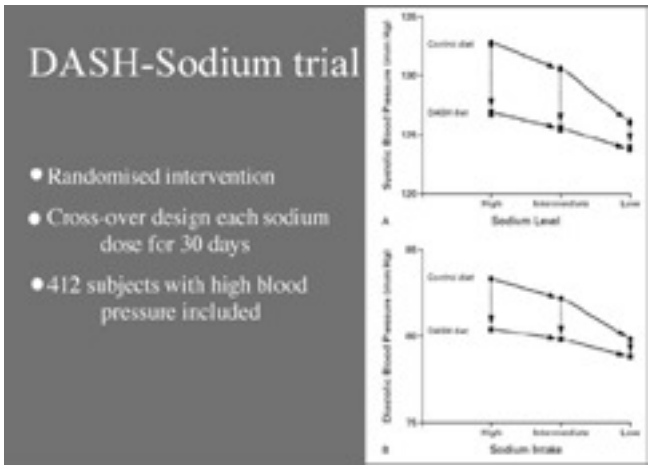
I read an abstract book from the Athens meeting last month that was organised by Professor Trichopoulou, and I found an abstract on a pilot study carried out by a Spanish group called the PREDIMED study. I have only read the abstract and therefore I do not know very much about it, but it is interesting as it is a fairly large study covering 600 people – elderly people with asymptomatic cardiovascular disease, or pre-risk factors or diabetes. It is a randomised trial with intensive behavioural counselling, a nutrition education on the Mediterranean diet, plus free supply of virgin olive oil or nuts, and there is a control group. The results are that compliance has been good and there have been reductions in blood pressure, LDL cholesterol, a marker of endothelial function and a marker of sub-clinical inflammation, and a rise in HDL cholesterol. Unfortunately, the abstract does not mention body mass, glucose or insulin, so I am very curious about this study. Perhaps there is someone in the audience who knows more about it.

Finally, for this part of our talk, I would like to refer you to Poster 26. We are planning a controlled intervention ourselves with rigorous control of food intake. We will compare it with a high MUFA diet and we would like to study the Mediterranean diet. We have not yet decided what to do about alcohol and we welcome your advice as to which Mediterranean diet we should use for this intervention.

With regard to the Mediterranean diet as a whole, there have been studies and there have been risk factors, but they have not been too large yet. There are also other important dietary patterns which may have favourable effects. The Mediterranean diet seems very good, also from observational studies, but there are other possibilities, such as the DASH diet, which is the dietary approach to stop hypertension, and the PORTFOLIO diet for the lipids.

This slide shows the DASH diet pyramid, which has already been tested and published several years ago. It contains plenty of vegetables and fruit, grains, seafood, low fat dairy, legumes, beans, nuts and seeds, oils and a small amount of sweets. I should mention that when we look at blood pressure and at coronary heart disease, there are some interesting results for the sweet category, especially for chocolate. We have found that the more chocolate a person eats, the better their blood pressure is and the lower their risk of coronary artery disease. Perhaps we should examine this category of sweets in more detail.

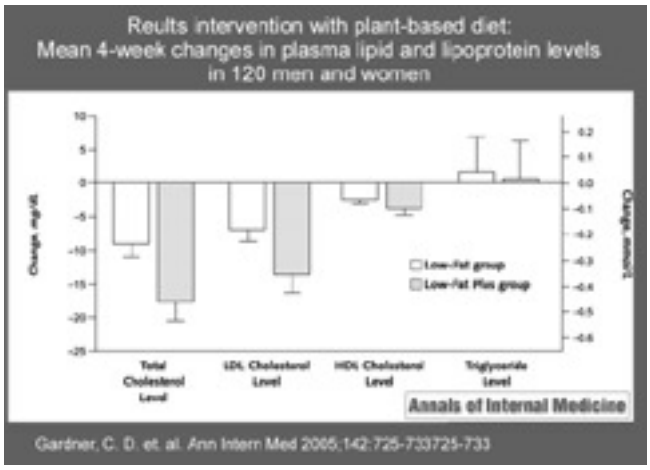
Here are the results of the additional DASH sodium trial, which is very important and which finally settled the dispute about sodium: sodium really is important for reducing blood pressure. Here we see the results for systolic and diastolic for the control diet. There is clearly a difference with the DASH diet with lower blood pressure, and this is true for every dose of sodium: high, medium or low. This was carried out on 412 subjects. Therefore, this is the DASH diet as it is advertised: vegetables and fruit, grains, some dairy products and no salt.



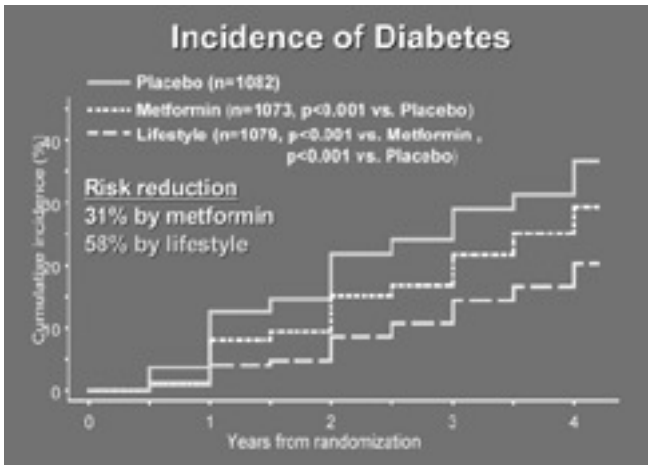
The second diet that I would like to discuss with you is also a diet that you must have come across. This is based on the work of people, such as David Jenkins, who worked on this Portfolio eating plan containing viscous fibres, soy protein, plants, cereals, and nuts such as almonds. He showed that the Portfolio diet may be as effective as statins and also reduces C-reactive protein, a sub-clinical inflammation. I saw a paper of his published in the 'American Journal of Clinical Nutrition' and there is a copy of it outside in the hall for you all.

David Jenkins noticed that his diet – which is quite rigorous because it contains all these types of foods which could be classified as 'functional foods' – may be slightly more expensive than just using the plant-based diet. This paper was published very recently, and I have not included it yet within my abstract. In this slide, we can see the four-week changes in plasma, lipids and lipoproteins in 120 men and women: a reduction in total cholesterol (both low fat diets – this is the plus group with the plant-based diet) and a larger reduction in LDL cholesterol. These results are quite impressive in the sense that there is not a large difference, so it is not as effective as Jenkin's diet, but it

only uses plant foods and grains which are readily available, so I believe that the implications of this are quite important.



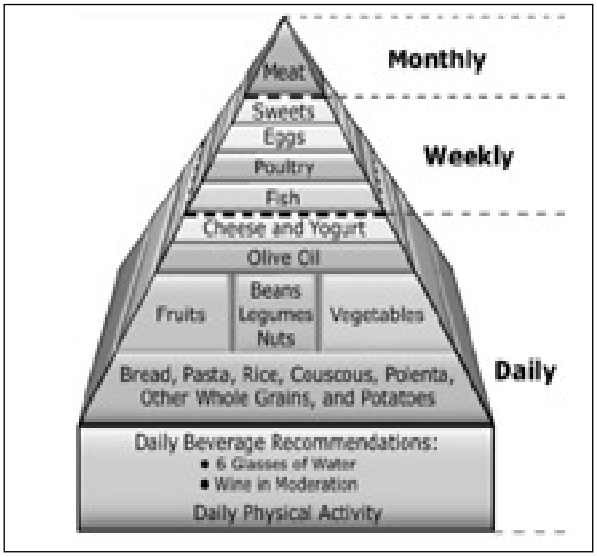
Insulin, diabetes, insulin-resistance and glucose are also risk factors for coronary heart disease. Therefore, when thinking about primary intervention it would be possible to consider these types of studies. This was explained very well by Professor Tuomilheto, so I will not discuss it too much. However, I would like to draw your attention to the fact that risk reduction by lifestyle was even greater than the risk reduction by metformin, and as Professor Tuomilheto demonstrated, after discontinuation of the study, the risk reduction by lifestyle was maintained, whereas with metformin it came down again to the level of the placebo group.



We carried out this type of study ourselves with Professor Tuomilheto in a small group in order to carry out more physiological tests. We did a randomised trial and used the national guidelines for a healthy diet with reduced saturated fat, increased vegetables and fruit and fibre, and we increased physical activity and supervised training. Of course, there was also a control group for the study.

Like Professor Tuomilheto, we only saw a 5% reduction in body weight on this programme, although when looking at the results of the 2-hour glucose, which is an independent risk factor for coronary heart disease, we see a steady increase in 2-hour glucose for the control group as the cohort becomes older, and a very large decline during the first year for the intervention group, and this difference between the two groups remains. Impaired glucose tolerance almost disappears in the intervention group, at least during the three-year follow-up.

One of the things that we have been discussing this morning is how we can make our interventions more cost-effective, and this is an extremely important issue. This slide includes the Mediterranean diet here, like the pyramid that you will all know, and includes physical activity here, beverages over there, wine and glasses of water over here, cheese and yoghurt are here, and it does not include any negative comments on tea and coffee.



The point that I would like to make is that all this may be successful in the Mediterranean area and is more or less similar to what the people there are eating know, or at least to what their grandparents ate, but to change the populations in the Netherlands in such a way will demand significant work and resources. Therefore, whilst we agree that this whole pattern is very important, we would still like to understand which one of all of these layers is crucial and should be of primary focus, as it is quite difficult for many to eat a Mediterranean diet in our country.

Therefore, more interventions of good methodological quality are needed (and we are trying to carry out a small one ourselves) because interventions really are the proof of the pudding. Perhaps I do not need to remind you about the confusion that we have now, for example, on the use of vitamin E and beta-carotene, observational studies that show preventive effect, intervention studies that show nothing, or about hormone replacement therapy? Or do we know enough and can we simply tell our people to eat as close to a Mediterranean diet as they can? I do not know. Which components are really essential? I would like to know, but I would also like to know which combinations are best as I am convinced that the key lies within the combinations.

In the Netherlands, we have an ongoing debate regarding whether or not we should use more or less dairy products. We believe that it may protect against diabetes, there is some evidence to suggest that it may not be good for hormone-dependent cancers, and there is some debate as to whether it is good or bad for osteoporosis. It is an interesting discussion because, as you know, dairy products are not part of the Mediterranean dietary pattern.

Finally, who would be interested in funding a large-scale primary prevention study on the Mediterranean diet with disease end points such as cardiovascular diseases, as we need to know where we can get the money for such research? Perhaps we can convince the European Union to fund such work. In addition to well-know European observational cohorts such as EPIC, we also need further intervention studies. Thank you.

Questions

Franco BERRINO
I would like to discuss the basis of your parameters. You included potatoes and polenta. I know that potatoes are very high on the glycaemic index and that maize is very high in starch and I wonder whether these two arguments bear any relation to the Mediterranean tradition. Perhaps the chairman can say whether the Mediterranean tradition included potatoes. I think that there are sometimes strange definitions of the Mediterranean tradition.

Edith FESKENS
Perhaps the chairman can answer first as I believe that potatoes are not really part of the Mediterranean tradition.

Salvatore PANICO
Potatoes are definitely not part of the Mediterranean tradition.

Edith FESKENS
Potatoes are the most important staple in our country. The glycaemic index of potatoes varies according to their preparation, and this can be confusing. In general, our approach for the dieticians is that they reduce the potato intake slightly and replace them with pasta or brown rice. This is the practical approach in our country. As far as couscous and polenta are concerned, they are not consumed much in the Netherlands, so I do not know much about them. As far as I know, polenta is typical of northern Italy. I do not believe that it is fibre rich.

Member of the audience
We need to refer to the traditional Mediterranean diet as it was in the 1960s in Crete, as this was the best example. However, we need to realise that these people at that time were very poor peasants from a small village in Crete with a very traditional poor diet, and these people were farmers and had very high levels of physical activity. It is a good reference, but if you would like to plan an intervention study now, with people with very low levels of physical activity, I believe that it is far more complex. Therefore, I believe that we do need to refer to the Mediterranean diet so that everyone uses the same parameters, but it needs to be adapted to context, as few would tolerate the traditional Mediterranean diet. Furthermore, if you wish to transfer the Mediterranean diet to a northern country, this also presents some challenges. For example, in the south we do not use the potato much as we use more greens. In the north, the situation is different. This merits important discussion.

Edith FESKENS
I would like to add, before someone else asks me, that potatoes are the most important source of vitamin C in our country, not because they contain large quantities of vitamin C but because we consume so much of them, far more than vegetables and fruits. Therefore, we have to be very careful not to throw out the potatoes and replace them with pasta. We need to maintain a balance.

Member of the audience
I have two questions relating to fish. Could you clarify whether there was any fish in the Indo-Mediterranean diet?
Secondly, we have heard about GISSI, but there were two trials on fish in the United Kingdom: DART 1 and DART 2. Whereas DART 1 demonstrated a protective effect, DART 2 showed a significant adverse effect in the fish group. Do you have any views on this?

Edith FESKENS
With regard to the Indo-Mediterranean diet, I would need to refer to the paper as I did not pay too much attention to fish consumption, although I assume that they did use fish because they increased their long chain PUFA and I would imagine that this came from fish as well as oils, and I believe that the intake increased.

In relation to your question about fish, the evidence from the GISSI Prevenzione, and from some other trials examining sudden cardiac death, is quite impressive. In reference to the DART 1 study, I did not find anything for dietary fibre. I do not know about the DART 2 trial. I think that what is becoming clear is that fish does not work very well for non-fatal end points, but it is far clearer for the arrhythmia-related end points in sudden cardiac death. Therefore, I think that the primary end point in your trial affects the relative risk that you will observe in a fish intervention. However, I cannot remember exactly how DART 2 worked. I cannot imagine that increasing fish or n-3 fatty acids is detrimental for any disease that I know of.

The previous member of the audience
I cannot remember either, although it does raise LDL.

Edith FESKENS
It raises LDL, but it has to be an extremely high dose, so it would be important if you were using fish or fish oil alone. The American Heart Association recommends that 3 grams of fish oil per day is acceptable, although it says that the person should be under a physician's supervision, and up to 1 grams per day is recommended for any person, and that is reasonable. I have not seen any evidence of increased LDL or increased glucose levels with these moderate levels.

Member of the audience
I would like to add a comment regarding DART 2. As far as I know, they had difficulties with their study because they needed more than seven years to recruit their patients and they had to stop the trial for one year because they did not have enough funding. As a result, we do not know what happened to the patients followed by general practitioners.

Elio RIBOLI
Perhaps my question should wait until the final session, as I think it would be useful to discuss on why we are discussing the Mediterranean diet. It is one thing to discuss what the Mediterranean diet is from a historical and gastronomy point of view for which we need to look according to region and time: potatoes and tomatoes were not consumed that much in the 1700s in southern Europe.

The other issue is which components of a Mediterranean diet help prevent chronic diseases. There is a risk that sometimes the debate on what is historically accurate replaces the debate on which components help to prevent cardiovascular diseases.

Mediterranean diet and CVD: beyond cholesterol

Angela RIVELLESE
Department of Clinical and Experimental Medicine, University Federico II, Naples, Italy

Good afternoon. Firstly, I would like to thank Dr Panico and the organisers of this conference for inviting me to speak about the Mediterranean diet and cardiovascular disease: beyond cholesterol.

Like the previous speaker, I would like to start by discussing the Seven Countries Study, which is an obvious starting point when discussing the Mediterranean diet. Since the beginning of these studies, it was clear that there was an extremely significant difference for coronary heart disease mortality between Mediterranean and non-Mediterranean countries. This difference was ascribed to the different dietary habits. For many years, the beneficial effects of the Mediterranean diet was attributed mainly to its hypocholesterolemic action, but although this action is important, it is not enough to fully explain the beneficial effects of the Mediterranean diet in reducing cardiovascular risk. In fact, in the same Seven Countries Study at the same level of plasma cholesterol, there was a very large difference in mortality for cardiovascular disease, which suggested that plasma cholesterol is not the only way to explain differences in cardiovascular mortality. Moreover, the very impressive effects of the Mediterranean-style diet used in the Lyon Diet Heart Study on cardiovascular and non-cardiovascular mortality were obtained without any change in plasma cholesterol. Therefore, we have to consider whether the Mediterranean diet may act in reducing cardiovascular risk not only for its action on plasma cholesterol but also because this kind of diet may beneficially influence other mechanisms.

In my presentation, I shall focus especially on the possible effects that the most typical components of the Mediterranean diet may have on some of these mechanisms. In particular, I shall focus on insulin sensitivity, postprandial metabolism, both lipid and glucose metabolism, which are now considered to be more than simply new and emerging cardiovascular risk factors. Of course, one of the main components of the Mediterranean diet is monounsaturated fat, derived mainly in this kind of diet from olive oil. The beneficial effects of monounsaturated fat compared to saturated fat on classical risk factors, such as blood pressure and plasma cholesterol, is well-established, but what are the effects of a diet rich in monounsaturated fat on insulin sensitivity, and why is the possibility of influencing insulin sensitivity considered to be so important?

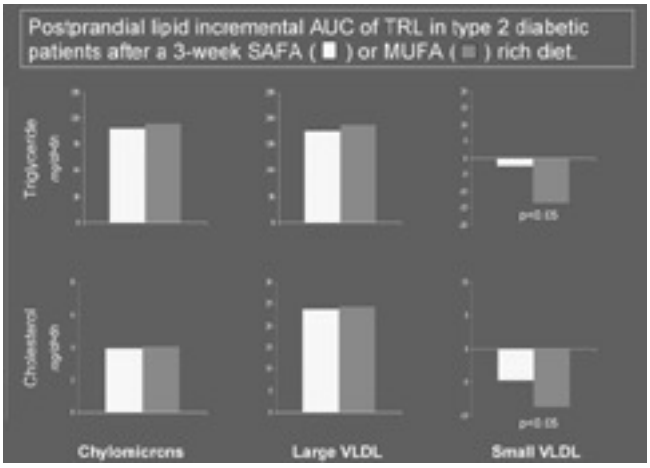
Insulin resistance is now considered to be a very well-established risk factor. Insulin resistance may lead to artherosclerosis through many mechanisms, some very well-known as blood glucose or plasma lipid abnormalities, and other newer, such as oxidative stress, muscle cell proliferation, and so on. Therefore, the possibility of modulating and reducing insulin resistance means the possibility of improvement of all these other mechanisms, resulting in a synergistic amplified effect in the reduction of cardiovascular risk. We tried to clarify this point – the possibility of influencing insulin sensitivity by substituting monounsaturated fat with saturated fat – in this multi-centre international study, called the KANWU study, performed in five different centres in Europe.

In this study, 162 healthy people were randomly assigned to two kinds of diet: a diet rich in saturated fat, with approximately 17% of total energy from saturated fat, and a diet rich in monounsaturated fat, with approximately 22% of total energy from monounsaturated fat. At the end of a three-month period, some parameters, including insulin sensitivity, were evaluated. In relation to the effect on insulin sensitivity, the high saturated fat diet significantly deteriorated insulin sensitivity in these healthy people, whilst the high MUFA diet significantly improved insulin sensitivity, with a significant difference between the two diets of more than 20%, although this only occurred in the group with a moderate total fat intake, less than 37% of total energy. The beneficial effect of the high monounsaturated fat diet was completely lost when the total fat intake was higher than 37% of energy. Therefore, it seems that one component of the Mediterranean diet – monounsaturated fat – is able to improve also insulin sensitivity in healthy people, but only when the amount of total fat is not very high.

I do not wish to speak about fish or fish oil too much, but I would like only to underline that in the KANWU study, where people following the two diets were randomized to a moderate supplementation with fish oil [2.7 grams per day] or placebo, fish oil supplementation did not change at all insulin sensitivity. Therefore, the beneficial effects of fish oil on the reduction of cardiovascular risk must be related to other effects of this dietary component.

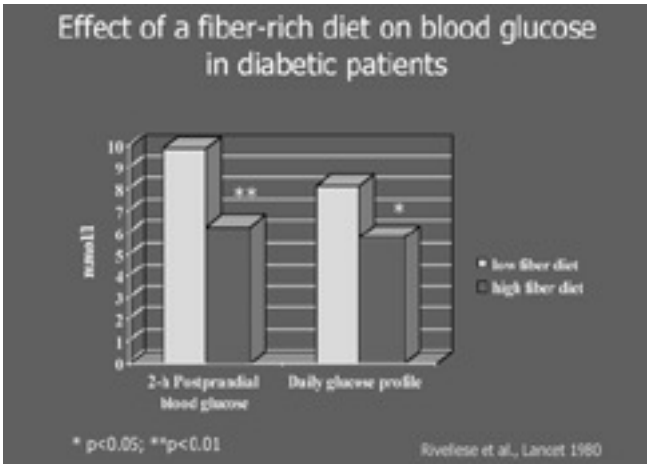
Another new and emerging cardiovascular risk factor is postprandial lipid abnormalities. This aspect has attracted a lot of attention over the last few years because human beings spend large periods of time in a postprandial state. Abnormalities in the postprandial metabolism are mainly characterised by an increased concentration and prolonged residence time of small particles of remnant particles in particular, both of endogenous and exogenous origin, and these particles are considered to be highly atherogenic as they can trigger the atherosclerotic process at different levels. In truth, the effects of monounsaturated fat compared to saturated fat on postprandial lipid metabolism has not been studied in depth, and the results of these studies were extremely conflicting, with some showing a higher postprandial chylomicron increase after the MUFA diet, but especially after acute experiments.

We have started to study this matter using the same diet as that used in the KANWU study, this time in type 2 diabetic patients with a cross-over design. The two diets were followed for three weeks. Here are the preliminary results on 11 type 2 diabetics in relation to the six hour postprandial incremental area of chylomicrons, large VLDL and small VLDL, after a standard meal rich in saturated fat, which were given to patients at the end of the two dietary periods.

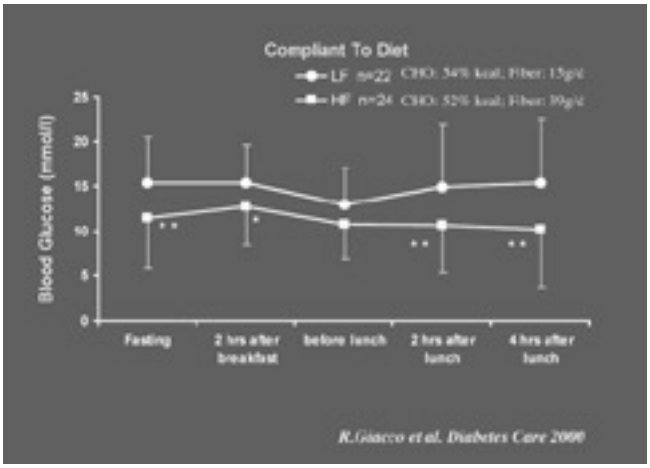


It can be seen that there is no difference for the cholesterol and triglyceride incremental areas with respect to chylomicrons and large VLDL. In relation to the small VLDL, which includes the large parts of remnant particles and which tends to decrease during the postprandial period, there is a significant high reduction after the MUFA diet, which suggests that a monounsaturated fat rich diet may induce a small but significant decrease in these remnant particles. Therefore, to summarise the first part of my talk, it can be said that monounsaturated fat, as opposed to saturated fat, certainly reduces LDL cholesterol and blood pressure, but may also improve insulin action and may reduce postprandial lipoprotein remnants.

Let us consider the other typical component of the Mediterranean diet: dietary carbohydrates. I think that it is very important to evaluate the possible beneficial effects of carbohydrates on insulin sensitivity, postprandial blood glucose or lipid metabolism, because there have been several studies over the last few years that have shown that carbohydrates may have a detrimental effect on these parameters. When we talk about carbohydrates, it is important to remember that carbohydrates are a very heterogeneous family of foods. It should also be remembered that the quality of carbohydrates is more important than the quantity. In fact, it is only when both of these aspects are considered, using the glycaemic load of the diet, that a clear relationship with cardiovascular risk is evident, in the sense that the higher the glycaemic load of the diet, the higher the cardiovascular risk, at least in overweight or obese women. Therefore, it is important to reduce the glycaemic load of the diet, which may be achieved by choosing the right carbohydrate rich foods, that is foods rich in dietary fibre. Again, it is important to look at the possible effects of this kind of diet not only on LDL cholesterol, blood pressure and so on, but also on insulin sensitivity, postprandial blood glucose and postprandial lipid metabolism. It has recently been shown that a diet rich in fibre with low glycaemic index foods is able to improve insulin sensitivity significantly, also in type 2 diabetes patients, characterised by a long-standing state of very high insulin resistance, which is very difficult to change.

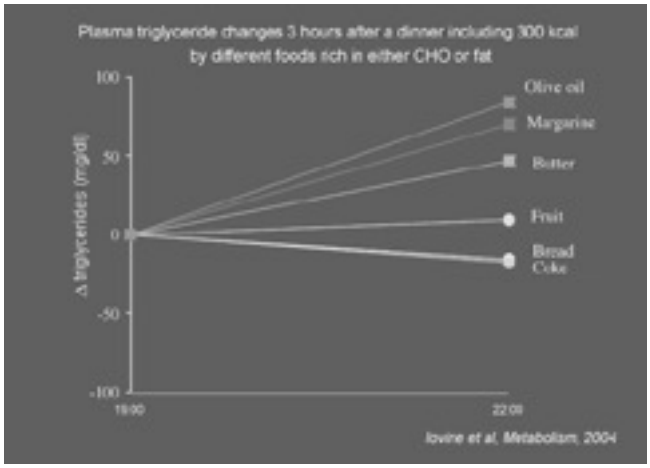


Moreover, one of the most important effects of this kind of diet is the improvement of blood glucose control. This improvement is mostly due to the fact that this kind of diet is able to significantly reduce postprandial blood glucose levels. In this study, after a short period of intervention, there was reduction of more than 20%. The effects of this kind of diet are also evident after a longer intervention period, as shown in the study on this slide.



We can see that after six months on a high fibre diet, type 1 diabetic patients show a daily blood glucose profile that is significantly lower compared to the daily blood glucose profile of type 1 diabetic patients on a low fibre, high glycaemic index diet, and this result is even more significant in the postprandial period. The relevance of this effect on postprandial blood glucose, which is also present in non-diabetic subjects, was not really understood when these studies were performed. Only recently this aspect has been fully understood, when it has been demonstrated that postprandial blood glucose levels may be considered as an independent cardiovascular risk factor. This effect has been further emphasised by the results of the acarbose: the treatment with acarbose reduces significantly the incidence of cardiovascular events compared to placebo. These results come from a post hoc analysis; therefore, they should be considered with prudence. However, it is important to remember that acarbose reduces postprandial blood glucose levels and that this effect is very similar to the one obtained with foods rich in fibre and with a low glycaemic index.

Another point that I would like to consider is the effect of carbohydrate rich foods on postprandial lipid metabolism. We already know that high carbohydrate diets increase fasting triglycerides and this has been considered an adverse effect with respect to cardiovascular risk. However, very little is known about the effects of carbohydrates and the different kinds of carbohydrates on postprandial lipid metabolism. We have started to examine the possible effects using acute experiments looking at the changes in triglycerides in hypertriglyceridemic subjects after a standard dinner containing 300 calories derived from different foods rich in either carbohydrates or fat.



It can be seen that 3h changes in triglycerides are significantly higher in the group receiving foods rich in fat compared to the changes in triglycerides obtained after foods rich in carbohydrates. This suggests that during the postprandial period, at least, the main determinant of the rise in triglycerides is the amount of fat rather than that of carbohydrates. Moreover, the quality of the carbohydrates may also be important, not only for the purposes of moderating blood glucose control after a meal but also with respect to postprandial lipid metabolism.

This is shown in another acute experiment where the rise of plasma triglycerides, of APO B100, which is the apoprotein of endogenous lipoproteins, and the rise of Apo B48, which is the apoprotein of exogenous lipoproteins, are significantly lower after a meal containing a large proportion (17 grams) of slowly digestible carbohydrates compared to the increase of these parameters obtained after a meal with the same total amount of carbohydrates, but with a lower proportion of slowly digestible carbohydrates.

This suggests that the quality of the carbohydrate may be important in modulating postprandial lipid response in relation to lipids of both exogenous and endogenous origin. Therefore, to summarise this second part of my presentation, it can be said that high fibre low glycaemic index foods certainly reduce LDL cholesterol, but they may also improve insulin action and reduce postprandial blood glucose as well as postprandial exogenous and endogenous lipoprotein.

In conclusion, I think that it is possible to say that a Mediterranean diet or, more in general, a healthy diet, which should be tailored to fit the dietary habits also of non-Mediterranean countries, may have an impressive effect on the reduction of cardiovascular risk since the ideal combination of the different foods acts synergistically throughout different mechanisms. However, I believe that it is also important to stress that when we speak about the Mediterranean diet, we are referring to the Mediterranean diet followed by Mediterranean people of, at least 50 years ago. If we believe that it is important to adopt this kind of diet, it is also essential to consider that we should try to optimise this kind of diet by choosing the foods that maximise the reduction of cardiovascular risk. I would further like to stress that 50 years ago, levels of physical activity were much higher and it is therefore necessary to adapt the amount of food to the actual needs.
Thank you very much for your attention.

Questions

Member of the audience
I would like to make a comment on your first slide, which was a study looking at cholesterol and heart disease mortality across Mediterranean countries. I think that this study underestimates the true impact of saturated fat because it appears to show the same cholesterol levels with much lower mortality in the Mediterranean than there is in the north of Europe. However, I think that this is because they relied on a single measure of cholesterol, whereas if there were a regression to the mean, the lines become shorter and steeper, and then it is no longer clear whether there is a real difference at each cholesterol level. We should not downgrade the major importance of saturated fat and cholesterol.

Angela RIVELLESE
I completely agree. I do not wish to suggest that the hypocholesterolemic action is not important, but we must also consider the other possible effects in order to be able to choose the right foods and adopt a diet that can maximise its effects on the reduction of cardiovascular risk.

Didier CHAPELOT
I would like to make a comment on the importance of the postprandial diet. It is really related to the first question. In general, HDL or LDL cholesterol levels are considered as independent factors because they are measured at the fasting state and it is a reflection of lipid synthesis but in fact, it is very important, it happens after meals every day, which is also the case for glycaemia, so fasting glycemia is an artefact, which only occurs for a few hours at the end of the night. The same can be said for lipids. After breakfast, the baseline for triglycerides will not be reached until the end of the night. Of course, it is possible to measure triglyceride in the fasting state at 7 o'clock in the morning, but it is just a reflection. What is most important is what is happening after every meal in terms of metabolic response. In this respect, abnormal accumulation within the circulation of glucose and also triglyceride with lipoprotein is the most important thing in terms of long term effects on health. This is also the reason why, depending on the study, markers that are measured in the fasting state tend to be different because what is important is the dynamic during the postprandial state, which is effectively much more difficult to measure.

Angela RIVELLESE
The problem is the measurement of these parameters in the postprandial state.

Member of the audience
Do you have any data enabling a distinction between different categories of fibres, such as soluble fibres or insoluble fibres coming from fruits or whole grains, on these effects?

Angela RIVELLESE
In relation to the metabolic studies, soluble fibre rich foods are more effective. However, it is also important to remember that in observational studies, and epidemiological studies, the relationship with cardiovascular risk is particularly present with cereal fibre. Therefore, I think that both are important and act through different mechanisms.

Cardiovascular disease preventable fraction in the population through adherence to Mediterranean diet

Salvatore PANICO
Dipartimento di Medicina Clinica e Sperimentale, Università di Napoli, Federico II, Naples, Italy

I would like to begin by talking about one of the main issues of this meeting: moving from research to action. One of the questions that need to be asked is whether it is necessary to promote dietary change when we can rely on effective drugs which favourably modify these factors. We already heard the story about the magic hormone replacement therapy, which was considered for decades to be a solution for the prevention of coronary disease in post-menopausal women. Now, it is the era of statins. We know that they are very potent and effective drugs against cholesterol, inflammatory markers, blood pressure and even cancer. Public health has the major task to qualify all these pieces of scientific information as effective and convenient on the large scale as well as to raise the issue of feasibility both in terms of costs of and compliance to the suggested solutions.
I would like to show you some slides looking at the situation in the United States but which can also be applied to Europe.

If we take the main three risk factor distribution statistics and apply the current evidence-based guidelines on the risk factors, using either American or European guidelines, there are large amount of people between the ages of 45 and 64 taking more than one drug – and if we look at those over 65, there are very few people without drugs. The problem is that with all these indications, the situation can become confusing and it becomes possible to lose the desired direction. We also know that there could be a pill (known as the polypill) that could prevent 80% of coronary heart attacks: a pill composed of all of these drugs, which are effective and, when combined, could reduce the risk of strokes by 80%. We also know that we could use selected food items as pills (known as the polymeal), even though this idea was not taken seriously when it was initially published in the British Medical Journal. Therefore, we are facing the possibility of extremely important levels of prevention of coronary heart disease, and cardiovascular disease in general, simply by taking a pill or by using food items like components of a pill – you would take a clove of garlic and a piece of chocolate like a pill.

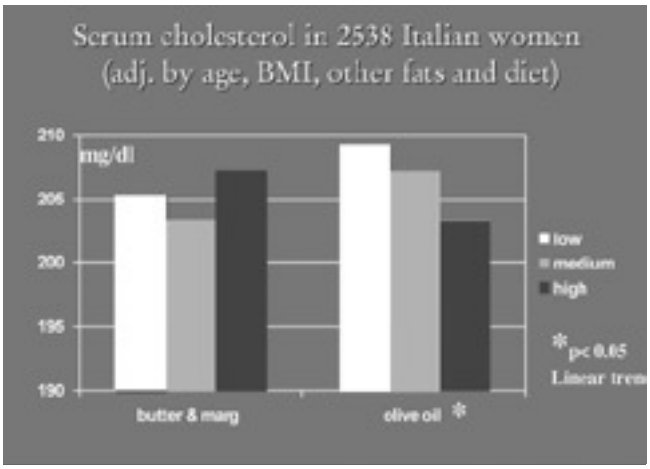
The problem is that we like to eat for pleasure, especially in Europe, and food cannot be dealt with like a medical remedy. Therefore, if we wish to have a basis for reasonably effective preventive action in public health, we must take into account that diet and dietary habits need to be considered as a whole. There are some issues which need to be considered, such as the modernity of the Mediterranean diet, which is now very different from the original Cretan diet. Is it still protective? Then, there is the problem of the visibility and the application of this diet. There are two main problems involved here: one is internal and derives from the fact that even in Mediterranean countries, investors in industrial food preparation rank profit as their top priority above consumer sales. The other problem relates to external issues, such as the transferability of the Mediterranean diet to other cases and contexts. There is also the problem of lack of experiments, as already suggested today: there are no experiments in the use of the Mediterranean diet using our end points. Do we need this? Then, there is the problem of looking at the size of the Mediterranean diet effect now. For this reason, I will start with some recent data on a Mediterranean cohort study within the framework of the EPIC Italy collaboration and which is important in order to establish the weight of the argument for the modern Mediterranean diet. This data was collected in the 1990s.

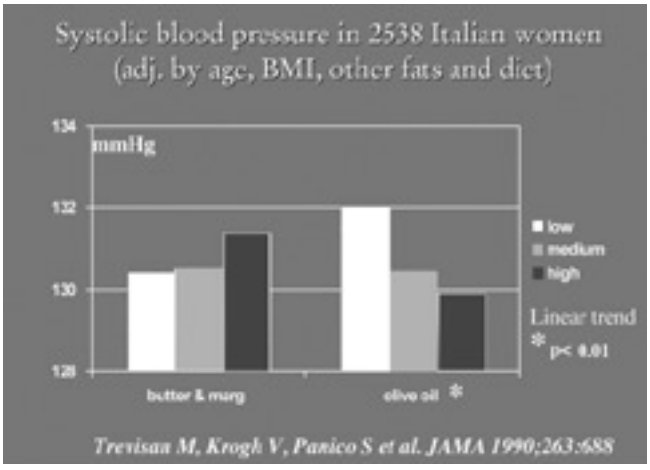
The EPIC Italy collaboration included centres spreading from northern Italy to southern Italy. These are the groups who produced this data and I would like to thank them for this data. These are the numbers: there are almost 50 000 people under observation and another 52 000 women. For the women cohort, we have tried to study the incidence of cardiovascular disease and the effect that diet has on it. They have used a dietary lifestyle questionnaire, anthropometry, blood pressure, and a vital statistics follow-up. This slide shows the well-known Mediterranean index score and these are the 9 items that we have used to compose the score, whose origin comes from the work of Greek colleagues, using the median value of the distribution of these components and using a score of 0/1 according to the position in respect to the median value.

This is what has been done to collect and validate data on the incidence: use of hospital admission data and in-cohort surveys. We know that incidence data are crucial for cardiovascular disease because case control studies are difficult to interpret. As to mortality we have examined all fatal cases, starting with the death certificate and then assigning the diagnosis. As to incidence of non-fatal cases, we have validated the data case by case according to medical notes. We have observed 129 cases of ischemic heart disease; then we have performed a statistical analysis on the incidence data, using the Mediterranean index as the variable to evaluate, and making adjustments for age, location, status, education, body mass index, levels of physical activity, smoking, total energy intake, risk factor status and history of angina. We have used different models, including treatment for risk factors, with no meaningful changes of the results. There is significant reduction of ischemic heart disease incidence according to the different tertile of distribution of the Mediterranean index: the risk is almost halved in the group with the highest adherence to the Mediterranean style.

We have applied this risk estimates to achieve attributable risk at population level to know something more in terms of public health. Going through from the first tertile, which includes the diet scores up to 3 (an indication of the lowest adherence to the Mediterranean style), it is possible to prevent 28.5% of coronary events: these events include myocardial infarction and coronary re-vascularisation.

However, as known by epidemiologists, there are some problems of precision and interpretation of the estimate which are linked to the use of a simple formula. Firstly, it is problematic to extrapolate population attributable risk from epidemiological studies. Sometimes, all these risks are calculated using components deriving from different sources, which is not the case here. Another issue is the lack of confidence intervals: We have improved the precision of the estimate by using a specific multivariate formula that enabled us to adjust all the variables together in the evaluation of the population attributable risk. We estimated a 27.4 preventable fraction in the passage from the low- to the high adherence tertile: we had a high proportion of the events among the exposed in the first tertile (including the women who followed less a Mediterranean-type diet), more than 61%.

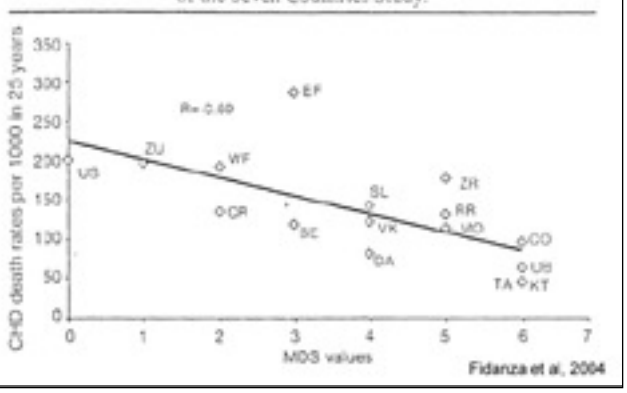




These results come from the first investigation on a female Mediterranean cohort, as most cohorts are male, or if they are female, they tend to be in North America or Central Europe. This data confirms that in the 1990s, women on what we know now as the modern Mediterranean diet, whilst not the traditional one, were still protected. This was consistent with data from studies on random samples of the Italian population 15 years ago, which showed that, the major risk factors, like cholesterol, systolic blood pressure, and glycemia, were lower in people consuming more olive oil than butter and margarine, as indicator of a Mediterranean dietary style.

To look at the Mediterranean picture, examining recent data from Greece and Spain, in case control studies, we see that adherence to Mediterranean diet, measured through a Mediterranean index, provide protection toward acute coronary syndrome. In a recent analysis of the data from Seven Country Study, the Mediterranean score provide comparable results for risk reduction in men.

FIGURE 1
MDS values vs CHD mortality in the 16 cohorts of the Seven Countries Study.



Therefore, given the risk reduction through the Mediterranean diet, the one we have now, it appears that there is no variability in the three Mediterranean countries as far as coronary disease is concerned. I think that it is reasonable to assume that the estimation we have provided (almost one woman over four) can be saved from ischemic heart disease just going through a feasible passage: increasing consumption of at least one or two of the nine dietary items characterising the Mediterranean type of diet. This is of public significance.

For the purposes of comparison, I would like to talk about the Nurses study, which also took into account this relationship with attributable risk. Whilst it did not concentrate on diet alone, having a diet score in the upper two quintiles, non-smoking nurses performing vigorous exercise have a risk reduction higher than ours with 54% of population attributable risk.

Another comparable estimation of the risk reduction, performed in a Dutch population, indicates that the prevented proportion of individuals with chronic disease - using fruit and vegetable indicators - is about 16% (focusing on mortality from cardiovascular disease).

I have two final comments and then we shall open the discussion.
a) Even in "modern times" Mediterranean type diet appears a feasible, safe and effective tool for preventive action against cardiovascular disease, especially coronary, in the population living in the Italy, Spain and Greece (the olive oil congregates).
b) The size of preventable fraction of cardiovascular disease – mainly coronary - is significant and approximate one third of the total events, for simple changes in dietary habits.
c) This estimate provides important public health information to decide on the adoption of more "chronically oppressive" tools like drugs and selected food items promotion.
d) Eating for better health still may means eating to be pleased and happy.

Are there any questions? Perhaps you would just like to have an open discussion.

Questions

Frank HU
That was very interesting data. I have a question regarding the individual components of the Mediterranean diet. As you know, the overall dietary score in the original Greek study had significant benefits in terms of total mortality, cancer and cardiovascular mortality. However, none of the individual components showed any significant effects. Did you look at the association between individual components of the Mediterranean dietary score and coronary heart disease?

Salvatore PANICO
We carried out analyses relating to this, and we know that the ratio between monounsaturated and saturated fat and alcohol consumption are the main significant components of this score, at least as far as our cohort is concerned.

Member of the audience
This question is very interesting. With regard to the "Mediterranean diet" - also known in the south of the Mediterranean and the south of France - the onion and garlic are often regarded as the most important food. One often intends to say that the presence of garlic and onion in a house moves away the disease. It is completely possible to live by consuming olive oil and flours of durum wheat, like in 'couscous' or bread. My parents and grandparents lived with onion, garlic, bread and olive oil. Garlic was evoked like a food making it possible to decrease the blood pressure but the onion also reduces the sugar rate in the diabetes. They are important food of the Mediterranean meal.

Salvatore PANICO
I can confirm this empirical experience and scientific evidence on the protective factor of onions and garlic on these two risk factors. I would like to say that when we talk about the dietary index, we are discussing comprehensive patterns. If we wish to talk about single food items, this is another matter. We need to know much more about all of them, and the extent to which people would be ready to start consuming certain items on the basis of recommendations. Would anyone else like to make a comment?

Edith FESKENS
I would also like to comment on this matter. In relation to garlic, we have seen that there has been an analysis showing some beneficial effects. It is being sold in our country as 'The Pill', and I know that in our elderly men's study over the seven countries, many people use these garlic pills even though they do not have any disease. There was greater opportunity to study the health effect of onions and we carried out some extensive studies on the micronutrients amongst these components in the diets, such as red wine, apples and onions, and we showed that the higher the intake of the flavanols, the lower the risk of coronary heart disease. In our study, this was mostly due to consumption of tea and apples, but we did not consume as many onions so they were not studied in the same amount of detail. However, I think that it would be really interesting to see what is in these vegetables and fruit.

Member of the audience
I have a question for the whole panel. If we are now promoting the Mediterranean type diet, is it a diet that everyone, from children to the elderly, should follow? There are so many differences between people, their habits, whether or not they smoke, their genetic make-up and metabolisms and so on. Should we really be promoting one diet?

Roberto MARCHIOLI
I agree with you that there are different Mediterranean diets. If we think about the diets in Greece and Italy 50 years ago, we can see that they were very different from diets in those countries today. However, as Salvatore Panico said earlier, the so-called Mediterranean diet is good for health.

I would like to answer your question with a question that a cardiologist asked me when we were asking cardiologists to join the GISSI Prevenzione trial. He asked: 'But why are we going to study fish oil in Italy when we have so much olive oil?' My answer to him was that as we had so much olive oil, perhaps we needed some fish oil. There could be a mix of the two situations: cultural dietary habits associated with lower cardiovascular mortality; and in addition, an improvement of the diet, with some pieces taken from other protective dietary habits.

Angela RIVELLESE
I think that it is important to promote not necessarily a Mediterranean diet, but a healthy diet on the basis of all of our knowledge. This diet then needs to be tailored to fit the dietary habits of different populations. Some of the typical and most important components of this diet should be a reduction of foods rich in saturated fat compensated by an increase in foods rich in fibre and using the low glycaemic index. This is the basis, and all the other minerals and vitamins come naturally with this kind of dietary pattern. This may seem very simplistic, but I think that it is important to ensure that the message is clear.

Edith FESKENS
I am a member of a national health council for the recommended dietary allowances and I have been on the committee for dietary fibre. I think it is clear that what we advise in terms of nutrition for adults is different from what we advise for children. Of course, it is necessary to look at the personal make-up, age and body weight of each person.

Speaking of body weight, one of the intriguing things I have found is that people on the Mediterranean diet had a lower body mass index and as a result, they lost weight. This is intriguing because it is important and it is also contradictory to what I remember seeing. For example, in the EPIC cohorts in Spain, the prevalence of obesity in women and children is quite high. Therefore body weight is very difficult to manage, but it does have to be managed as a first priority.

Finally, with regard to genetic susceptibility, we all carry the genes that make us susceptible to type 2 diabetes and obesity, as Jaakko Tuomilheto explained this morning. There are people who are more susceptible to certain types of cancer or other types of disease. We need to look at this in more detail, but I think that this would be very costly and we need to provide advice to the general public. There may be people who do not respond very well, but this information is not dangerous to anyone. However, we can be optimal by refining what we already know, such as typical genetics, but this is a difficult area and I do not predict that there will be any real progress in this area in the next few decades.

CVD diet visavi other CVD risk factors

Göran BERGLUND
Department of Clinical Sciences, Malmö University Hospital, Malmö, Sweden

I am the chairman of the last session (CVD – II). We will start the session on dietary factors and cardiovascular disease. I shall start with an introduction to put dietary factors into perspective along with the other cardiovascular risk factors of which you are aware, and look at how important diet is compared to smoking and so on. Margaret Leosdottir, from Iceland, will then continue with energy and fat intake and their relationship to cardiovascular disease. Rodolfo Saracci will subsequently present a recent paper on the EPIC heart study. Finally, Dr Schulze from Germany will talk to us about dietary patterns and the risk of cardiovascular disease.

I would encourage everyone to ask any questions they may have as they arise at the end of each presentation.

Let us quickly look at the well-known array risk factors of cardiovascular disease: age, male gender, smoking, blood pressure, lipids, diabetes, low physical activity, low social status, and markers of inflammation such as the CRP. We have already discussed dietary factors and we have seen many slides on this subject today. They are: the high intake of saturated fat, the low impact of monounsaturated and polyunsaturated fat, low intake of fruit and vegetables, low intake of fibre, and high energy intake, which is something that we would also like to present some data on.

The epidemiological cornerstone for the dietary-cardiovascular relationship starts with the Seven Countries Study, as already mentioned by several speakers here today, and I will provide some more critical information on this study as it has been so very important to the whole area of dietary recommendations for the last 20 years.

We all know the Western Electric study from the Stamler group, the Framingham study, and the Oslo Intervention study, all three of which were carried out in 1981. The latter showed a 50% reduction of the multivariate intervention, data that has been very difficult to replicate.

I will give some data from two more recent studies – the Health Professional Follow-up Study and the Nurses Health Study – in order that we may examine how the large-scale American East Coast studies work and what results they have obtained.

I shall also examine the INTERHEART study in more detail to put the dietary factors into perspective compared to smoking, hypertension, diabetes, lipids etc.

There is also the beacon of light offered by the EPIC Heart Study that is now ripe to bear results, and we will hear the first results on anthropometry here today from Rodolfo Saracci.

The current dietary guidelines are also being shown on the slide: total fat intake < 30, total saturated fat <10. In addition, in the American Heart Association paper, there are some very strong statements claiming that saturated fat intake is the principle dietary determinant of LDL. It is quite difficult to find a scientific basis on which to base such a statement, considering all the studies conducted to date. Cholesterol intake <300, 2 fish servings per week, five servings of fruit and vegetables per day, limitation of salt to less than 6 grams per day – which is easier said than done – and limit alcohol with no more than 2 units per day for men and 1 for women: these were the 2001 guidelines.

I will comment briefly on the Seven Countries Study. There is an impressive array of well-known epidemiologists behind this study. The main results were that all death rates were negatively related to the ratio of the monounsaturated to saturated fatty acids. Furthermore, the inclusion of that ratio with classic risk factors – age, blood pressure and others – accounted for 85% of the variance in deaths from all causes, almost all variance of the coronary heart disease mortality, 55% of the variance for cancer and 66% of the variance for strokes.

I will focus mainly on all-cause mortality and coronary heart disease mortality. A very encouraging statement comes at the end of the conclusion. With olive oil as the main fat, all-cause mortality rates and coronary heart disease rates were low. This is very encouraging for this audience here, as well as for the Italian and Greek populations.

The aim was to relate each nutrient contributing to energy to deaths from all-causes, and death from coronary heart disease, stroke and cancer. There were 11 000 men aged 40-59 years old in 15 cohorts. In most centres they came from very rural areas. The Dutch cohort was a random sample of all men in Zutphen; the US and Rome cohorts were railroad men, and the Serbian men were largely from an agricultural cooperative. There was a very high participation rate of 90%. We will never see that again. In Scandinavia we have seen the participation rates go down from 75% to 60% to 40% as new populations come into our country.

I would like to put this into perspective by focusing on a number of points. EPIC has individual dietary data on over 500,000 people. In the Seven Country study, dietary data was collected from between thirty and fifty men in each cohort. Each centre had slightly different methods. An important part of the Seven Countries Study was that all food and drinks were weighed and recorded for seven days in the participating centres. Duplicate samples were sent to the laboratory for chemical analysis. There was also a spread over seasons, which is very important in this type of study.

They observed very striking differences in the 50-year death rates between the participating countries. Look at the coronary heart disease death rates from East Finland to Crete. Today we never see these differences. I looked carefully at the diagnosis of the cause of death. In some cohorts, only a minority died from coronary heart disease or cancer. It is difficult to see the validity of the diagnosis here and it is also difficult to see what they really died from. When looking at rural areas one also has to question whether the vital status is really valid in this study. Furthermore, are the data from East Finland to Crete really compatible with longevity data from the larger areas these samples are taken from? I think these are very important questions.
The well-known finding here is that if you take the ratio of monounsaturated to saturated fat, you can explain 72% of the observed deaths. This is a very strong correlation and is due to the fact that the results are the mean of the cohorts, so this is an ecological study and not individual data here.

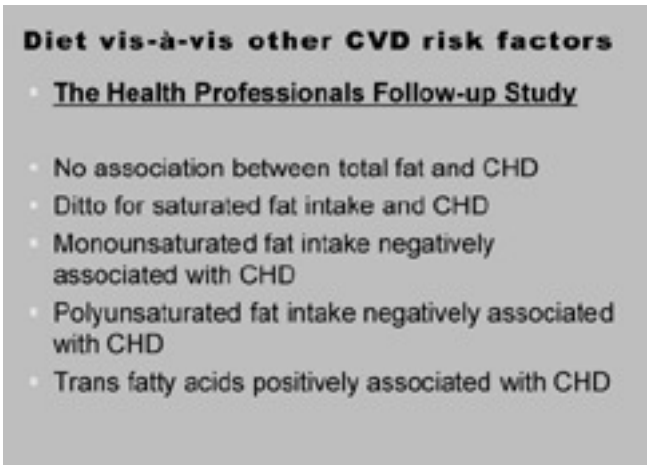
When it comes to the same analysis ratio for monounsaturated to saturated fat for coronary heart disease mortality, they can explain only 44% of the observed deaths here by this ratio. This means that there are some discrepancies in the findings.

When you add classic risk factors of age, body mass index, systolic blood pressure, cholesterol and the number of cigarettes smoked, you can explain nearly 100% of the variation in a highly complex chain of events that leads to death from myocardial infarction.

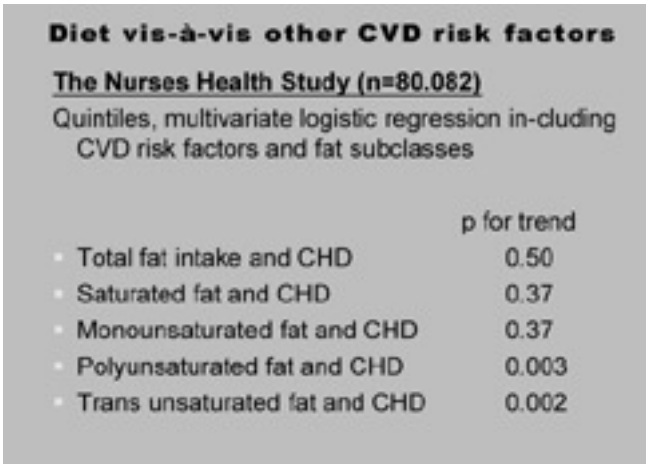
Reading the Seven Countries Study now, with all the new knowledge around, it should be remembered that this is an ecological study that uses population means. Very few subjects were used to obtain dietary means and the dietary methods differ between centres. One could postulate that the centres were representative of Europe at that time and probably not at all of the Europe of today. Furthermore, the design overestimates true associations because population means are used. However it has had a huge impact throughout the Western World on dietary recommendations.

It is important to remember that risk of saturated fat intake should be mediated through a high serum cholesterol level. A high saturated fat intake should increase your serum cholesterol. Most feeding studies show that, but they are short-term and do not offer much information about long-term effects. However most studies within cohorts have had difficulty in showing any relationship between saturated fat intake and serum cholesterol levels, even if you take several cholesterol measurements. We have this problem in the Swedish populations that I am aware of and work with; we have great difficulty in showing significant correlation. This could be due to regression dilution bias, although this could be a way to explain something that has not been found.

The next generation of studies, the Health Professionals Follow-Up Study published in 1996, showed no association between total fat and coronary heart disease. In these East Coast studies there were no association between saturated fat intake and coronary heart disease, but there was a negative association between monounsaturated fat and coronary heart disease: it showed that the more monounsaturated fat you eat the lower your risk of coronary heart disease. The same is true for polyunsaturated fats, but the opposite is the case for trans-fatty acids, which increase the risk of coronary heart disease. This is a large study on men with a long follow-up and carries considerable weight.



The same is true for women – the Nurses' Health Study had 80 000 participants. Multivariate regression analysis including cardiovascular disease risk factors and fat sub-classes. Quintiles 5 to 1 showed no significant association between total fat intake; saturated fat CHD, and monounsaturated fat and CHD. Polyunsaturated fat and trans-unsaturated fat are strongly significant and are negative and positive respectively.



I will finish by discussing the INTERHEART study in order to put the dietary factors in perspective with the other strong cardiovascular risk factors. INTERHEART is a case control study. It carries weight as it has 15 000 hospitalised myocardial infarctions, which means that at least 40% of the study in cardiac deaths are not included, but it is impressive nonetheless. The participants are from 52 countries from all continents. The design could be open to question with regard to controls. The odds ratios and the population relative to the risk have been calculated. For myocardial infarction, this was done using nine modifiable risk factors: smoking, history of hypertension or diabetes, waist/hip ratio, diet, physical activity, consumption of alcohol, apo B to apo A1 ratio and social factors. The last of these is a difficult score to understand as many questions are incorporated in this psychosocial score.

With regard to the results, 90% of the variation in men and almost 95% in women could be explained for the population relative to the risk figures. Smoking, the apo B to apo A1 ratio and diabetes were all strong risk factors, however they explained different components of the population attributable risk, as these have high prevalences in the population. The same is true of psychosocial factors: one third of the risk can be explained by psychosocial factors. The only significant dietary factor was the daily fruit and vegetable intake, which came out with 14% of the population's attributable risk. Alcohol consumption and physical activity were also significant but account for lesser degrees of the population's attributable risk. This provides a good estimate of the importance of various risk factors for having a myocardial infarction.

In summary, nine modifiable risk factors accounted for most of the risk in both men and women. They conducted a good analysis showing this was true for all continents, both sexes and all ages. Intake of fruit and vegetables explains 14% of the variation of risk; findings suggest that changes in lifestyle (because all of these things were modifiable) have the potential to prevent the majority of premature cases of myocardial infarction. The question is to what extent diet could contribute to the risk decrease.

In my view, the old ecological analyses of prospective cohorts do not form a very valid base for dietary recommendations. The more recent cohort studies do not really show clear-cut results for some major dietary factors. In my view, we need to continue this work; we need large prospective cohort studies. Most importantly, we need dietary intervention studies to be able to design effective programs for the prevention of cardiovascular disease. Bearing this in mind, I am glad that we have the EPIC study with more than 500 000 participants on which we have dietary data.

Are there any questions?

Questions

Franco BERRINO
I would like to challenge your proposal. I imagine that you agree that saturated fat has something to do with the level of cholesterol in the blood.

Göran BERGLUND
The problem is that it is very hard to show that in free-living people.

Franco BERRINO
But there is evidence that by modifying the diet and reducing saturated fat the cholesterol goes down.

Göran BERGLUND
All the feeding studies show that to be true. For the observational studies there is probably some form of regression dilution bias and it is hard to assess how big that bias is.

Franco BERRINO
Yes, because cholesterol is related to cardiovascular disease. Perhaps it is our ability to measure saturated fat with questionnaires that explains that conundrum.

Göran BERGLUND
This is at least one possibility.

Energy and fat intake and CVD risk

Margret LEOSDOTTIR
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The topic of my talk is "Energy and fat intake and cardiovascular disease risk". I will focus mainly on fat intake but also briefly mention energy intake. I will start by going over dietary recommendations on fat and examining how they look today. Then I will spend most of my time talking about our research and results from Malmö. I will then try and put our results in perspective with other similar studies conducted in the field, and then conclude with a hypothetical idea of how dietary guidelines for cardiovascular disease should look.

Scientific studies on cardiovascular disease began in the early 20th century with animal studies, where you could see that by feeding research animals a fatty diet you made the animals atherosclerotic. With regard to human studies, one of the first studies was Ancel Keys' Seven Countries Study, which showed that high intakes of animal foods (excluding fish) increased the risk of coronary heart disease and also showed a high monounsaturated/saturated fat ratio being beneficial in preventing coronary heart disease.

These findings were later strengthened by dietary intervention studies, mostly with surrogate endpoints such as blood lipid levels. However, results from epidemiological studies conducted at this time and later were not as convincing – especially not concerning total fat and saturated fat intake. Many of these studies had non-significant findings.

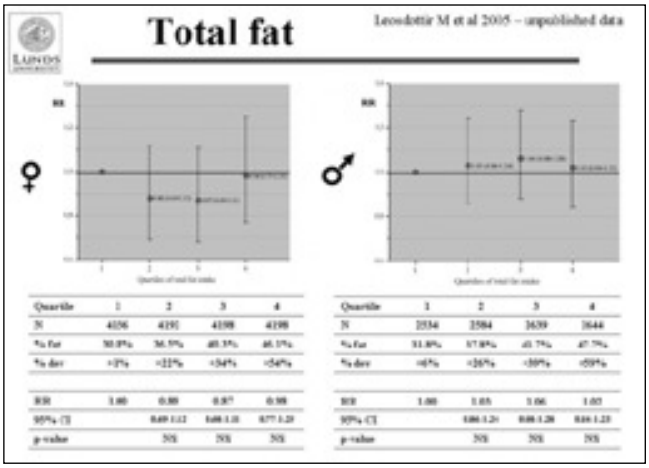
Nevertheless, dietary guidelines started appearing at a similar time, generally promoting low fat diets with special emphasis on saturated fats. The core message of the dietary guidelines today remains unchanged: reduce fat intake to less than 30% of total energy intake and saturated fat to less than 10% of total energy intake. These recommendations are seen in the American Heart Association guidelines. The same goes for most nationally used guidelines – although these are of course released to promote general health and do not focus only on cardiovascular disease. All the same, they have the same core message: reduce total fat to less than 30% of total energy intake and saturated fat and trans-fatty acids to less than 10%, monounsaturated fat to 10%-15%, and polyunsaturated fat to 5%-10%.

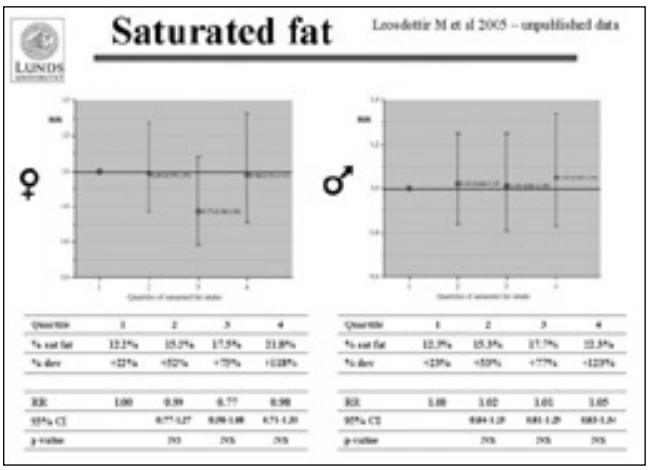
With regard to total energy intake, reference values are given in most dietary guidelines. These are usually acquired from biological studies on humans on energy expenditure and not on disease or mortality data. In Swedish dietary guidelines reference values are around 2 700 kilocalories per day for grown men and 2 200 kilocalories per day for women.

I now come to our Malmö study: the Malmö diet and cancer study is one of the EPIC cohorts. It was designed in the early 1990s to detect dietary factors in relation to cancer risk. The cohort includes just over 28 000 middle-aged individuals who were living at the time in Malmö – the third largest city in Sweden. Sixty-one per cent were women. Dietary composition was evaluated with a food frequency questionnaire and a seven-day menu diary. A physical examination was conducted, blood samples were drawn, and each subject answered an extensive questionnaire regarding lifestyle, disease history, etc.

The aim of the current analysis we have been doing on the Malmö diet and cancer material was to examine whether total energy intake, total fat intake, saturated, monounsaturated or polyunsaturated fat intake are independent risk factors for cardiovascular disease and mortality. We divided the material into quartiles of energy and fat intake, respectively, using the first quartiles as a reference groups. We adjusted for age, smoking, physical activity, socio-economic status, marital status, dietary fibre, alcohol consumption, systolic blood pressure and body mass index. Endpoints were cardiovascular events: acute coronary events or ischaemic strokes, fatal or non-fatal, and we calculated relative risks with the Cox regression model.

During a follow-up time of 8.4 years, 1 556 endpoints were registered. Results for total fat can be seen in figure 1. In the first quartile for women and for men, subjects were eating approximately in accordance with dietary guidelines. Individuals in the fourth quartiles were ingesting 46%-48% fat as a proportion of total energy intake. As seen on the graphs, there was no significant difference between the quartiles concerning cardiovascular disease risk. The same was observed for saturated fats (figure 2). Individuals in the first quartiles received on average 12% of their total daily energy from saturated fats, compared to 20% in the fourth quartiles –over 100% more than recommended. Still we did not observe any increase in cardiovascular disease risk.





Also, for monounsaturated and polyunsaturated fat there was no significant difference between the quartiles. Note though that there is a significant limitation to the unsaturated fat analysis, which will be mentioned shortly.

We also looked at the ratio between the saturated and unsaturated fats in a similar way as was done in the Seven Countries Study, where individuals in the first quartiles had the most beneficial ratio – the highest intake of unsaturated as opposed to saturated fat – and those in the fourth quartile had the least beneficial ratio. No significant difference between the quartiles was observed.

Concerning total energy, individuals in the third quartiles ingested approximately in line with dietary guidelines, and those in the fourth quartile ingested 20%-30% more than recommended. No increase in risk was observed for individuals in the fourth quartiles.

Taken together, we observed that individuals getting more than 30% of daily energy from total fat and more than 10% from saturated fat did not have increased cardiovascular disease risk – even individuals receiving 45%-50% of their daily calories from fat or 20% from saturated fat did not have increased risk. Benefits of ingesting relatively large amounts of unsaturated fat were not observed in our cohort, and men and women ingesting 20%-30% more calories than recommended did not have an increased risk.

There are some important considerations to be taken into account. Firstly, the subjects were already middle-aged at a baseline, or between 55 and 57 years old. This can be of significance, as other studies have indicated that dietary factors are more important at an earlier age. For example, the recently published 20-year follow-up from the Nurses' Health Study showed this, as did the Framingham Study. Another limitation in the Malmö material is that trans-fatty acids were not registered as a separate variable and are thus included into the monounsaturated and, to some extent, polyunsaturated fat variables, which can have confounded the results considerably.

I will come to the matter of trans-fatty acids again shortly, but first, a quick mention of the sources of unsaturated fatty acids, which is also very important when talking about the effect of unsaturated fat on health and cardiovascular disease risk. In the average Malmö diet, most monounsaturated fats come from dairy products and margarines, while in the Mediterranean diet for example, the monounsaturated fats come mostly from olive oil. These are two completely different types of fat which are coupled to different dietary patterns. This must be taken into account when drawing conclusions from dietary studies.

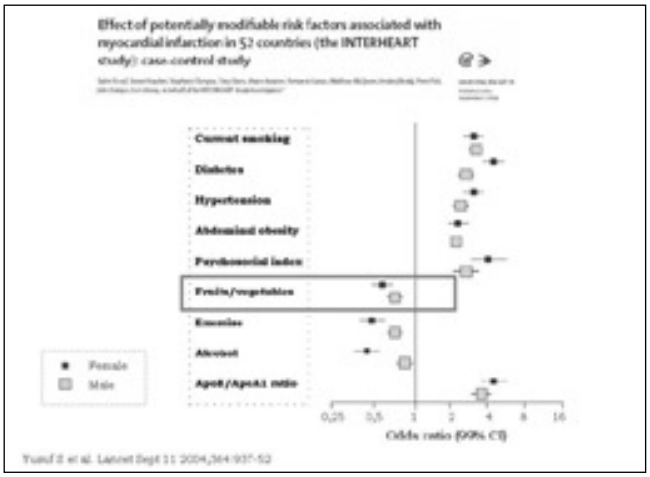
Returning to the trans-fatty acids - data from the 20-year follow-up publication of the Nurses' Health Study shows clearly the harmful effects of trans-fatty acids in the diet, giving an increased risk of coronary heart disease. As you can imagine, when combining trans-fatty acids and unsaturated fat variables as unfortunately was done in the Malmö Diet and Cancer study, it is maybe not surprising that we did not observe any significant beneficial effects of unsaturated fats in the diet.

Another thing I would like to point out from the Nurses' Health Study are the results obtained on total fat and saturated fat, which as in our study had no significant effects on coronary heart disease risk.

With that in mind, I would like to return to the Swedish dietary guidelines which, like many other dietary guidelines, group together saturated and trans-fatty acids in the recommendations, saying that you should limit these two types of fat to under 10%. This in my opinion is not fair to the saturated fatty acids, as these two types of fat do not have comparable effects on health.

Another thing that should be taken into account, when discussing the effect of dietary fat on health and on cardiovascular disease, is what characterises the individuals who eat fatty foods? One very important factor is fibre intake – we know that fibre is protective against cardiovascular disease. Data from our own material shows that with increasing fat intake, one can observe a significant decrease in fibre intake for both men and women. The effects of fibre on cardiovascular disease were shown very clearly in the Health Professionals' Follow-Up Study in their multivariate analysis. When fibre intake was added to their multivariate adjustment model a significant drop in the risk for the upper quintiles of fat intake was observed. The same pattern was observed for saturated fats.

With this in mind I will return to the previous epidemiological studies just to point out that adjustments for fibre intake were generally not mate in these. Vegetables and fruit are also a very important thing to think about when looking at dietary fat and cardiovascular disease. Analysis from the Malmö diet and cancer study material shows across quintiles of fat intake how intake of fruit and vegetables decreases and, as we know and have heard a lot about here today, fruit and vegetables protect against cardiovascular disease. This is a very important thing to take into account when looking at such data. The INTERHEART study depicted the effect of fruit and vegetables on cardiovascular disease very nicely (figure 3). As was talked about earlier, fruit and vegetables were the only dietary factor that showed some significance in their analyses, underlining the importance of taking this into account when evaluating cardiovascular disease risk.



We should also bear in mind that individuals who eat fatty foods also eat more on average, and that people who eat calorie rich foods often eat relatively fatty foods. Smokers and individuals of lower socio-economic classes also often eat fattier foods. All these factors are important when looking at the fat-cardiovascular disease relationship. Perhaps instead of looking at fat as the culprit, we should look at the behaviour (both the dietary and lifestyle behaviour) of those who eat fatty foods and how those factors are coupled to cardiovascular disease.

To conclude, current internationally used dietary guidelines on total and saturated fat intake are not strongly scientifically supported when it comes to cardiovascular disease risk. Saturated and trans-fatty acids do not have a comparable effect on health and as such do in my opinion not deserve the same treatment when it comes to dietary advice. Fat intake is strongly coupled to intake of dietary fibre, fruit and vegetable intake, all of which have proven cardio-protective effects. This could have considerably biased results of previous epidemiological studies on the effect of dietary fat on cardiovascular disease incidence.

If basing dietary advice concerning cardiovascular disease on the degree of scientific evidence available, one should stress a diet rich in fruit, vegetables and fibre with a focus on fat quality and not fat quantity.

For the ideal dietary guidelines, if we try to prioritize the factors that have the strongest scientific evidence, I would say that we need to stress that people adjust energy intake to energy expenditure, avoiding over-consumption of calories. They should maintain a balanced diet including calories from all energy sources including fat, but shifting fat consumption toward non-hydrogenated, unsaturated fat from plant sources and from fish. They should avoid trans-fatty acids entirely and, even though I have not covered this in my topic, they should shift carbohydrate consumption away from refined carbohydrates to more complex ones, and prioritize vegetable, fruit and fibre-rich products in the diet.

Finally, it is perhaps not ideal to talk about dietary guidelines, but rather about lifestyle guidelines, because diet is inevitably coupled to lifestyle factors and we should take this into consideration.

Questions

Member of the audience
Having served on several expert panels trying to figure out what the totality of evidence is, I would like to remind you that you are reporting the results of one cohort study. I personally obtained identical results concerning fatty acids 10 years ago from the ATBC trial, except that we did find trans-fatty acids to be harmful – which we know – so I ask that before you spread this new information further, you remind the audience that you are reporting the analysis of one cohort study.

Margret LEOSDOTTIR
This is of course true, and it is not my intention to "spread news", but to represent results from our study and other similar ones to this audience of fellow researchers gathered here today. However, I think we have to critically evaluate the scientific evidence we have from all studies on the diet-heart relationship and that is what I was trying to do here.

Frank HU
You found an inverse association between energy intake and coronary heart disease. This result is consistent with several previous studies, so the interpretation of total energy in these kinds of studies is not just about calories but is a marker for increased physical activity. Here, the data tells us that increase in physical activity is associated with decreased risk of coronary heart disease, so the results are not really surprising – the interpretation is just more complicated.

My second comment is related to saturated fat. I think we probably put too much emphasis on saturated fat. Even though we know that saturated fat increases HDL cholesterol but it also increases LDL cholesterol, it does not have a very strong impact on the ratio of HDL cholesterol to LDL cholesterol. This ratio, as we know, is the strongest predictor of coronary heart disease. Also, if you compare saturated fat with refined carbohydrates, it actually decreases triggers for this. This is why if you compare saturated fat with carbohydrate, which is mostly refined carbohydrate, you are not expected to see a major impact, as has been found in the Seven Countries Study.

Margret LEOSDOTTIR
Concerning energy intake, I agree with what you have said, and this is perhaps why I have not gone into detailed discussion about our energy findings. These are in line with other findings. This is a very complicated relationship between not only physical activity, but also basal metabolic rate, spontaneous body movements, vitality and premature ageing. These all affect total caloric intake, so it's a very complex relationship that is perhaps hard to assess through epidemiological studies. I also agree on the matter of saturated fats.

Edith FESKENS
This was an intriguing presentation. I have some comments. Firstly, to follow up on the energy issue, one of the factors which may play a role is under-reporting by overweight people. I think one of the main problems we have with observational studies looking at diseases which are associated with being overweight may be under-reporting. It may also be beneficial to look not at cardiovascular disease in total but coronary disease and stroke, because there are different ideologies from a dietary point of view. You talk about the Seven Countries Study: I think you do the study an injustice because there was an adjustment in the study for fibre and an adjustment for vegetables and fruit that appeared in later publications. What we saw in the publications was that rates within the ecological study were explained by saturated fat, smoking and the intake of flavinols, such as creatine in foodstuffs, tea and red wine, and indeed, that was taken into account.

I am on the Netherlands Health Council involved in preparing the recommended dietary allowances. The recommendations for dietary fibre we are currently preparing in the Netherlands are the first recommendations based on epidemiological data. So far, all the recommendations (and I am sure that this is also the case in Sweden) have not been looked at from the point of epidemiological studies of cohorts because of the problems of confounding causation etc. They all looked at intervention trials and there were recommendations made for trans-fatty acids and saturated fatty acids, which are separate in most countries, and for all the types of fatty acids in the studies by Martine Katan, for example, which are exactly the same as was done by Ancel Keys in the 1950s with regard to total cholesterol, LDL and triglycerides and HDL from saturated fat, monounsaturated fat and polyunsaturated fat. Only the trans-fatty acids have additional influence on CHD apart from the lipoproteins, so it is worth mentioning them separately.

Results from the EPIC Heart

Rodolfo SARACCI
Italy & IARC-WHO
IFC-National Research Council, Pisa, Italy
International Agency for Research on Cancer, Lyon, France

Thank you. My presentation will be in two parts. The first will be a rapid overview of the EPIC study design. I have borrowed several slides from Dr Elio Riboli who has been the co-ordinator for more than 15 years and was the initiator of this study. I think it will be useful for his presentation tomorrow, and that of Dr Marzano, if I pave the way by presenting a summary for those of you who are not familiar with the structure of the study. Then, as a way in which this study, which originated focusing on cancer, can be used to probe questions of ideological intervention in the cardiovascular area, I will examine some of the preliminary results on the anthropometric indices. The EPIC heart collaboration is the EPIC-based study on cardiovascular disease which has started looking in particular at systolic heart disease.

We move on to the simple and basic public health principle which we have already touched upon today. Obviously each person can eat only one diet. We have seen recent recommendations by the American Heart Association, the Diabetes Association and the American Cancer Society. Finally if you think in terms of what the cardiovascular epidemiologists (unlike most of the other epidemiologists) call primordial prevention for the general population, you obviously have to give some general advice to the general population. Does that not imply that you then have to target special sub-groups, for example if you have subjects that are in pre-diabetic conditions or other special groups?

The EPIC heart study's strengths are both from the research viewpoint – the EPIC infrastructure of larger exposure of variables and also biospecimens and uniform study criteria – and from the public health viewpoint. The results for both ischaemic heart disease or other endpoints and cancer will be obtained in the same population from the same methods. This is one advantage, to the extent that one often has to take evidence from different types of studies and collate them into what appear to be translatable recommendations in the form of guidelines.

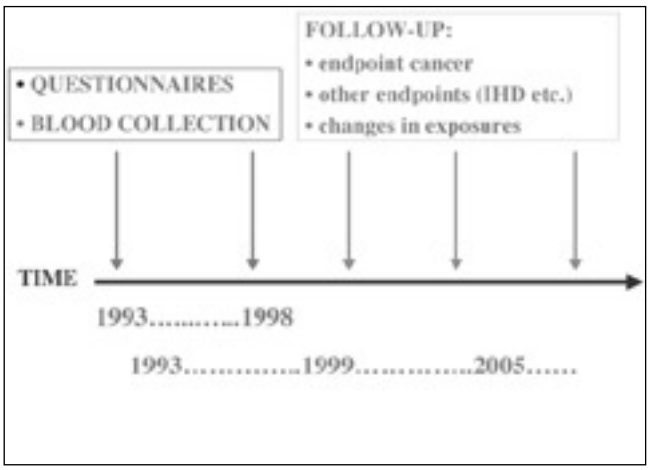
The ten EPIC heart countries are the same as for the major EPIC countries and are all located here in Western Europe. There are 23 collaborating centres in the EPIC heart study and they are in the same countries. Some countries have only two centres and others more; some large countries, such as France, have a nation-wide collection in a special cohort of female teachers. Other countries have centres which are geographically distributed – Italy and Spain, for example. The samples that have been taken are in a sense opportunity samples that were suitable for collecting from a very large cohort in the different countries.

Lifestyle and personal history was taken from questionnaires and addressed questions of tobacco, alcohol, reproductive history, occupation, past and present illnesses, medication, physical activity and socio-economic status variables. We then took the anthropometric measurements: height, weight, waist, hip, and sitting height. Not all the measurements are available for the whole cohort (as I will comment on later) and an additional measurement of blood pressure is also available.

One of the interesting things about EPIC is that there are two dietary measurements in the sub-samples. There is the main dietary question on usual diet from each of the 1/2 million subjects with methods which are based on the same principle, although the actual articulation of the questions is different in different countries to make allowances for local circumstances. These are designed to rank the subject from high to low. Then, there is a second measurement in a 7% sub-sample comprising approximately 38 000 cohort subjects. This is intended to offer an instrument of standardisation, or rather of calibration, of the question of measurement against the common standard, which was a very laborious activity. This was carried out by nutritionists from the different countries and a central group of nutritionists at the IARC. It gives very detailed open-ended reporting on over 3 000 foodstuffs and 700 recipes. It is designed to calibrate data measurement in two ways: to re-scale between centres the absolute quantities (the top quartile in Sweden of fat that corresponds in Italy and to which absolute amount) and for attenuation purposes (when one studies the relationship between exposure and the outcome – cancer or other endpoints).

The EPIC blood collection in storage contains plasma, serum, buffy coat and red blood cells. There is a bank of approximately 300 000 subjects centrally collected and approximately 100 000 total subjects for which it is available. Some biological specimens are available – close to 400 000, if I am correct – about 80% of the total cohort of about 1/2 million. Not all of them have this banking in Lyon but the samples are available.

The physical system that has been used for long-term sample storage is in liquid nitrogen in the central bank. This may be to do with the design of the study: this is a collection typical of the different cohorts which have worked on a rolling system depending on when each cohort started. They started between 1993 and 1998 and the follow-up has now begun.



The follow-up includes cancer and other endpoints – ischaemic heart disease, stroke etc. – with questions on their own changes in exposure. While this was a study initially designed for investigating cancer, it has also been designed to obtain cancer incidence figures via cancer registries or similar systems for the active follow-up and registration of incident cases. For the other endpoints, for the time being the only form in which these

endpoints come is mortality: causes of death for ischaemic heart disease stroke, diabetes etc. It would be good to investigate further, but this is one of the limitations of the study.

I will now consider ischaemic heart disease, which is the first of the other endpoints which has been considered. There are a number of analyses which are in progress. In fatal cases ischaemic heart disease ICD 9 410-414 ICD 10, I 20, I 24. We have left out the sudden death category in the ICD 9 7 8 9 7 8 8 7 8 9 as there were so few cases that for practical purposes it was not interesting to put them in.

The non-fatal cases will form a new additional database, with the same ICD categories in two steps. The first step will comprise diagnosis as available at participating centres. We are fortunate that at a number of participating centres (for reasons totally independent of EPIC), collection of incident cases of myocardial infarction or stroke, or both, was going on. This was a lucky coincidence.

Step two: later on, we will have procedures for standardising the diagnosis for the future collection of the incidence cases. We are now concentrating on the first part: the fatal cases. In fact, the EPIC heart collaboration design and work plan those from the exposure and anthropometric questions, and data from all cohorts are analysed. We will do the same on fatal and non-fatal cases as soon as we have the incoming new database. There will then be laboratory studies on phenotypic and genetic biomarkers using the method case control design.

At the present, statistical analyses are in progress depending on the interest of the different members of the group. We have to set statistical analysis in motion using anthropometric and questionnaire data: anthropometry, meat and processed meat, fish, dairy products, fruit and vegetables, nuts, alcohol, blood pressure and tobacco smoking. There are nine different groups working in different centres on this set of exposure variables. We will have these results by the end of the year and we will publish our findings early next year.

Number of IHD deaths and crude death rates (per 100,000 p-y) by centre and sex [1]

Centre	Deaths		Rate	
	M	F	M	F
1.France	-	13	-	3.6
2.Florence	10	3	53.6	5.3
3.Varese	5	6	39.7	9.6
4.Ragusa	8	-	42.2	-
5.Turin	9	2	21.8	6.8
6.Naples	-	2	-	6.0
7.Asturias	11	-	55.6	-
8.Granada	5	5	42.5	13.6
9.Murcia	14	2	82.7	5.5
10.Navarra	19	3	84.6	9.7
11.San Sebastian	15	1	55.7	3.5

Number of IHD deaths and crude death rates (per 100,000 p-y) by centre and sex [2]

Centre	Deaths		Rate	
	M	F	M	F
11.Cambridge	315	113	361.8	114.3
12.Oxford	133	99	162.3	35.5
14.Bilthoven	42	11	63.9	13.8
15.Utrecht	-	29	-	27.1
16.Greece	79	26	200.4	45.4
17.Heidelberg	71	10	109.3	13.4
18.Potsdam	72	10	110.4	10.1
19.Malmo	179	57	244.6	51.9
20.Umea	63	11	84.6	13.1
21.Aarhus	22	7	72.9	22.3
22.Copenaghen	47	10	66.7	12.4
23.Norway	-	9	-	6.1

I will now talk about anthropometry, simply because that is what I have mainly been involved with. I would like to point out some of the present limitations we have because of the deaths. The number of ischaemic heart disease deaths includes death rates here in the different centres. There are two slides about this. You can see that the numbers are quite small by centre. Though the total is 1 500, this is largely driven by some centres. We cannot really hope therefore at this stage to be able to make a consistent verification as to what we find throughout these centres. There is an additional aspect which is in this representational limitation. If we want to exclude those who had a previous myocardial infarction, namely a myocardial infarction revealed by the questionnaire at the time of enrolment, the size comes down.

There is a third limitation to the anthropometric data: not all the data are uniformly available for all the centres. We really need to have the non-fatal cases as soon as possible to obtain meaningful statistics.

There are various interesting aspects to the anthropometric variables. The first two are the merits of this variable: they are markers of adult energy, metabolism and balance and they are markers of adult material metabolism and lipocytes, and we know what they do. We had a presentation this morning in particular in which we heard about obesity and visceral fat and their possible implications in a series of metabolic steps in the pro-inflammatory process were examined.

There is a third point of interest: markers for physiological adult and pre-adult processes prior to the time of subject enrolment. This applies to all studies, like the EPIC studies, which do not have birth cohorts, and now there are birth cohorts being included. However, we would like to see whether the results can be replicated, and out of the few markers that one has available, although their status is an initial status rather than having a clear meaning, they are just the anthropometric variables. From a public health viewpoint they are easily measured by health monitoring instruments and in fact they are very much advocated as such, particularly in developing countries, as a means of monitoring the next wave of likely diseases to affect the population.

The total cohort I showed you before in detail by centre is a total of 463 000 subjects. If you calculate the ratio, you find that the average follow-up is approximately 6 years, and ischaemic heart disease deaths are a little more than 1 500 up to now. This is a large number, but it is inadequate for certain types of comparison and sub-analysis that one would like to do. The preliminary analyses were done using the Cox proportional hazard model using age as the time-based variable. These are stratified by sex and centre, including alcohol, smoking, education and physical activity as independent variables. Shown here are the results for these two variables, weight and height, or BMI. These are available for virtually every subject in the cohort.

First, I will show you how the confounders – alcohol, smoking, education and physical activity – behave in the Cox proportional hazard model equations. These are summarised concisely in a single table. The other ratios are shown here as highest versus lowest exposure category for each one. This is not the best way of expressing alcohol because the open category, which is 40g or more, includes the fact that the risk increases, and the penultimate category, the next to the highest, had another even

lower ratio of 0.58. Then, it goes up. That just gives you an idea that things are going in the right direction. This is smoking. Now look at the educational level, which is 0.45. Physical activity, which is a global index that pools together recreational, occupational and home activity, does not seem to stand out. Let us look at the anthropometrics. Weight has been adjusted in this equation, and here is one fifth of that distribution. We give actual values for males and females but this is a combined one adjusted by stratification. Weight risk goes up from 1 to 1.88 and there is a very highly significant trend. Height has a spectacular inverse association, which has been observed in many studies, but here it is really quite impressive and is consistent in both sexes. When weight and height are replaced by body mass index in a separate equation, without putting everything together, again BMI comes out very much as the weight was before, and in fact the meaning of the BMI is simply that you consider height as a disturbing variable; you cancel it out and you have the weight aspect of the adiposity.

Both height, which has a declining ratio in the last quintile, and educational level are two variables which are fixed by the age of 20. As I said before, not all anthropometric indexes are available in the whole cohort. Waist and hip ratio are available for almost the totality of the cohort, but sitting height at 20 years of age, which really would complete the set, are available from far fewer people.

I conducted an exploration into waist and hip data on a sub-sample that was considerably smaller simply because the guiding variable was sitting height and therefore it reduced the sample down to around 500, or just one third of the total we showed before. Preliminary analyses used the same Cox model and weight/height ratio and then the waist/hip ratio, or alternatively, BMI and waist/hip ratio. When waist/hip ratio is inserted into the equation and adjusted for alcohol, education, physical activity, etc., in the equation in which weight and height are present you can see that the waist/hip ratio has an independent contribution here. When it is inserted in the equation in which BMI appears instead of these two variables, you can see an independent contribution with a highly significant trend in weight and height: weight retains its independent contribution in that equation in which you have waist/hip ratio, and height is still a slightly less marked trend but is still quite significant. You should bear in mind that the significance of this sample is badly affected by the fact that it represents only 500 events.

I then worked on an ambitious exercise looking at leg length. Existing evidence is confusing. In literature, leg length should help to split the period that comes before you are 8, to 20, when your height is fixed in a sub-period because the leg grows particularly in the pre-pubertal period. When adult, you have a trunk to leg ratio of about 1:1, but at birth the trunk represents about two thirds of total height. The responsibility of the inverse relationship of height with ischaemic heart disease, which is clear here and has been shown by other studies, has been tentatively attributed to leg length, and therefore inferentially to possible nutritional influences taking place during the pre-pubertal period.

The results observed here were the other way around, but the sample was small, so I would be curious to see when we look at more data what the results will be and whether they will be different. None of these results are particularly significant.

This is where we stand now. The anthropometric data will be refined and completed and we will try to use all the sub-cohort available for this using all measurements for the subject: waist, hip and also sitting height at age 20. We need to work out some function of age at 20 which can also be inserted in the equation; that is the programme that we have. We will carry out a second step of the same exercise as soon as the new database on non-fatal cases is in, and then there is a separate part of the programme which targets on the laboratory component.

Göran BERGLUND

I think that there will be a very interesting development in the EPIC cohort. I see how the plans are for both biomorphics and for genetic analysis and how big the sample will be within half a year's time with more than 7 000 myocardial infarctions, which will give us impressive power to detect even small differences.

Dietary patterns and risk of CVD

Matthias SCHULZE
German Institute of Human Nutrition, Dept. of Epidemiology, Nuthetal, Germany

I have the pleasure of giving the last talk on dietary patterns and the risk of CVD today and I will focus largely on cohort studies and not on intervention studies. In observational studies, we usually measure food intake with an FFQ or with other assessment methods. One strategy is to relate the intake of single food items or food groups to the risk of CVD. Another strategy is to derive through food composition tables the intake of nutrients and to relate those nutrients or constituents of food items to CVD risk. A third approach, which has been used more and more commonly within the last five or ten years, is the analysis of overall dietary patterns which reflect the consumption of different foods and nutrients in composition, and therefore reflect the effects of overall diet and cumulative effects of these components. In terms of observational studies, there are essentially two different strategies for defining these dietary patterns. The first uses prior information on possible or known effects of single components or nutrients or food items on risk, and this information is used to define a dietary index or score: a classic example is the Mediterranean diet score. The second method, the exploratory method, uses the data at hand and data reduction techniques, cluster analysis and principal component analysis, to define the common patterns that exist in the study population of interest.

Another technique, which is called reduced rank regression, uses both prior information and data at hand to define these patterns, and this method has recently been introduced by our group from Potsdam. I will give two examples of its application on CVD.

The first question is whether dietary patterns relate to CVD risk markers, and there are several metabolic pathways by which diet may relate to the risk of CHD which could be considered here. We have heard about one study already today: the Mediterranean style diet may affect blood pressure, blood lipids and also inflammatory markers. These effects are independent of effects on body weight. So, even though subjects in the intervention group lost more weight than those in the control group – the effects on inflammatory markers, for example, were independent of this.

There are also observational studies which link dietary patterns to cardiovascular risk markers. One such example comes from the National Health and Nutrition Examination Survey in the United States which identified two patterns. One is the Western pattern, which is high in processed meats, red meat and high in dairy. This pattern is related to somewhat lower HDL cholesterol but also to lower folate levels and higher HbA1c and higher insulin levels. On the other hand, an American healthy pattern, mainly consisting of vegetables and salad dressing, did not show any appreciable associations with these risk markers.

There are three more studies which relate overall dietary patterns in an observational setting to cardiovascular risk markers, and two of them come from the Harvard group [Figure 1]. In both studies, the Western and the prudent patterns were observed by using factor analysis or principal component analysis. While the Western pattern was associated with risk markers such as higher insulin, C-peptide and leptin, higher homocysteine or lower folate levels and also inflammatory markers, the prudent pattern showed somewhat opposite effects on these risk markers. The Morgen Study from the Netherlands identified three patterns. The cosmopolitan pattern is somewhat similar to the prudent pattern in the US, but with more vegetables. The traditional and refined foods patterns both share components of the Western pattern in the United States. What the investigators saw is that the cosmopolitan pattern was associated with lower blood pressure and higher HDL cholesterol, while the traditional and refined foods pattern was associated with a biomarker profile that reflected a higher risk of CVD. These effects were adjusted for known risk factors and potential confounding factors.

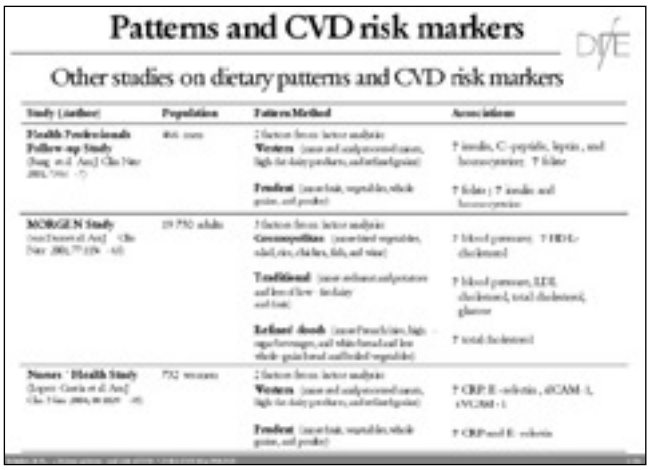


figure 1

The second line of evidence comes from observational studies on dietary patterns and the risk of CVD. I would like to acknowledge the two secondary prevention trials published so far on the Mediterranean style diet and the risk of cardiovascular disease. However, most of the evidence for primary prevention comes exclusively from observational studies. One good example is the Health Professionals Follow-Up Study, in which the prudent pattern was associated with a decreased risk of CHD and the Western pattern showed a positive association with the risk of CVD. This was not totally explained by nutrients which may be related to this pattern. Both patterns were associated with risk after adjustment for these nutrients.

Another example comes from EPIC-Greece where a diet score predefined as a Mediterranean diet was related to all-cause mortality but especially to mortality from coronary heart disease. This was again adjusted for potential confounding factors and anthropometric measures [Figure 2].

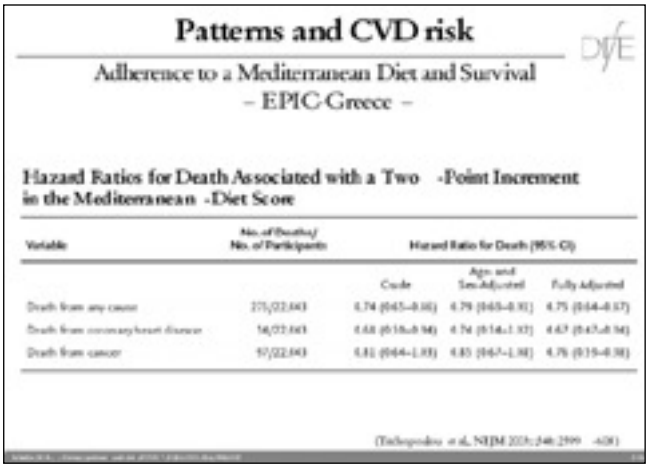


figure 2

There are many more observational studies on CHD and this table shows some which used predefined dietary scores. A study by Kant and colleagues recommends a food score essentially based on fruit and vegetables, whole grains, lean meats and poultry, which was related to a decreased CHD mortality. Stamper and colleagues used a dietary score based on six nutrients which have been shown to reduce CHD. This score was also related to decreased CHD risk. The other three studies evaluated the healthy eating index – which is based on the new USDA dietary guidelines - or the modified Healthy Eating Index. The Healthy Eating Index was associated with MI and stroke risk. The alternative healthy eating index was more strongly related to these endpoints.

Four other studies derived dietary patterns using exploratory methods – in this case, with principal component analysis. There are two studies from the Nurses' Health Study which is similar to the Health Professionals' Study. They define two patterns, both the Western and the prudent pattern. The prudent pattern was consistently associated with a decreased risk of CHD, while the Western pattern was associated with an increased risk. The same was the case for stroke. In the studies by Osler and colleagues, they defined two factors by principal component analysis and also a predefined dietary score. While the prudent pattern was associated with CHD mortality, it was not associated with CHD. The Western and the healthy food index were not related to either CHD mortality or total CHD risk.

Using principal component analysis in one particular data set always gives the same patterns, no matter what kind of disease you are interested in. So using the Nurses' Health Study data will give the Western or the prudent pattern, no matter whether we look at CHD or diabetes or different sorts of cancers. This approach is probably not optimal in defining the best dietary patterns in the sense of reducing CHD risk or reducing the risk of other chronic diseases.

It might be useful to use an approach that somehow incorporates prior information. This can be done using a newer technique called reduced rank progression. Basically, you can define a set of CVD risk markers – so-called responses. The method tries to define dietary patterns which explain variance in these responses or cardiovascular risk markers. This should give dietary patterns which may be more strongly related to cardiovascular risk. This method can also be adopted to other endpoints using different sets of biomarkers.

One study, published by our group last year, looked at different blood lipids, C-peptide, and the inflammatory marker C-reactive protein, and used this set of biomarkers to define a dietary pattern using this new technique.

The data came from the CORA study, which is a case control study on myocardial infarction in women in northern Germany. What we observed was that the dietary pattern was related to lower HDL cholesterol and much higher C-peptide and C-reactive protein levels where there was no relation with LDL cholesterol and lipoprotein(a) The food groups which contributed to this pattern were red meat, poultry, sauce, margarines, and "other vegetable fats and oils", which is somewhat surprising. This "other fats and oils" group does not include olive oil. There were, however, negative correlations with plant-based foods, such as vegetarian dishes, vegetables, whole grains, and also with wine. In this case control study this pattern was very strongly related to the risk of myocardial infarction. However, these data are probably too good to be true and this result is to be reproduced in a prospective setting.

We have just finished working on a different data set. This is the same study - the CORA study - but using a different set of responses which are related to the homocysteine pathway. We were able to derive a pattern which was related to higher folate levels, higher vitamin B12 levels and lower homocysteine levels. The food groups that contributed to this pattern were mainly mushrooms, olive oil, fruits, wine, vegetables, nuts and whole grains, while fried potatoes were negatively associated with this pattern [Figure 3].

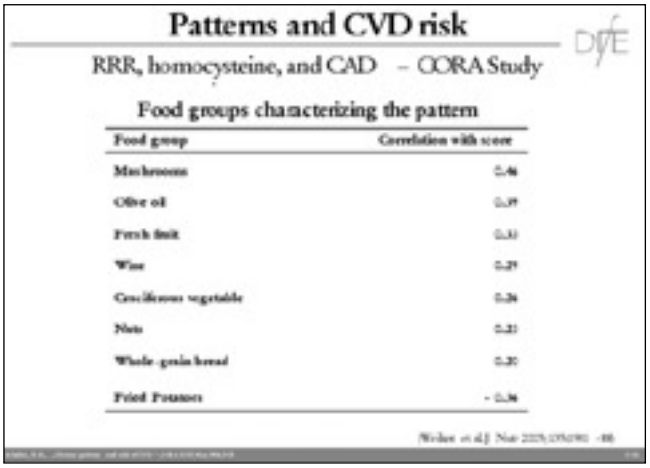


figure 3

This pattern was associated with a decreased risk of myocardial infarction in the study [Figure 4].

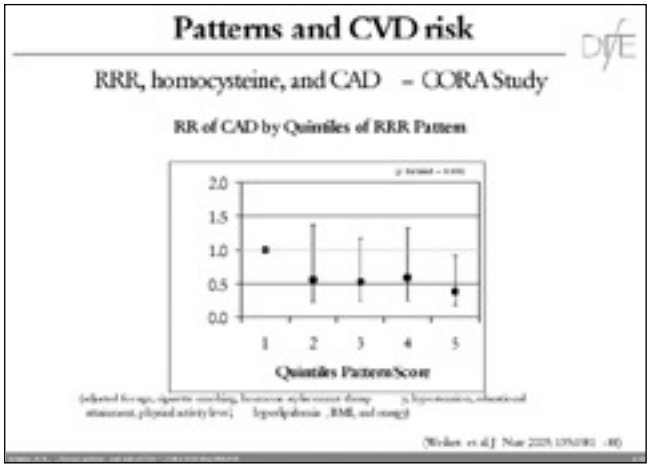


figure 4

We tried to replicate this finding in a prospective study, using data from the EPIC-Potsdam centre, which is a prospective cohort study. With about 27 000 participants free of CHD at baseline, we observed 157 incident myocardial infarction cases until April 2004. Fortunately, CORA uses the same FFQ (Food Frequency Questionnaire) as used in EPIC-Potsdam, so it should not prove problematic to assess dietary intake between both studies. We tried to mimic the pattern we observed in CORA by using the food items I mentioned before to define a dietary pattern score based on the previous results. In this prospective EPIC-Potsdam study there was still a significant trend for a decreased risk with this pattern, although the risk was somewhat smaller than we had observed in the CORA study. This, of course, was adjusted for a number of confounding factors.

In summary, there are many observational studies which show that a Western style diet comprising red and processed meats and refined grains is associated with both risk markers of CVD and an increased risk, and on the other hand that plant-based diets rich in fruits and vegetables, whole grains and also healthy sources of fat reduce the risk of cardiovascular disease by

affecting blood pressure, inflammation and lipoproteins. If we are looking at studying more dietary patterns in relation to cardiovascular disease in observational settings, the application of this new pattern method may be a good chance to do so, despite the ongoing interest in factor analysis and cluster analysis in this field.

Questions

Edith FESKENS
Thank you for your very nice overview. I am very interested in your reduced rank regression, which I think is a very good method.

The Ministry of Public Health recently asked us to look at dietary patterns and dietary indexes, so we looked at the literature a little bit like you did. Their question was as follows: which type of nutrient-related or diet-related problem is worst in the Netherlands? They could then use this dietary index to pinpoint the biggest problem for our diet in the Netherlands. If they conduct monitoring studies and they observe a reduction in folate or beta-carotene intake, for example, what should they dedicate most attention to and what should they put their money into? This was their question. They asked us whether we could look into this matter and look at dietary indexes from that point of view, which, as you can imagine, is very difficult.

But I would like to challenge you. Could we use dietary indexes, factor analysis, principal component analysis or even reduced rank regression to weight the various dietary components to see which dietary components have the greatest weight to predict longevity and then focus on that dietary component? This is a different way to use the indexes.

Matthias SCHULZE
I think it is very hard to go from an overall dietary pattern, which we observed, to focusing on single components. This is precisely the opposite of what you intend by evaluating dietary patterns. It is of course the case that some food items contribute more to a dietary pattern and some contribute less to a pattern, which may indicate that something is more important or less important. I do not believe that it is worthwhile to conduct factor analysis and principal component analysis, because this method only focuses on defining a pattern that explains variance among the food items. That meat intake is slightly better explained by the pattern than refined grain intake is insignificant from a health point of view; it does not explain whether the pattern is related to a disease or not.

Edith FESKENS
Perhaps I can ask a second question. This is also directed to Professor Trichopoulou. If you look at these dietary indexes, for example the Mediterranean dietary score or the healthy eating index, you judge the diet, awarding one or two points for the highest group for olive oil or the groups for vegetables and fruits. Has anyone ever looked at weighing coefficients of these various components? We simply add them up and end up with a minimum of zero and a maximum of 10 points, for example, so that unhealthy fruit carries the same weight as unhealthy alcohol. What is your opinion on that?

Matthias SCHULZE
I think that this is a very good idea. If you are aware of nutrients or specific foods which have been shown to relate to a disease and the effect and attributable risk is known, then this should be incorporated by putting weights on them, so that alcohol and plant food oils will not carry the same weight in such a score.

Edith FESKENS
Where should we get those weights? From EPIC?

Matthias SCHULZE
Not by evaluating overall dietary patterns. I think that needs to be done in studies looking at the specific nutrients or foods.

Göran BERGLUND
Are there other questions?

Antonia TRICHOPOLOU
Thank you for giving me the opportunity to speak briefly about the Mediterranean diet score. We have also been working on principal components. In the Mediterranean diet score, in contrast to the principal components analysis, there is a real diet behind the Mediterranean diet score – a diet which exists and is clearly defined. In the context mentioned and according to the request of your Ministry of Health, what we have done is to analyse the traditional Mediterranean diet based on the Mediterranean diet score for seven days. At the end of those seven days, we observed that the traditional Mediterranean diet offers many many more nutrients than the diet habitually mentioned in our dietary guidelines. You would be surprised to know that we consume equal amounts of catechins as the Netherlands, but catechins are sourced from ten different vegetables – in the Netherlands, catechins are mainly sourced from tea – so that means something for the synergistic effects of the various components of the pattern. I think that there is a long way to go before we can decipher the beneficial effects of the traditional Mediterranean diet.

Göran BERGLUND
Thank you all. In this session we have analysed the effect of important sub-classes of fat intake and also put the finger on a new and important pattern tool to be used in the future analysis of foods and risk of disease. It will be very interesting in the EPIC study, which has centres from Athens to Tromsø in Norway, to see how this new tool can be used for better evaluation of risks. Thank you.

Sophie VILLERS
General Direction of Nutrition, Ministry of Agriculture, France

Good morning. I have the pleasure to represent Mr. Bussereau, the French Minister of Agriculture, to this third international conference on health benefits of the Mediterranean diet. On behalf of Mr. Bussereau, let me apologize for his absence today, and thank the Italian Health Ministy, which provided, with the French Ministry, great support to this conference, granting us this great Roman venue, at the heart of the Mediterranean culture. Let me also address our special thanks to Pr. Antonio Trakatellis, representative of the European Parliament, Mr. Wilfried Kamphausen, from the DG Sanco, and Mr. Elio Riboli, who is the president of this morning session and whose EPIC study is a great reference.

I am happy to open this session, which, I hope, will result in concrete actions to encourage balanced and diversified food consumption. Such an objective will not be reached without a consistent food policy from producers to consumers, which stands for a priority in the view of the current Minister.

"Nutrition is our first medicine", said Hippocrates. This does not mean that food should be regarded as a drug, but it stresses the fact that a diverse, well-balanced and pleasant diet that matches our specific needs is a way to remain healthy. As shown in more and more studies, in particular the 2003 WHO report on nutrition and prevention of non-contagious diseases, the relationship between nutrition and health is incontestable. Yet we must remain cautious not to medicalize food to avoid confusion in the mind of consumers. It is essential to promote dietary models such as the Mediterranean diet. Those not only emphasize the importance of dietary balance through food diversity but are built on cultural references that represent reliable landmarks for consumers, thus allowing for a better understanding and effectiveness of the message. Because of our lifestyle and the lack of connection between food and consumers, people have lost their nutritional landmarks. The dietary model approach is an important tool in policies that aim at fighting chronic diseases and obesity in particular. Such an approach covers various aspects of diet and nutrition, thus guiding consumers towards healthy choices, notably through food balance and awareness of the link between what we eat and what we are. Taste, pleasure, food culture, food origin, production and preparation that impact on health, all prove important. I hope all Mediterranean countries share this view. This seemed obvious in the debate around the tentative regulation on allegations at the European council. Southern European countries have asked that we take food cultures and traditions into account while elaborating nutritional profiles, in order for these to be easily achievable and to avoid confusion. This positive approach of food promotes the role of several types of foods for our health, according to the well-balanced combination of a diversity of foods. We must keep this essential idea in mind, which also underlies the French nutritional policy: there are no good or bad foods but they are more or less adequate diets for our needs and appropriate nutritional behaviors.

But how about implementing a new food policy? Informing consumers on possible benefits of a rich and well-balanced diet is not enough. Once nutritional recommendations based on nutritional models have been developed, the issue of behavioral changes remains. Concrete measures must be implemented by the authorities and the private sector in order to promote such changes. Nonetheless, their effectiveness still depends on our ability to integrate them into a real food strategy.

This will be discussed during the afternoon session, but we may already underline that food policy lies at the crossroads of health policy and agricultural policy. Thus, it is essential to seek overall consistency of public interventions in the field of food and nutrition. In France, the PNNS, National Program for Health and Nutrition, which will be presented by the vice-president of the supervising committee Mr. Hercberg, translates such an effort towards consistency. Beside his role in the definition and implementation of actions defined by the PNNS, the Minister is also required to help provide consumers with a high-quality food supply. The ministers of Agriculture and Health must also ensure the availability of high-quality foods. The services of the General Direction for food and nutrition are working on the implementation of the concept of accessibility through concrete actions at the level of supply and demand. When we recommend consumption of at least 5 pieces of fruit and vegetables a day, we also must ask other questions, such as: are fruit and vegetables easily accessible to consumers? Are they tasty, easy to eat on the go? How can they be prepared and complemented? To answer these questions, the Ministry of Agriculture, together with field professionals, has created pilot programs which aim at improving control over prices and nutritional quality of products, as well as the convenient aspects of their consumption and proximity of distribution points. The question of employees' lunch cannot be neglected either. Nowadays, special attention must be put on school restaurants as well. Thus, measures such as fruit distributions in schools are currently under consideration. Actually, school restaurants have already received specific nutritional recommendations; the General Direction of food and nutrition is currently evaluating their implementation and will strengthen the mechanism if necessary.

Together with the authorities, all actors must come together to conduct effective field activities. As far as field work is concerned, I would like to stress the importance of partnerships and voluntary actions on the side of economic actors. This is also the view of the European Commission which is currently working with several European federations within the framework of the network for common actions for nutrition, physical activity and health. Mr. Kamphausen will probably tell you more about this.

It is possible to achieve synergies among fields towards the promotion of diversity, balance and pleasure in dietary habits as a whole. I would like to thank each and every French field for their dynamic role in this regard. The Minister encourages them to build local partnerships in order to facilitate information and accessibility of basic products within the framework of nutritional education activities. As an example, I would like to mention EPODE (Network for the prevention of childhood obesity). Local authorities are conducting local actions with partners from the health, education and production sectors, so that children can be encouraged to modify their dietary behaviors, exercise more and that overweight/obese children find counseling. Production fields naturally play a great part in this multi-partnership and local approach. In this regard, I would like to thank APRIFEL for organizing this international conference over the years, as well as for its various actions towards the improvement of fruit and vegetables accessibility. This afternoon's presentations will allow us to underline the role of agro-food industries in the supply and distribution of foods of high nutritional quality. Despite the constraints, French companies have shown their awareness and are working, either individually or collectively, to attain this goal. The PNNS

provides a framework for all types of actions. In that sense, companies have, for example, voluntarily agreed on the reduction of salt content of processed food.

As a conclusion, let me thank again all actions that bring partners together on a voluntary basis in order to promote diversity, balance and pleasure in dietary habits through the improvement of supply and dietary habits.

In this regard, all the links of the food chain are concerned: farmers, transformers, distributors, consumers, researchers and education actors. We will mobilize all actors towards the fight against non-contagious diseases which are unfortunately spreading steadily in our populations. However, the fight will be all the more successful as we keep in mind that food plays a role in our “nutrition”, our “health” but also in our “dreams”. Thank you very much.

Introduction

Elio RIBOLI
International Agency for Research on Cancer (IARC-WHO), Nutrition and Hormones Group, Lyon, France

We wish to thank Ms Sophie Villers, from the French Ministry of Agriculture, for her participation and her important declarations which show serious, active and long-term commitment to the implementation of the French National Program for Nutrition and Health (PNNS). France is one of the few European countries to have developed such a plan as a framework for intervention towards better nutritional standards, food quality and health. This cutting-edge approach should be adopted by other European countries.

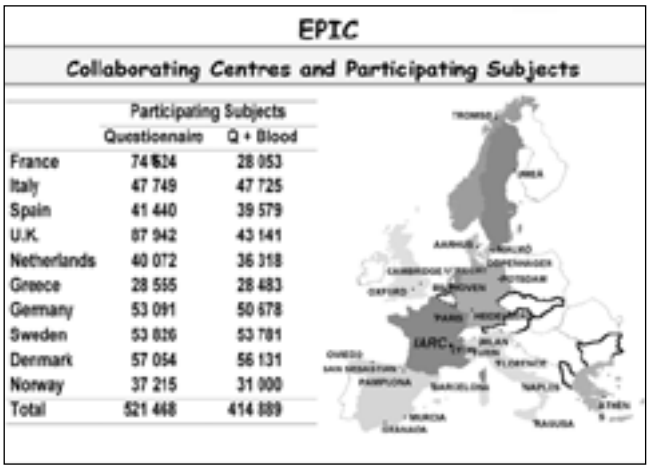
I would like to elaborate on one of the ideas that were raised earlier regarding the medicalization of food. Today, as more and more messages seem to encourage a health benefits based approach in food consumption, we tend to forget that our consumption should be essentially driven by the taste of foods we eat. Of course, eating does play a part in the improvement of our lifestyle but it should not be perceived as an obligation or duty.

Let us open the first session of the day, on the relationship between food and cancer. We will hear four interventions about four types of cancer. I will introduce these sessions with the EPIC study whose main characteristics were presented yesterday by my colleague and friend Rodolfo Saracci.

Where do we stand in the search for the nutritional causes of cancer?

Elio RIBOLI
International Agency for Research on Cancer (IARC-WHO), Nutrition and Hormones Group, Lyon, France

The presentations will essentially be based on EPIC results. EPIC is a prospective study on approximately half a million subjects. The study was conceived in the early 90s, when I was working with Rodolfo Saracci at the Unit of Epidemiology at the International Center for Cancer Research, WHO, Lyon. We were seeking proper actions to be conducted by the United Nations centre in France, in order to improve knowledge of nutrition and cancer while capitalizing on our international and European outreach. We then adapted the concept of the Seven Countries Study on cancer with a more modern approach. We wanted to investigate the relationship of nutrition, cancer and other chronic diseases by studying individuals' dietary habits and their relation to several cancerous and non-cancerous pathologies.



We also intended to make use of the great variability in terms of diet and lifestyles from the North to the South of Europe. Since they were already conducting similar studies, three Scandinavian cohort studies joined EPIC.

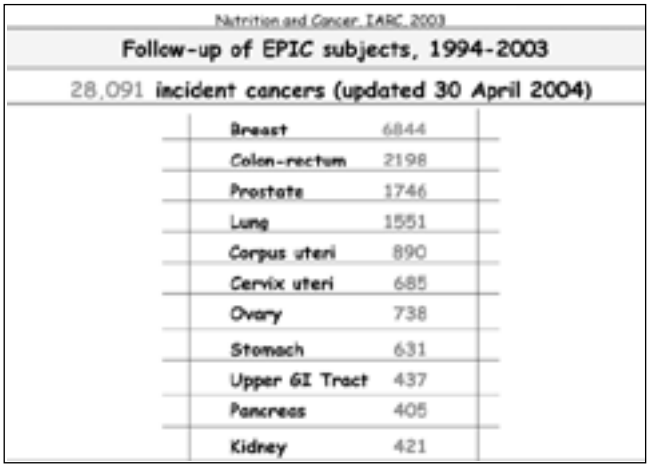
A prospective study requires means and time in order to collect data on lifestyles and habits of the subjects. A follow-up mechanism had to be implemented. In Europe, we have an excellent network of cancer databases that allows for the close monitoring of the half-million of individuals that participate to the study. It thus becomes possible to study the link between cancer, coronary diseases – and soon, diabetes – with data about lifestyle and other characteristics about the subjects before and at the time of inclusion in the study.

EPIC is the first study in the world to have collected blood and DNA samples in order to analyse the relationships between genetic and diseases in all the cohort.
EPIC is an EU-financed consortium that gathers 24 centres and was created fifteen years ago. It is managed by an executive committee that represents the EU countries. As a group and in a very friendly manner, these centres actually planned and prepared the scientific implementation of the project. Initially conceived as a cancer-oriented project, EPIC was gradually broadened to include other chronic diseases and conditions. Some members of the project are here with us: Antonia Trichopoulou, University of Athens, who is responsible for the 'Epic Elderly', Ken Derlee, who has just received new contributions from the EU for studies about the dietary recommendations, Rodolfo Saracci, who initiated the "cardiovascular" side of the project with EPIC HEART, and Nick Wareham from the Cambridge Medical Research Council, in charge of the "diabetes" component.

At the beginning of our study, we had 14 000 subjects with diabetes. During the follow-up, more than 15 000 have developed the disease. This is turning to be the most important study ever conducted with a sample of 30 000 diabetics. We are also analyzing total mortality, i.e. general survival, which is one of the best indicators of the relation between lifestyle and life expectancy. A specific sub-project on obesity titled EPIC PANACEA is also underway and we are very hopeful that the EU will support it.

A half-million study is not an easy thing to manage. It was built upon a huge database with thousands of variables for each subject, as well as a network of biological databanks, which makes it the most important biological databank for biomedical research in the world. All samples were stored at –196° C.

This morning's presentations were based on the outcomes of EPIC and other studies of diagnosed cancers for which we had reliable data for the first 6-7 years of follow-up. We rely on precise data for 28 000 cases of cancer.



As a conclusion, I would like to share with you the scientific approach we have been following along the project. Research relies on ideas. Yesterday, a speaker stressed that research has nothing to do with chance. The relationship between hormones and breast cancer, or the protection against cancer through specific foods should be integrated in etiological and biological models. To do this, a prospective study, with nutritional, anthropometric and metabolic components, and with biological samples, constitutes a useful scenario.
The concept of "evidence-based medicine" is very important. Replication, i.e. the repetition of studies among diverse populations, proves essential. EPIC does allow for replication since it was led in 10 countries simultaneously. Replication therefore stands for an implicit component of the project.

Above all, we should never forget that, unlike laboratory mice, people have their own lifestyles, which may vary and are linked to dietary habits. We are conducting such a research on the relationship between nutrition and health because we all share the desire to see our work benefit the people; in other words, we want to see scientific results translated into public health measures, to avoid pointless projects. This is a long-term process that will require broad-based support and participation.

Nutrition, steroid hormones and breast cancer

Franco BERRINO
Istituto Nazionale per lo Studio e la Cura dei Tumori, Epidemiology Unit, Milano, Italy

Thank you very much and good morning. The history of hormones and breast cancer is a very long one. The relationship between ovarian activity and breast cancer has been known for over a century, but it has been in the last 50 years that many different hypotheses came out and started fighting one against the other. There have been many hormonal hypotheses on breast cancer. Almost each hormone has been considered by different authors in different periods as responsible for the growth of breast cancer, either for the initiation, promotion or progression of breast cancer. Now things are a bit clearer.

In 2002, the Endogenous Hormones and Breast Cancer Collaborative Group put together all the available prospective data on hormones and cancer in post-menopausal women (nine prospective studies with biological banks carried out in Italy, Japan, UK, and the United States). The results were based on over 600 cases of cancer that occurred in these nine cohorts. For several types of oestrogens there is a clear trend of increasing risk with increasing plasma concentrations. However, not only oestrogens are involved in breast cancer aetiology; androgens are involved too, at about the same strength of association (Figures 1 and 2).

Figure 1. Relative risk of postmenopausal breast cancer by fifth of hormone concentration: pooled reanalysis of 9 prospective cohort

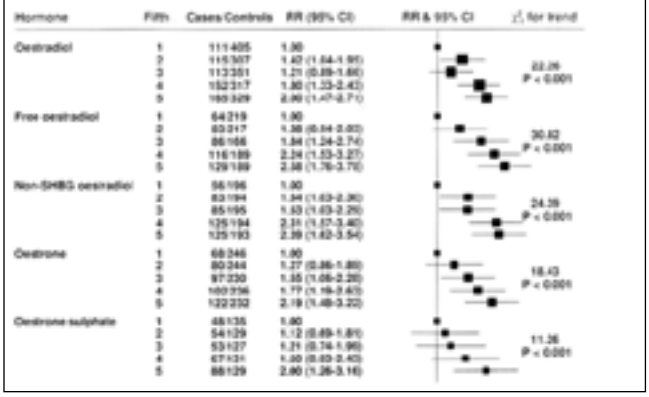
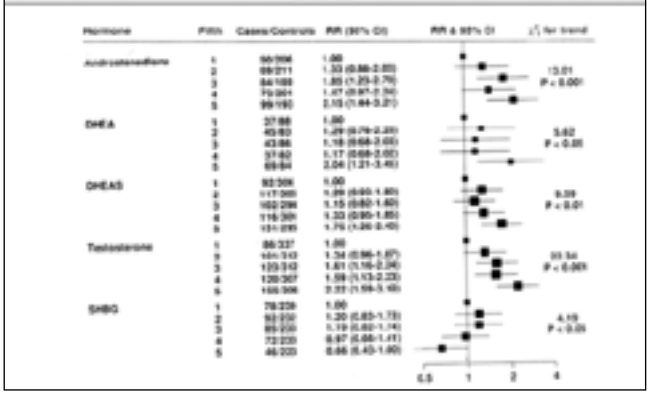


Figure 2. Relative risk of postmenopausal breast cancer by fifth of hormone concentration: pooled reanalysis of 9 prospective cohort



This is not only because androgens are a precursor of oestrogens. When androgen levels are adjusted for oestrogen levels, and vice versa, both maintain a significant association. We do not know exactly what the mechanisms are for these different hormones, but we can say beyond reasonable doubt that an increased level of sex hormones is associated with an increased risk of breast cancer.

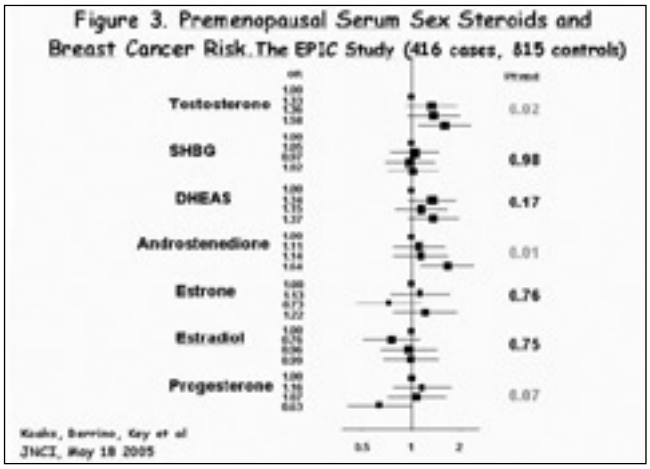
Recently, the European Prospective Investigation into Cancer and nutrition (EPIC) confirmed all these results in post-menopausal women, with almost exactly the same results as in the pooled analysis, in a single study with over 600 incident breast cancer cases. In this analysis we excluded all the women that were under hormone replacement treatment. So we know fairly well what is the pattern of endogenous hormones associated with post-menopausal breast cancer.

Things are much more difficult before the menopause because the hormone levels vary over the ovarian cycle. It is actually a mess: we would have to take blood every day of the cycle to understand anything, and even that would not be easy to interpret. Things are difficult in particular for studying the role of progesterone, which is only produced in the second half of the cycle. Its levels may vary a lot depending on when blood is taken in this phase of the cycle: in a normal 28-day cycle progesterone is usually high between the 20th and 24th day of the cycle, but if the cycle is shorter, these days could be at the end of the cycle, when progesterone is low. If the cycle is long, these days could be near the ovulation when progesterone is also low, so it is really very difficult to plan a study of this type. The issue is important because there are conflicting theories about the role of progesterone in breast cancer: according to one theory, a well-functioning ovary producing progesterone in the second half of the cycle is associated with a lower risk; according to another theory, a normal production of progesterone is associated with an increased risk.

Our ORDET (Hormones and Diet) prospective cohort study is relatively small compared to the huge volume of studies such as EPIC: we recruited only 11 000 women, 5 000 post-menopausal and 6 000 pre-menopausal, but blood was collected from fasting women, between 8 and 9 o'clock in the morning, between the 20th and 24th day of the menstrual cycle, and we also collected the date of the previous and the following menses. To synchronise the moment of blood collection of cases and controls over the cycle we took into account in the analysis the length of the cycle, the distance from the subsequent menses, and the LH/FSH levels, which may indicate if blood was taken near the ovulation. We also excluded women who had menstrual irregularities suggestive of perimenopause, for whom it is very difficult to interpret the menstrual phase. The results showed a strong association with total testosterone, but an even stronger association with progesterone – in the sense that women with a high progesterone level have a significantly lower risk of breast cancer (Micheli et al., 2004). This, however, was based on a small number of cases.

A much larger study on breast cancer cases occurred in pre-menopausal women recruited into the EPIC study has just been published. This study very neatly confirms that the level of androgens – the level of testosterone in particular – is associated with pre-menopausal breast cancer risk, and that the level of progesterone is negatively associated (Figure 3) (Kaaks et al., 2005). When the analysis was restricted to pre-menopausal women younger than 50 years of age at recruitment in order to avoid perimenopausal irregularities, the protective association of

progesterone was more evident. Unfortunately, the EPIC study did not collect blood in a given day of the cycle but the dates of previous and subsequent menses were usually available and we could work on over than 400 cases, so we were able to produce robust analyses that corroborated the results of the ORDET study. Before menopause there was no association with oestrogen levels (Figure 2).



So we now have a clear pattern of association: after the menopause, breast cancer is associated with androgens and oestrogens; before the menopause, there is a positive association with androgens, a negative association with progesterone, and no association with the level of oestrogens. This does not mean that oestrogens are not important before the menopause – they are always very high and always at a level sufficient to promote the development of breast cancer. After the menopause, we see an important effect of a doubling of the level of oestrogens – a doubling of the level of oestrogens after the menopause still means that it is ten times less than the level of oestrogens before the menopause. However, oestrogens cannot be used as a risk indicator before menopause.

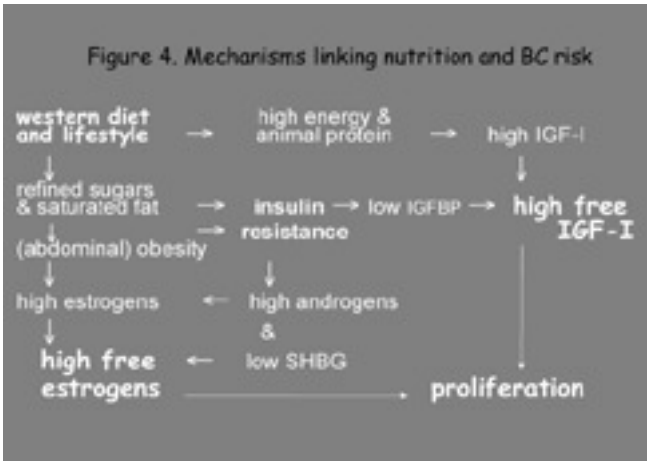
The history of progesterone is a long history. The hypothesis was that a normal menstrual cycle would be protective, while chronic anovulation syndrome associated with an increased production of androgens and a luteal insufficiency. The hypothesis was formulated in the early 1960s. In 1964, Professor Grattarola, from our institute published a study in which he evaluated anovulation with endometrial biopsies. He found that breast cancer patients very frequently had a proliferative hyperplasia of the endometrium in the second half of the cycle instead of a secretory one.

Twenty years later, Dr Secreto from our institute published a case-control study based on the measurement of testosterone and progesterone in blood, and the results were consistent with the original hypothesis.

Again, 20 years later in 2004, Dr Micheli published our first interpretable results on pre-menopausal women and breast cancer, confirming that high androgens and low progesterone are associated with breast cancer risk. The EPIC study now corroborates this hypothesis.

Also a recent publication on the risk associated with hormonal replacement therapy in the French section of the EPIC study – the E3N prospective study of 100 000 teachers in France – falsify the hypothesis that progesterone may increase breast cancer risk. France is the unique country where a natural progesterone – the micronised progesterone – has been widely used in the hormonal replacement treatment of menopausal symptoms. In all other countries, particularly in North America and northern Europe, the progestins associated to oestrogens have been of a different type – medroxyprogesterone is being used mainly in North America and nortestosterone derivatives in northern Europe. The association of oestrogens plus progestins was usually found associated with an increased breast cancer risk. The risk is very high with nortestosterone derivatives that have a strong androgenic activity, and a moderately high with medroxyprogesterone acetate that has less androgenic activity. The French study did not evidenciate any increased risk when natural progesterone was used, but confirmed the increased risk with synthetic progestins. These results corroborate our hypothesis that natural progesterone is not a risk factor for breast cancer, and that actually women who have a normal menstrual activity are at lower risk.

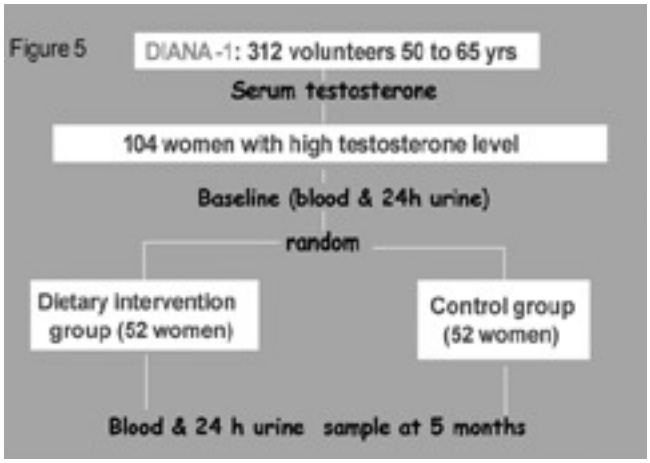
Another field of research on hormones and growth factors in breast cancer aetiology has to do with the glucose metabolism. In our study, we found a significant association (only in pre-menopausal women) with glycaemia (within the normal range), some association with insulin and a significant association with the level of IGF-I. Other studies have found the same. It appeared at the beginning that this association was prevalent only in pre-menopausal women; other studies suggested that there is also an association after the menopause. However, there are some inconsistencies in these results. Also, the genes involved in the synthesis of insulin and IGF-I and in the regulation of these factors are being systematically examined, but again, there is no strong association with the genetic effect, at least up to now, while there is some association with the dietary pattern. In particular dietary proteins, mainly animal proteins and milk proteins are associated with a somewhat higher level of IGF-I in the blood.



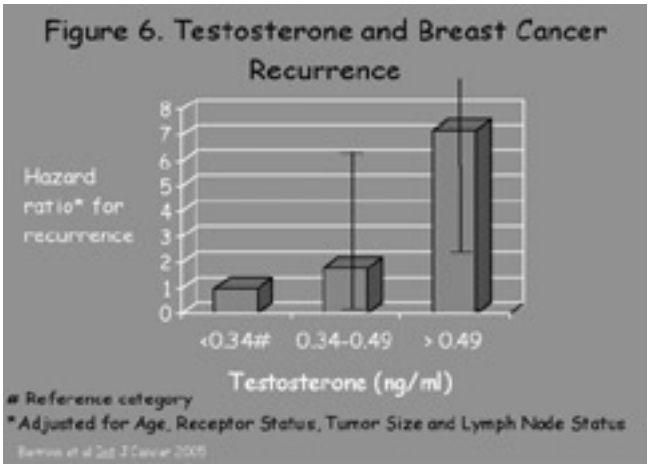
On the basis of this knowledge, we developed the hypothesis that we might modify the level of sex hormones and growth factors by modifying the dietary style. Figure 4 illustrates a simplified mechanistic interpretation of the relationship of western diet with breast cancer: western diet is associated with high energy and animal proteins that determine a high level of IGF-I; western diet is associated with refined sugars and fat that in turn are associated with insulin resistance; insulin has a gonadotropic activity, stimulates the synthesis of androgens in the ovary, and inhibits the synthesis of SHBG, the sex hormone binding globulin that regulate the bioavailability of circulating androgens and oestrogens; insulin, moreover, inhibits two of the IGF binding proteins. This means that both oestrogens and IGF, which co-operate for the proliferation of epithelial breast cells, including breast cancer cells, are more available.

According to the above rationale we designed a first randomised dietary intervention study – the DIANA (diet and androgens)

study. We randomised 104 women who were in the upper tertile of the blood distribution of testosterone, and we modified the diet of half of them. We measured the level of hormones in the blood and urine again after five and a half months (Figure 5).



The dietary intervention was a diet based mainly on unrefined cereals, a lot of pulses and vegetables, no sugar, and a little meat, cheese and milk, based on the traditional Mediterranean diet and macrobiotic recipes. We avoided foods such as white bread, potatoes and cornflakes, and we used highly satiating food. All of these women lost some weight – 4 kilograms on average – and we found that they tended to eat less just because the diet we proposed was fairly satiating. These women came twice a week to eat with us and to follow kitchen courses. We organised 50 different menus in order to show that we may have a wide variety in the diet even with these principles. Their testosterone decreased, together with free oestradiol, insulin and glucose, and also cholesterol and triglycerides went down. On the contrary SHBG and IGFBP1 and 2 went up. IGF-I, however, did not change significantly, perhaps because we did not decrease protein in this diet – we just shifted from animal to vegetable proteins.



The second trial we carried out (DIANA 2) was with breast cancer patients. The study included 110 disease free breast cancer patients who followed our diet for one year and the incidence of recurrence, including of local recurrence, distant metastasis and contra-lateral breast cancer, was recorded over 5.5 years. Previous studies had suggested that several diet-related factors may affect the recurrence of breast cancer: obesity, weight gain during adjuvant treatment, hyperinsulinemia. The results of our study showed that also high serum testosterone is a major determinant of breast cancer prognosis (Figure 6). To a lesser degree, also oestradiol, body weight, glycaemia, as well as the presence of metabolic syndrome affected prognosis.

The numbers are small, but when we classified women according to whether they succeeded in reducing their testosterone level from above the median value to below the median, those who succeeded had a lower frequency of recurrences (Berrino et al., 2005) suggesting that breast cancer patients may reduce their risk of recurrence through a change in their diet. Thank you very much.

Questions

Elio RIBOLI
Thank you, Franco. You cannot present everything in half an hour, but could you say a few words on what make you think that these results are important for public health? In this randomised trial, you started with changes in diet and lifestyle. To what extent do you think these changes are within the reasonable reach of feasibility for the normal population?

Franco BERRINO
In this study, we put a lot of effort into changing these women's diet in a radical way, and we invested a lot in psychological assistance. However, there is more and more evidence that all the factors defining metabolic syndrome – high blood pressure, low HDL, high triglycerides, high glycaemia and waist circumference – are associated with breast cancer. As you saw yesterday, there are several ways that are not necessarily dramatic to improve metabolic syndrome. Metabolic syndrome is associated in women with a high testosterone level, and so it is reasonable to hypothesise that an even less dramatic change will reduce incidence and improve survival.

Nick WAREHAM
One of the things we observe from diabetes epidemiology is marked variation in the prevalence around the world, with some particular populations having an extraordinarily high prevalence. The question is really an ecological one: does that variation map at all to breast cancer incidence?

Franco BERRINO
I would say yes, the diabetes map is quite consistently superposable on the breast cancer incidence map. The relationship between diabetes and breast cancer is a little confused. It did not appear in the old studies, but then I was very impressed by a study showing that women with breast cancer had a higher risk of diabetes. This is interesting because the problem is not that diabetes per se increases the risk of breast cancer, but the pre-diabetic condition, when insulin is still high, may increase the risk. At the end, when the pancreas is not producing more insulin in sufficient quantities, there is probably not a strong association.

Elio RIBOLI
There is a study within EPIC where we investigated and measured the C-peptide. C-peptide is a small peptide that belongs to the insulin molecule that is removed from insulin, and then insulin becomes biologically active. C-peptide is a good marker in blood of a high insulin production level by the pancreas. We measured the C-peptide in blood samples collected many years before the development of breast cancer and in women who did not develop breast cancer. We are now analysing the result and we find that a high level of C-peptide is associated with a significant increase in the incidence of breast cancer, which means multiplying by 2.5 – the high level versus the normal level – in women older than 65 or 70. There is a weaker association in women between 50 and 60, and there is almost no association, or no effect, below 50.

This is extremely important if we think that overweight does not increase the risk of breast cancer before the menopause, while overweight is strongly associated with an increase in breast cancer after the menopause, and in a way, C-peptide is closely related to overweight. So we have a situation where overweight after the menopause and what is called insulin-resistance, which is a poor utilisation of insulin and glucose by the organism, are associated with breast cancer.

Member of the audience
In relation to the level of testosterone in the intervention with the Mediterranean and macrobiotic diet, I would like to know something more about the combination of the two diets and what you mean exactly by macrobiotic intervention.

Franco BERRINO
Next time, we will organise lunch using the DIANA diet for you to see that it can be appreciated by everyone.

The typical diet we used was a vegetable soup or a mixed salad, followed by a main dish, with cereals every day, like wheat, rice, buckwheat, millet or barley, and with various kinds of pulses and cooked vegetables. There was also a desert almost every day, which was made without sugar, milk, butter or fats. There was a wide variety of macrobiotic deserts and also a lot of nuts. We are fairly confident that the recommended dietary allowance was respected for all essential nutrients.

We are now carrying out the DIANA 3 study on young women – this is a low-protein diet with just 9% of calories from proteins – in order to see if we are able to act more on IGF-I.

Member of the audience
Do you mean vegetable proteins or also animal proteins?

Franco BERRINO
Mainly vegetable proteins – these women are advised to have animal protein only once a week.

Diet, obesity, physical activity and colorectal cancer

Teresa NORAT
International Agency for Research on Cancer, Unit of Nutrition and Cancer, Lyon, France

I will present some of the results from the EPIC study on the association of diet and colorectal cancer. Some of the results are preliminary and some of the results have already been published. Specifically, I will present the preliminary results on obesity and physical activity, fruit and vegetable intake, and dairy products intake; and I will present our published results on fibre (with a new update), and meat, fish and poultry.

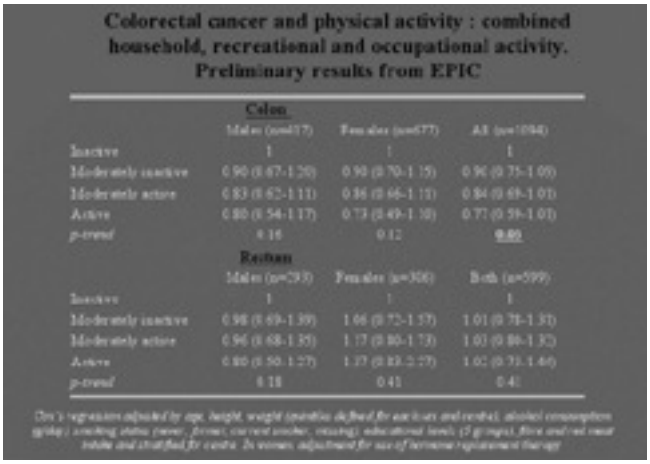
Colorectal cancer represents one of the most frequent causes of cancers in the world. We can see in the figure the rates of incidence and mortality of colorectal cancer in developed and developing countries. The rates are increasing in developing countries. Changes in incidence rates together with studies in migrant populations showing that the rates in the immigrant population approach the rates of the host population have suggested that colorectal cancer risk is related to lifestyle.

In EPIC, we have the advantage of having cohorts from 10 different countries, which allowed us to investigate populations with very diverse dietary practice. We have followed the subjects for cancer incidence and mortality through cancer registries in 7 of the participating countries, while we have a combination of methods to identify incidence and mortality for colorectal cancer in three other countries through active follow up. To date, we have been able to identify close to 1 800 cases of colorectal cancer that we have included in the analyses presented here.

Recently, an important meeting was held at the International Agency for Research on Cancer to evaluate the evidence concerning the association of overweight, obesity and physical activity with risk of several cancers. This table used for the expert group in that meeting, showing the results of all case-control and cohort studies published at that time, shows that subjects in the highest level of physical activity, compared with subjects in the lower level of physical activity, had a reduced risk of colorectal cancer.

In EPIC, we have collected information about work-related, household and leisure time physical activity in the participants at recruitment through questionnaires. Measuring physical activity in population studies is very difficult. The studies that have been published have measured physical activity using different questionnaires, but the measurements have not been validated in most of those studies. We have collected the frequency and duration of different types of physical activity, but we do not have measurements of the intensity for many activities. We know how many hours a person walks by week, for example, but we do not know the speed the person walks at. As in other studies, our results are subjected to measurement error.
In EPIC, physical activity at work was classified by level of intensity as sedentary activity, standing, manual or heavy manual activity. For non-occupational activities, the metabolic equivalent of energy expenditure (Mets) was applied. The participants in EPIC were categorized in quintiles of Mets and an index of total physical activity created by combining occupational and non-occupational levels of activities. We used this index to investigate the association of physical activity with colon and rectal cancer risk.

Here we see the results of the study on colon cancer in males. The inverse trend of colon cancer risk across categories of inactive, moderately inactive, active, and very active subjects are statistically significant. The trend in women was in the same direction but not significant. However, the results for men and women are not statistically different, so we could combine them. When men and women are combined, we observe a significant inverse trend between colon cancer risk and physical activity. The subjects who were classified as active in our study had a relative risk of 0.77 compared to the inactive, while for rectal cancer, as in other studies, we do not see any association.



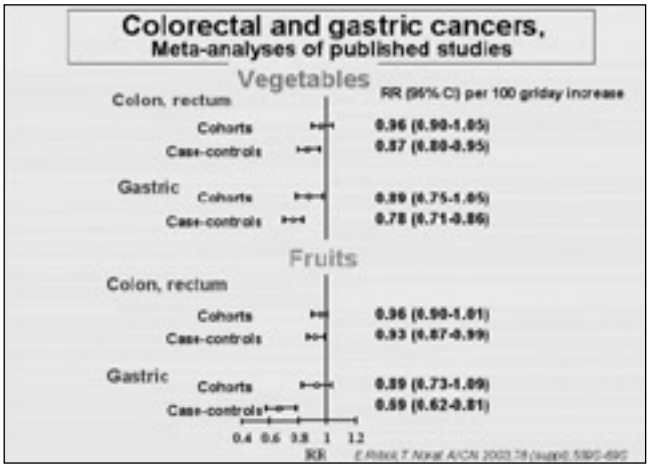
These analyses has been adjusted for age, height, weight, alcohol consumption, smoking status, educational level, dietary fibre and red meat intake, and stratified for center. We also adjusted for the use of hormone replacement therapy in women.

In this figure, extracted from the IARC report on overweight and physical activity, we observe the relationship between body mass index and risk of several cancers in published cohort studies. The values are the relative risk when comparing groups of subjects with the highest level of body mass index versus the lowest level of body mass index in each of the studies. The comparisons are not strictly the same across studies, but in most of the studies, the highest level was "higher than 28 kg/m^2" versus "less than 22 kg/m^2" of body mass index. We can appreciate the positive association between body mass index and colon cancer risk.

In these preliminary results of EPIC, we observe a significant positive trend between colorectal cancer and body mass index; increasing body mass index is associated with significant increased colon cancer risk in men, but this trend is not significant in women in EPIC. Rectal cancer risk is not associated to body mass index in this population. This is consistent with most of the other studies.

When we analysed an index of abdominal obesity – the ratio of waist to hip circumferences – we observed that in both men and women, the ratio of waist to hip is significantly positively associated to the risk of colon cancer in women and men.

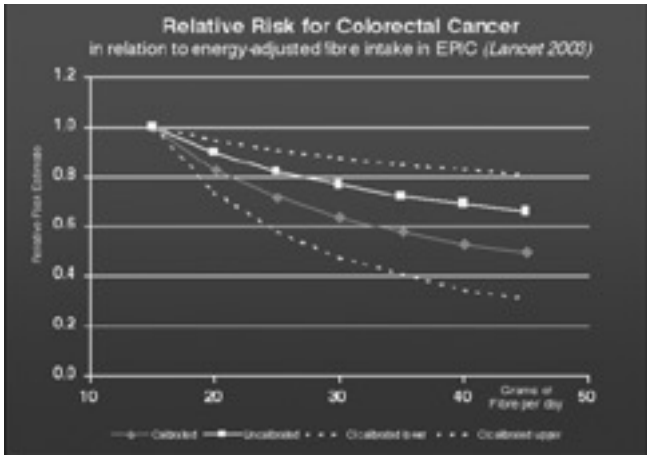
The association of colorectal cancer with fruits and vegetables has been investigated in several case-control and cohort studies. We published a meta-analysis of published studies showing that the overall results of case-control studies suggested a significant association between vegetable intake and colorectal cancer, but that this association was not confirmed by cohort studies, for which the overall results showed an inverse but not significant association.



The analyses on fruits and vegetables we are showing are preliminary and include only the cases reported until five years ago. We are now re-analysing the information, with the latest update. In the preliminary analyses, we observed a significant inverse trend for vegetables and for fruits and vegetables combined, while no association was observed with fruits.

We published a paper about the association of nuts and seed intake with colon cancer risk in EPIC, showing an inverse association of nuts intake and colon cancer risk in women but not in men. These results have to be confirmed by other studies.

The study of the association of dairy products and colorectal cancer in EPIC is ongoing. Interestingly, our first results are consistent with the results of the Pooling Project of cohorts, published last year. In EPIC, we observe an inverse association of milk intake and colorectal cancer risk, and inverse but not significant for cheese and yoghurt. The analysis was adjusted for sex, energy intake, height, weight, physical activity, alcohol consumption, smoking status, dietary fibre, folic intake, red and processed meat. We are working in the classification of the dairy items to differentiate milk according to its fat content in EPIC.



The results on the association of dietary fibre and colorectal cancer risk were published in the Lancet two years ago. The hypothesis that dietary fibre is protective against colorectal cancer is a well established hypothesis, but most of the recent studies have not found an association between dietary fibre and colorectal cancer risk. There is a wide variability of fibre intake across countries. Most of the fibre comes from cereals in EPIC but vegetables and fruits are other important sources. The results published in Lancet showed a significant inverse association between fibre intake and risk of colon but not rectal cancer.
Why have these results not been found in other cohorts? We think that the wide range of fibre intake in the EPIC population allowed us to detect this effect. We repeated recently the analysis with two more years of follow-up and in addition, we adjusted for the dietary folate for which we could not adjust in the first analysis, and we obtained exactly the same results as in our first paper, which are mainly that that the association of fibre is mainly with tumours of the left colon, is not significant with tumours of the right colon, and there is no association with risk of cancer of the rectum. With almost 700 more case subjects and a better adjustment, we see the same protective effect of dietary fibre against colon cancer as in the previous study.

The first cohort study that published that the risk of colon cancer was positively associated with high red meat consumption was the Nurse's Health study in 1990. Several studies have replicated this finding. The ecological correlation between meat consumption and the incidence of colon cancer was already showed in an interesting article published in 1975. These two maps show the concordance of geographical distribution of red meat intake and colorectal cancer risk. These are based on updated information on cancer incidence from IARC, and estimates of food availability from FAO. We published a meta-analysis of case control and cohort studies, showing that colorectal cancer risk was inversely although no significantly associated with fish, no associated with poultry, and positively significantly associated with the consumption of processed meat and fresh and processed meat combined. Processed meat is a very heterogeneous category in which you can find sausages, dried sausage, raw and cooked ham, different types of bacon and other types of processed meat. Most of the processed meat at the time the studies were published was from pork.
There is a high heterogeneity of consumption of fish, red meat, processed meat and poultry in the EPIC population. Interestingly, the consumption of processed meat in Greece is the lowest in EPIC. The highest consumption of processed meat in EPIC is in the German countries. The consumption of red meat is the highest in the nordic countries; the consumption of fish is the highest in Spain and some of the nordic countries.

In EPIC, we observe a significant increase of colorectal cancer risk associated to the intake of processed meat, and red and processed meat combined. There is no association with poultry. There is a significant inverse association with fish intake, and we see a significant protective effect associated to the consumption of fish. To investigate if the increased risk associated to red and processed meat, or the protective effect of fish, were explained by displacement of red meat by fish and vice versa, we did cross-classified analysis categorising the subjects according to the intake of red and processed meat – low, medium and high – and simultaneously to the intake of fish, in low, medium and high intakes. The protective effect of fish is observed for all the levels of intake of red and processed meat. The subjects with a high consumption of red meat and a low consumption of fish have a relative risk of colorectal cancer of 1.63 compared to subjects with a low consumption of red and processed meat and a high consumption of fish.

Since we observed a protective effect of fibre and subjects who eat more red and processed meat tend to eat less fibre, we did a similar analysis combining the consumption of fibre with the consumption of red and processed meat, and there was no statistical interaction.
There are well established mechanisms supporting the role of fibre in the protection against colorectal cancer: There are suggestive mechanisms supporting the role of meat in the association of colorectal cancer, in particular the presence of some carcinogens formed during the cooking of meat at high temperatures for long periods of time, and the endogenous formation of nitroso-compounds, that can be mutagenic. In the EPIC study we observe a positive association of red and processed meat and an inverse with dietary fibre. Our results suggest that fish could be protective against colorectal cancer. Thank you.

Questions

Franco BERRINO
My question refers to poultry, for which you showed an insignificant negative association. I wonder if this negative association would disappear if you adjust for red meat. I would like to ask you what could be the reason why red meat could increase the risk and poultry does not increase the risk. Poultry also contains haeme iron in different quantities according to the type of poultry, and heterocyclic amines are formed while cooking poultry. The type of fat is different, but the type of fat does not seem very important for the risk of colon cancer. What is your idea about that?

Teresa NORAT
You are right, when red meat and poultry are together in the model the non-significant association with poultry is even more attenuated. When beef, pork and lamb are together in the same model, only the association with pork remains significant. When ham, sausages and bacon are in the same model, none of them explained the association independently. There are no clear mechanisms to show why processed meat should increase the risk more than red meat, but we do know from the metabolic studies conducted in Cambridge that in subjects fed with red meat there is an increase in total apparent nitroso-compound in the faeces – this is catalysed by iron coming from haem iron, but not for inorganic iron – while no increase in the total nitroso-compound in the faeces is observed in subjects fed with white meat. This study has been published and is probably the most supportive of our results.

Regarding the formation of carcinogens in meat, fish and poultry when they are cooked, these hypotheses have been explored in a few epidemiological studies. We do not see an association with fish and poultry, although there are heterocyclic amines in fish and in poultry. This can be explored in association studies in subjects with certain polymorphisms of metabolic enzymes participating in the activation of these carcinogens. The Colorectal Cancer Group has recently published a study in which they studied genotypes associated to the carcinogen activation and their results are not supportive of the effect of heterocyclic amines. I think that the endogenous nitrosation in the presence of haem iron iron could explain the association with red meat. We do not have a hypothesis to explain why processed meat should increase the risk more than fresh red meat, although we have observed that in our meta-analysis.

The other interesting topic related is dietary patterns. We have a project on dietary pattern. It is very interesting that the apparent noxious effect of red meat was attenuated in subjects with a high consumption of fibre. These results need replication.

Member of the audience
Could you recap your preliminary results done on fruits and vegetables and maybe give a little more detail?

Teresa NORAT
As I said, these results are preliminary. At that time, we only had about 700 case subjects. We do not know what the results are now with a longer follow-up. Preliminary, we observed an inverse association of vegetables, and fruit and vegetables combined with colorectal cancer risk. When we examined the different types of vegetables, the association was significant with green leafy vegetables. However, there are questions of measurement error and we cannot exclude that measurement error of intake varies according to the type of vegetable, at least in European populations. If the association exists, it is probably weak, because several other studies have not found a significant association.

Member of the audience
I have a brief question on the protective effect of milk. Is there any chance that the cases would have avoided milk for some reason, for example hyper-lactation or something like that, or just not feeling well so they avoid milk?

Teresa NORAT
The proportion of non-consumers of milk in our population is very low – so low that we could not make a category of non-consumers.

Elio RIBOLI
I interpreted the question in a different way, but I will pose another question anyway. Did you look at the association with milk specifically for the cases occurring in the first few years of observation? I understood that some bowel dysfunction that may be related to that diagnosis could modify the milk consumption.

Teresa NORAT
In almost all the cases, the diagnosis is after the first two years of follow-up. Thu, the results are very much driven by the cases diagnosed after the first two years.

Elio RIBOLI
To follow this question on changes in diet, this may be related to symptoms preceding the appearance of the disease. What we systematically do in EPIC and other cohort studies is that we look at the association with the cases that are diagnosed during the first year, and those during the second period of either 3 to 4 years or 5 to 6 years. There is no real indication that this has any impact on the association with disease risk and sometimes it becomes even stronger.

Member of the audience
I would like to add to Elio's comment that in our cohort, we never see a difference, excluding or not cases diagnosed during the first 2 or 3 years.

I would like to ask if you have looked at butter consumption.

Teresa NORAT
Butter is highly correlated with dairy product intake but we did not see a significant association. I do not remember the exact figures of hazard ratios. The problem with butter is also measurement error.

The previous member of the audience
Because in our data, I was seeing an inverse association as well.

Teresa NORAT
I think we have a non-significant inverse association, I am not sure now, but I interpreted it as driven by the correlation with dairy products.

Coming back to the haeme iron hypothesis, we did an analysis of offal intake and we did not see any association. I think you published a paper recently on liver and colorectal cancer recently. Would you like to comment on it?

The previous member of the audience
We have been studying black pudding, which has a very high concentration of haeme iron, and we see a very strong association with this special food item, and with haeme iron – our intake level of liver is very low so we could not recognise an association.

Elio RIBOLI
The catalysing effect of haeme iron on the endogenous formation of nitrogenic compounds that has been clearly shown by metabolic studies on volunteers I think are of major importance for the mechanistic interpretation of what happens in the lumina and in the colon, and that corroborates very nicely for the first time the results of our epidemiological study.

Vegetarianism and cancer risk

Tim KEY
Cancer Research Epidemiology Unit, University Oxford, UK

I would like to thank the organisers for inviting me to Rome for this meeting. I would like to speak about vegetarianism and cancer risk, and I am going to speak on that topic even though there is not an awful lot of data on that specific question.

I will start off by making clear what we are talking about with vegetarianism. This is the definition: vegetarians do not eat meat or fish of any type. Sometimes people forget bacon or sausages or salami, but vegetarians do not eat any meat, and that includes poultry, and they do not eat any fish at all. That is the definition I will be working with this morning.

We also have a sub-group of vegetarians called vegans, who do not eat any animal products – they do not eat any animal products, do not eat any dairy products and they do not eat eggs.

I am going to divide my talk into 5 sections. I will start by telling you why there has been interest in the possibility that the vegetarian diet might alter the chance of getting cancer. Then I will explain what data we have to look at the questions, then a little about what vegetarians actually eat – how does their diet differ from that of people who are not vegetarians in terms of foods and nutrients that might be relevant to cancer? I will then move on to the actual data we have on cancer rates, focusing on the 3 common cancers that have been focused upon at this morning's meeting as well that we think might be related to diet particularly, which are colorectal, breast and prostate. I will then draw some conclusions.

In terms of where this hypothesis comes from, I think it really dates back to the work of people like Armstrong and Doll in the 1970s looking at the ecological associations between what different populations ate around the world and their cancer rates. We have seen some of those data earlier this morning.

I would like to show some data from that publication for colon cancer rates in men in 23 countries around the world. I have put the correlation coefficients for four animal foods – meat, animal protein, eggs and milk – and also for cereals. Dr Teresa Norat showed the slide of the correlation with meat; that slide she showed you corresponds to the correlation coefficient of 0.85, so a very strong correlation. Countries where they were eating a lot of meat in 1965 had high colon cancer rates. There were also quite strong positive correlations with an estimate of animal protein (0,74), and also with eggs and milk, whereas cereals had a moderately strong negative correlation – those countries where people ate a lot of cereals had lower rates of colon cancer. So you could say that people who do not eat meat and eat a lot of cereals, a vegetarian diet, might not get colorectal cancer. There are similar correlations, but not quite as strong, for both breast and prostate cancer. So there had been an underlying idea that a vegetarian diet might be protective against these 3 common cancers.

I would like to make one more comment on this question because when we are looking at vegetarians now – and that really means that the data we have is from vegetarians living in industrial countries like Britain and America – these people's diet has very little in common with that of the poor semi-vegetarians who were living in the countries that had the low colon cancer rates in this slide – places like old-time Japan, rural China, India, etc. These were countries where the population were poor; a lot of them would have liked to eat meat but they could not afford it. The western vegetarians have got lots of money, they eat as much as they want of everything, and the vegetarians who are not vegans actually eat eggs and milk by definition. You can see here that although the correlation with meat is the highest, we have also got positive correlations with both eggs and milk. So the hypothesis is not very well thought out and maybe we should really be focusing within western society on vegans, because these are people who have zero intakes of all the animal products and they are probably a little closer in terms of nutrition to the old-time low-risk populations.

In terms of what data we have to look at, there are quite a lot of, what we might call cross-sectional studies, where a group of vegetarians and a group of meat-eaters living in the same place and compared them – compared their diets, weighed and measured them, took blood samples and conducted biochemistry. There are quite a lot of data of this type, but obviously that does not tell you about cancer rates.

In terms of studies that have real data on cancer in vegetarians, there are very few. There are a few cohort studies and these are cohorts where a large percentage of the people in the cohort were vegetarian because that is the way it was designed. For example, in the Seventh Day Adventists cohorts, the Seventh Day Adventist Church recommends that a healthy diet should have zero or low amounts of meat and fish, so a lot of Seventh Day Adventists are vegetarians and if you recruit a cohort among those people, you can compare the people who do not eat meat with those who do eat meat. However, they are fairly similar in terms of other background, because it would be unhelpful if we compared vegetarians with national rates because they would be different in so many ways.

We have a few cohorts of that type: we have the Seventh Day Adventists, two older British cohorts set up in the 1970s and 1980s, a small German cohort. There are two case-control studies of breast cancer using Indians, where a large proportion of the people were vegetarian. Finally, we have one component of the EPIC study – the EPIC-Oxford cohort – where we deliberately went out to recruit as many vegetarians as possible. We have ended up with about 65 000 people in EPIC-Oxford, and about half of those people do not eat meat. That is the largest cohort so far where we have data on people who do and do not eat meat that have been recruited in the same way from a broadly similar background.

I will show you some data from all these cohorts, but I will particularly concentrate on EPIC-Oxford as a source for showing you some descriptions about what vegetarians eat. In the total cohort at EPIC-Oxford we have 34 000 meat eaters and 10 000 people that we call fish eaters – people that do not eat meat but do eat fish. That may be a little confusing as you might think that these people eat fish all the time, but they do not eat an awful lot of fish, it is just that they are vegetarians who will eat fish. If you look at their fish intake, it is similar to that of the meat eaters. Then we have the strict vegetarians, about 19 000, who do not eat fish or meat, and then about 2 500 vegans.

These are data from the whole EPIC-Oxford cohort on intake of a few foods and nutrients, starting with fruit. We have them in four groups: meat, fish, vegetarians and vegans, men and women. Fruit intake in the whole cohort is relatively high compared with an average British person, because they have all

shown some sort of health consciousness and keenness to enter a study on diet and cancer. We can see that in both the men and women, the fish eaters and vegetarians have a higher fruit intake than the meat eaters, and that the vegans have the highest intake. The women eat a bit more fruit than the men. You will notice that although the vegetarians are a bit higher than the meat eaters (it is not a very big difference so they are not eating twice as much fruit, they are just eating a bit more), the vegans eat quite a lot more fruit. That same pattern keeps recurring: the vegetarians are always a little different from the meat eaters, the fish eaters always look almost exactly the same as the vegetarians, and the vegans are always at the extreme end and usually more different from the vegetarians than the vegetarians are from the meat eaters.

If we look at vegetables, not including legumes – which means beans, pulses and potatoes – they have very similar patterns, though relatively high intakes of vegetables for Britain: identical intakes in the fish eaters and vegetarians, which are a bit higher than the meat eaters, and then the vegans with the highest intake.

If we look at legumes – which means pulses, beans, lentils and includes soya beans, which is quite important in the vegans – then we find a much bigger difference, where the vegetarians are eating more than the fish eaters (probably because they have eaten beans instead of fish), and the vegans are eating much more (because legumes are a major source of protein and calories for the vegans). So there you see some quite extreme differences.

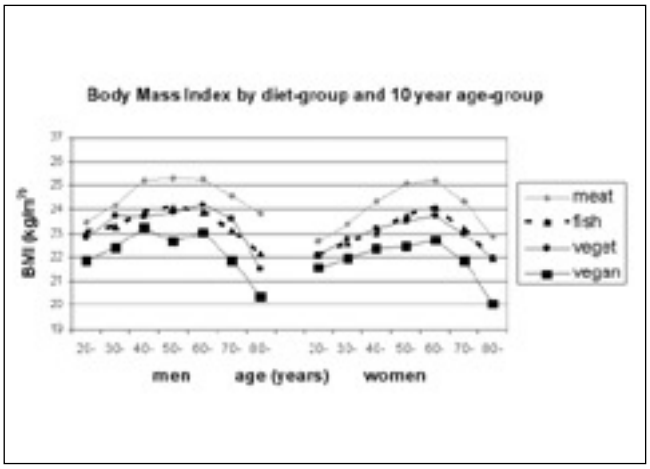
If we look at total fat intake, it does not vary much between the groups, but saturated fat does. Again, we have the same sort of pattern: fish eaters and vegetarians appear identical (they are lower than the meat eaters but the difference is really quite small, going down from 10.5% to 9.5% of energy from saturated fat – a highly significant difference but one that probably would not translate into much impact in this case on heart disease), whereas the vegans have really quite an extreme difference with their saturated fat intake at about half of that in the other groups.

For fibre intake, again there is a similar pattern: a fairly even trend across the groups with the vegans having the highest intake and being really substantially higher than that of the meat eaters, whereas the vegetarians' intake of fibre is higher, but only a little higher. If you think about the data that Dr Norat showed earlier on fibre and colorectal cancer, where you are looking at people in the top fifth of the whole population of EPIC compared to the bottom fifth, that difference in fibre intake from top to bottom fifth is much, much bigger than this little difference between vegetarians and meat eaters – so they do eat more fibre, but it is not hugely more.

Folic correlated with fibre with a similar trend, so a bit higher in the vegetarians, quite a lot higher in the vegans.

Finally, in terms of the cross-sectional data, this is body mass index in the 4 diet groups. We have men on the left and women on the right, and the mean body mass index in the groups in each 10-year age group at the time of recruitment into EPIC-Oxford. The first thing to note is that overall, our cohorts are relatively slim compared to the British average, with body mass indexes around 23 or 24, and obesity being rather rare.

You can see that in all the diet groups, people get fatter as they get older until they are in their sixties, and then people in their seventies and eighties get thinner again. That has been seen commonly in other studies, so whatever you eat, you get fatter on average. So you can see that there are big differences between the diet groups, both in men and women: the meat eaters are the fattest, the vegans the thinnest, and the fish eaters and vegetarians are in the middle and almost exactly the same as each



other. The difference here is about 1 unit between the groups, so compared to the meat eaters, the fish eaters and vegetarians are about 1 unit of BMI thinner, and the vegans are about 2 units thinner. When we come back to thinking about cancer, they are a bit thinner, therefore they should get less cancer of certain types, but 1 unit of BMI would not give you a very big reduction in risk.

Now I will focus on colorectal cancer. The problem we have been discussing this morning with colorectal cancer, in terms of trying to make sense of what variables to look at and how the whole pattern fits together, is that we do not yet have a well-established intermediate biochemical marker that links exposure with risk. With heart disease we have serum cholesterol; with breast cancer, as Dr Berrino showed you this morning, we have oestradiol, at least in post-menopausal women, and some other hormones. In colorectal cancer there are a lot of hypotheses, but we do not really know what to focus on in terms of intermediate markers.

I will show you a couple of things for which we have some data. At EPIC-Oxford, we looked at the frequency of bowel movements in the different dietary groups. The axis here is the mean number of bowel movements per week – once a day would give you a value of 7 – and we have it in the 4 diet groups. The first thing to notice is that men are ahead of women – men have about one more bowel movement a week than women – and that has been seen in other studies. If you look within the diet groups, this is based on 21 000 people in this analysis so there are very highly statistically significant differences. The fish eaters and the vegetarians have a higher frequency of bowel movements than the meat eaters, and the vegans are the highest, with about 2 more a week than the meat eaters both in men and in women. In fact we looked in this database at other things, including fibre, and diet group was by far the strongest predictor of bowel movement frequency – fibre went in the expected direction but was not as strong as diet group. It could be that is because we cannot measure fibre as accurately as we can measure diet group, but I think it may be because it is not just fibre – some of the foods that the vegans eat may have particularly strong effects on the bowel, particularly things like pulses, soya beans, etc.

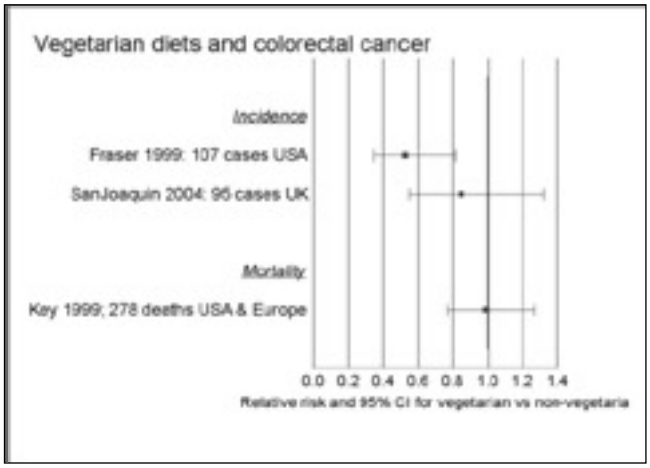
Other people have looked at other characteristics. This is another British study (not EPIC) looking at 3 indices of characteristics of faeces that might be important in colorectal cancer. There were 3 groups: white omnivores, white vegetarians, and Indian vegetarians. You can see that looking at faecal weight, it was higher in the vegetarians, and much higher in the British Indian women than in the British white women.

If we look at pH in the faeces, this is very impressive. This is relative to the meat eaters at 100%. This is a highly significant difference in that the Indian vegetarians have a more acidic pH

in the faeces than the white omnivores. This could be important because the pH determines the rate of metabolism of things like primary bile acids and secondary bile acids. There is one secondary bile acid, deoxycholic acid, which some people have suggested might be a causal factor in colorectal cancer, and the faecal levels of this are lower in both vegetarian groups than in the meat eaters.

You would think that there seem to be lots of factors in terms of colorectal cancer epidemiology that are going in the direction that the vegetarians should have less colorectal cancer: if the meat is important as you saw this morning, where you have the zero meat intake, they also have a slightly higher intake of fibre, fruit and vegetables, they are less constipated, etc., so you would think that they should have less colorectal cancer.

We do not have very much data. These are all prospective data sets looking at the rates of colorectal cancer in vegetarians compared with non-vegetarians within the same cohort. This study is within the cohort of the Seventh-day Adventists living in California, and we find a significantly lower incidence of colorectal cancer in the vegetarians than in the meat eaters in that cohort – 107 cases. We published last year, from the old Oxford vegetarian study on 95 cases, a non-significantly lower incidence of colorectal cancer in the vegetarians than the meat eaters in that old British study.



The other thing we published on is mortality, which give you bigger numbers – 300 deaths here – and this is bringing together all the data in the world on the cohort studies of vegetarians. Three of those studies did not have any data on incident cases, so we therefore looked at mortality as an index of risk because the mortality for colorectal cancer is quite high. Here, we saw a relative risk of exactly 1, so the mortality from colorectal cancer in these cohorts was identical in the vegetarians compared with the non-vegetarians. The results are still compatible with some reduction in mortality in vegetarians, but the point estimate is 1.

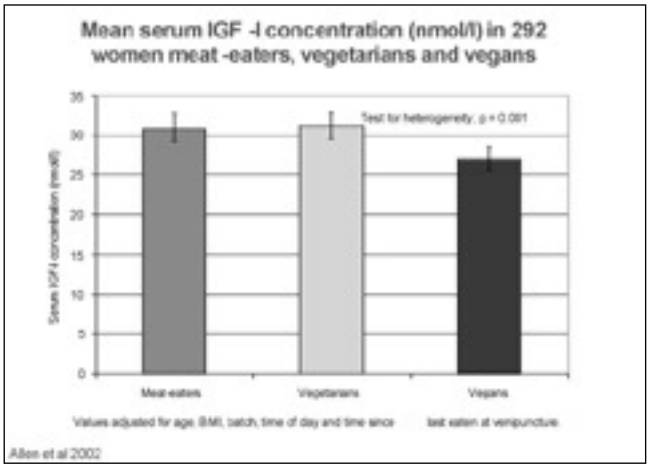
I quite often read books or articles saying that vegetarians have less colorectal cancer than meat eaters, but as far as I know, this is all the data there is in the world. It is hard to say that is true; it may be that there is a difference, but the evidence is not there.

Regarding breast cancer, as Dr Berrino showed you, we are a lot further forward in some ways in terms of intermediate risks, like hormones. I will show you some data on hormone levels in vegetarians, focusing on oestradiol and then on IGF-I.

As we have seen, high levels of oestradiol in the blood definitely predict breast cancer risk in post-menopausal women. The data we have for pre-menopausal women do not show this association, but there are serious measurement error problems in these women.

This is data from EPIC-Oxford where we looked at the oestradiol level in 1 100 women – meat eaters, vegetarians and vegans – and we split them into pre and post-menopausal. In pre-menopausal women, there was absolutely no difference between the groups that we could detect. In post-menopausal women, the vegetarians and vegans have very slightly lower blood levels of oestradiol than the meat eaters. Though it was not statistically significant, it is lower. It should be lower because they are a bit thinner, and if you adjust for the body mass index, that slight difference is eliminated. We conclude that there is no evidence that among pre-menopausal women oestradiol levels in vegetarians and vegans are different from those of meat eaters. They are very slightly lower in post-menopausal women, probably purely because they are a little bit thinner.

When we looked at IGF-I, the results were more interesting. We saw absolutely no difference in IGF-I between meat eaters and vegetarians, but the vegans have a highly significantly lower IGF-I. The difference is not very big at about 12%. However, I think a 12% difference in a hormone level is quite important because hormone levels are controlled by various means of homeostasis, and it normally takes a lot to shift them because you need the hormones to function. So a difference of 12% could be rather important. We cannot say why that difference is, but our analysis suggests it is most likely due to the difference in the type of protein intake. The protein intake in the vegans is low, but more than that, the intake of essential amino acids is lower. We do not think it is the energy intake because we have adjusted for BMI and for energy intake and it makes no difference, but we think it because of the difference in animal protein. If you think back to the definition, the gross dietary difference between vegetarians and vegans is dairy products – vegans do not eat them, vegetarians do – so it may be that the difference is due to dairy products.



There are slightly more data for breast cancer than for colorectal cancer because we have these 2 case-control studies focusing on Indian women. The first study was from California: there was a slightly, but not significantly, lower breast cancer incidence in the vegetarians. The data for the Indians do not suggest a difference. In the study that was actually done in India, the breast cancer incidence was insignificantly higher in the vegetarians; and in the British study, the risk was a bit lower but it was not significant.

In the mortality study, where we brought together all the data in the world from the cohorts of vegetarians, we found the risk of breast cancer was more or less identical in vegetarians as in non-vegetarians. I would say that overall, there is really little

evidence that breast cancer differs between vegetarians and non-vegetarians. It is not just western vegetarians in this case; we also have the data for Indian-type vegetarian diets.

Prostate cancer has some parallels with breast cancer in that hormones are likely to be very important, but we have not got quite as far in sorting out hormones in prostate cancer. The data that exist at the moment are rather weak on the main androgen testosterone, but there is a suggestion that there is a metabolite of testosterone that is an index of what is going on in the prostate itself that may be higher in men who get prostate cancer. There is also a little more data on IGF-I, suggesting it may increase prostate cancer risk. We have looked at both these types of hormones according to diet group.

For the sex hormones, we have a highly significant difference: vegans have significantly higher blood testosterone levels than meat eaters. In fact, this is potentially misleading because although testosterone is significantly higher in the vegans, the reason is because they have higher blood levels of SHBG, the sex hormone binding globulin. If you have more SHBG in your blood, you should have more testosterone because it is bound to the SHBG. The important fact is that the factor that is controlled by feedback in men is the level of free testosterone. Here, there is absolutely no difference between the 3 diet groups – it is identical in the vegans and the meat eaters. The vegans do have higher levels of SHBG and we are not sure why they are higher. Part of it is because they are thinner, but it may be because they have lower glycaemic index diets with therefore less insulin production, we are not sure. We are sure that the reason that testosterone is higher is because SHBG is high and free testosterone does not differ and androstanediol glucuronide is an index of what is actually happening in the prostate, and that did not differ either. Maybe that is to be expected because androgen levels are well controlled by feedback – they have to be controlled – and it seems that the dietary changes do not impact on the hormone levels.

However, when we looked at IGF-I., we saw results nearly identical to what I have shown you for women. The scale here has been truncated and the difference is not as huge as it might look. The results are highly significant here: the vegetarians and the meat eaters have absolutely the same levels of IGF-I, which is what we saw in the women, but the vegans have lower levels of IGF-I. As with the women, the most obvious thing is that the meat eaters and the vegetarians people eat dairy products, and the vegan men do not eat dairy products.

There is hardly any data on prostate cancer and vegetarians. The Seventh Day Adventists study published some data on incidence – 180 cases – and there is no significant difference, although the rate was slightly lower in the vegetarians. We looked at mortality in all 5 cohorts and despite having all the data in the world on prostate cancer mortality, we only had 137 deaths and the point estimate was close to 1. There is really no suggestion that prostate cancer is different in vegetarian men compared to meat eating men.

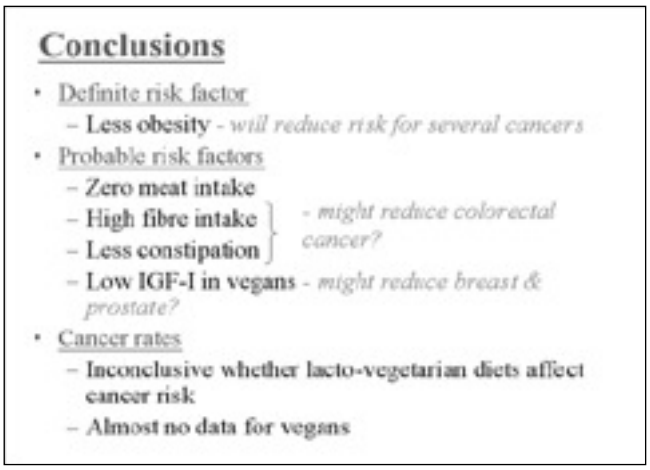
The main message emerging is that we need a lot more data – there is just not enough to draw conclusions. EPIC-Oxford will produce some, although it is still not really going to be big enough to answer all the questions; we will have to continue to try to pool all the data in the world.

I will just show you this one slide on the current situation in EPIC-Oxford. This is all cancers combined, because we do not really have enough to split it up. We have 1 400 incident of cancers in EPIC-Oxford. Splitting it up between the diet groups, if you take the meat eaters as the reference point, all cancer rates in the fish eaters and vegetarians and vegans are a little lower than the cancer rates in the meat eaters (this is after adjusting for smoking and age, etc.). So, this is not obviously explained by known confounding factors but none of them are statistically significant.

The conclusions are really quite brief. In terms of definite risk factors, I think the only absolutely certain thing is obesity that really consistently studies have shown that, on average, vegetarians are little thinner than meat eaters living in the same place. The definite evidence is that obesity does increase the risk of some types of cancer, particularly breast cancer, endometrial cancer, and adenocarcinoma of the oesophagus. As there is a little less obesity, therefore there should be a little less of those types of cancer among vegetarians. However, we will not see that difference in these types of studies because the effect on the relative risk will only be a few per cent. It is probably true that it is happening but we cannot detect it.

Turning to probable risk factors, vegetarians by definition have a zero intake of meat, their fibre intake is a little higher than that of meat eaters, and so they get less constipation. These sorts of factors may well reduce colorectal cancer, but the data we have got have not established that this is true. The data we have do not show that colorectal cancer is different between vegetarians and average meat eaters. That does not rule out the results we saw this morning that people with a very high intake of meat have an increased risk, because we are comparing only with the average. Nevertheless, it does not seem to me to fit very well, because you would think that if meat was really important, people who have not eaten meat for 20 years really would have a lower risk – and they do not.

The sex hormones do not really look different between the dietary groups, and I think that is because homeostasis works. However, the results on IGF in vegans could be potentially important. We have seen very clearly, both in men and women, lower IGF levels in vegans. If you think back to the start of this whole story and the aetiological studies, the populations that have had low rates of these western country cancers were the populations with low intakes of animal products and certainly not eating a lot of dairy products, so they may be closer to a western vegan-type diet in terms of a lower intake of animal proteins – the link there could be IGF-1, but we need a lot more information to be sure there is anything important going on.



The cancer data are really inconclusive on whether lacto-vegetarian diets have any effect on cancer rate. For vegans, there is a biochemical suggestion that there could be more important things going on, but there are almost no data at all on cancer rates in vegans so it is anybody's guess what they are. Thank you.

Questions

Elio RIBOLI
Thank you for this excellent review on vegetarianism and cancer.

Domenico PALLI
You mentioned 20 years as the length of time you have studied vegetarian subjects. I imagine that only a very small minority will have been raised from childhood as vegetarians. Most of these people with have decided at some time in their life to switch from meat eating to non-meat eating. Do you have any official information on this point?

Tim KEY
That is a very important point. I took the 20 years as an example but we do in fact have the data. You are right that in the British studies there are not many people who were raised from birth as vegetarians – there are some, but that is quite rare. I think that in our cohort the average was maybe 10 or 15 years, it is fairly long term. We looked at whether people had just become vegetarian and the bulk of them were quite long term. In the Seventh Day Adventists cohort quite a lot of them were vegetarians from childhood – in fact, they used the age at baptism into the church as a surrogate measure. In future we need to present those data more carefully.

We did publish something on body mass index showing that the long-term vegetarians were thinner and the short-term vegetarians were not.

Member of the audience
I did not understand the association between the consumers of meat, which is a protein, and the testosterone, which is a steroid hormone. The steroid hormone is generally synthesized by the acetate, which enters the luteal cells, and is transformed into cholesterol at the REL level, then in delta-5-pregnenolone at the mitochondrion level, to lead to the REL which gives testosterone. The testosterone would possibly come from the fatty acids, which are proteins. Consequently, why the testosterone rate would increase in the meat consumers?

Elio RIBOLI
The question is whether you could explain what is behind the association you have reported between meat consumption and testosterone levels. The questioner went into some detail about the production of testosterone by the Leydig cells and expressed scepticism about why there should be a link between meat consumption and testosterone levels.

Tim KEY
We were a bit surprised by this result because the hypothesis coming from world literature was that vegetarians, and maybe particularly vegans, might have lower testosterone levels in their blood. I do not know why, but that was the hypothesis. As you can see, this study is in 750 men. There were 250 men in each group: 250 vegans, 250 meat eaters. So there is a lot of statistical power and it is by far the biggest study in the world of this type. We found a highly significant difference in that the vegan men have higher testosterone levels than the meat eating men.

I think your question was that you did not believe that could be true, because where do they make the testosterone? Well, I think they do make it, because if you study testosterone levels in a bull, you will find they are quite high – and the bull is eating grass!

You do not get testosterone from meat; all these steroid hormones come from cholesterol. Everybody has cholesterol in their blood. The vegans have cholesterol in their blood – they have less than meat eaters because they eat less saturated fat, they are eating zero cholesterol. They have about 20% less cholesterol in their blood but that is hugely enough cholesterol to make as much testosterone as you would ever need, so I think the level of testosterone in the blood is in no way limited by what you are eating – every man should have enough nutrients to make plenty.

I think it is controlled by feedback, where the brain detects the amount of free testosterone in the blood and if there is not enough, it tells the testes to make a bit more. The system works.

Elio RIBOLI
I think this question is important because it addresses the fundamental design of research. There are many ways of investigating a biochemical and the chronological phenomenon. One way is to observe: you take men, women, obese people, lean people, and you measure something. You may find, as many studies have found, that obese men have lower testosterone than lean men. This is an observation, so it is what you see.

The second step is explaining why: what the biological mechanism is and why you see it. Researchers often find things that may be unexpected. This is extremely important because research progresses only when you find something you do not expect, because that springs theories and new observations. There is growing evidence that people with diabetes have a low incidence of prostate cancer – a big study on 650 000 Americans has found a 25% lower incidence of prostate cancer in men with diabetes. That shows that there are sometimes things you do not expect, so you then try to understand the mechanism behind. One American said that the difference between a researcher and a believer is that the researcher believes what he sees and the believer sees what he believes. It can be puzzling because it is contrary to what one might have expected.

Member of the audience
I wonder if you would comment on your Oxford meat eaters. You showed figures for the percentage of energy from saturated fatty acids, and that looked to be quite low – in fact lower than the mean that would be shown from the national diet and nutrition survey in the UK. Is part of the problem that you have particularly healthy meat eaters in Oxford?

Tim KEY
I would not use the word 'problem', but to some extent you are right. I would expect the people in the cohort to be a bit healthier than the average person in that country. The difference is more in our cohorts in EPIC-Oxford because we deliberately tried to recruit people with unusual diets. So in recruiting vegetarians, a lot of the people, when we were trying to recruit vegetarians, were meat eaters. They are certainly all shades, but they do have a relatively healthy diet compared with the average British person. We do have subgroups among the men so as in every other cohort, if we split those men up we will have some with higher saturated fats and some with lower. What you say is partly right, but if you look at saturated fat, we clearly still have a big difference within the cohorts because we have the vegans.

The other comment, which I probably should not make because it puts the spanner in the works of a lot of epidemiology, is that these data are from the food frequency questionnaire. The British EPIC questionnaire is an adaptation of the Nurses' health study questionnaire used in all the Harvard studies, and I think the estimates of some of these nutrients are not very accurate, particularly for saturated fats, which I believe are coming out a bit low. We have some data from the food diaries where both the total fat intake and the saturated fat intake, as estimated from the food diaries, are quite a bit higher than these data from the food frequency questionnaire. The difference between the diet groups remains more or less the same, which is why I felt it was alright to show it. The UK targets – that the government says we should not eat more than 10% energy from saturated fat – suggest the meat eaters are almost there on average. I think they are not; I think they are probably about 12%.

Member of the audience
According to different studies the amount of iron would be an important factor increasing colon cancer. From other Canadian and Japanese studies, the way the meat is cooked has an effect on the iron content. Do you have any data on this?

Tim KEY
In terms of the second question about the way of preparing the meat, we do not have data available on that from the food frequency questionnaire but we do have it from the food diaries, which we also have in Britain and we are coding that information at the moment.

Turning to the first question about iron, the situation is really quite complicated. If you look at iron intakes in the diet groups, it is a bit like the testosterone story in that the highest iron intake in our cohort is in the vegans. It is because a lot of plants do have quite a lot of iron in them, but it may be that much of that is not absorbed. The lowest iron intake is in the vegetarians, because they do not eat meat, and dairy products have almost no iron in them.

Coming back to colorectal cancer and iron, if iron was important then the vegetarians should have a slightly lower risk, but I think the difference would not be enough to be detectable. You are right that there is a lot of interesting work going on at the moment, but we are a long way from knowing whether iron has any relevance to colorectal cancer.

Elio RIBOLI
Research being done in Cambridge clearly indicates that the iron from vegetable sources does not work as a catalyser for endogenous N-nitrosation.

Franco BERRINO
I refer to the slide for sugar and carbonated drinks, which are not particularly healthy foods. Do vegans eat a lot of sugar?

Tim KEY
That is quite a hard question to answer because of the way the food tables are constructed. If you look at total sugar in the British food tables, the vegans come out at about the same as the meat eaters, but that includes fruits. You cannot get added sugar – like sucrose - out of the food table. We tried to do it by estimating which foods provide it. I think the vegans do eat a little less sugar, so they are slightly more health conscious in a way, but some of them eat very large amounts of fruit or dried fruit because they get hungry and they need to get calories from something, and one calorie-dense food is dried fruit. If sugar is bad for you, then it may not be that vegans are in a good position.

Elio RIBOLI
In a parallel analysis we have done on dietary habits in EPIC, we have seen that the vegetarians have a lower consumption of cakes and sweets compared to the non-vegetarians in the Oxford cohort.

Member of the audience
My question is about the morbidity and mortality rates you showed for the different types of cancer – the morbidity and mortality data. The mortality data were in general less conclusive. Nevertheless, you placed quite some emphasis on the mortality data, and I think it was because of the sample size because this was a bigger sample size. I am wondering about the value of such a finding. Is that not probably strongly biased by the assessment by death certificates which means that the cause of death is not properly assessed? Furthermore, does it rather show the successful medical treatment more than anything else?

Tim KEY
You are right that mortality is not the perfect thing to study if you are interested in incidence. It can be used in some cases as a reasonable surrogate; it depends on the cancer and the situation. The reason we used this was because we had 3 cohorts that had mortality data but did not have incidence figures, so the only thing we could look at was mortality. The mortality from colorectal cancer should be correlated with incidence. For some cancers, like prostate, there is an argument that it is better to look at mortality than incidence, because it eliminates the very small tumours that have a very good prognosis. I do not say that the mortality is excellent data for looking at risk but if there was a large difference between the vegetarians and the meat eaters in colorectal cancer, you would see lower mortality.

Member of the audience
What you say is very interesting but do you have any information about familial cancer history in this group? There is now a significant difference between non-vegetarians and vegetarians and vegans and this is surprising because we are always seeing low-risk recommended diets that are similar for cardiovascular disease and cancer. Maybe the difference in familial cancer history is also important in these 3 groups.

Tim KEY
We have not looked at that, but I only spoke about cancer because that was the title. We also published on coronary heart disease from the same studies, and there we found a highly significant difference. When we looked at mortality from ischemic heart disease in all the cohorts in the world – combined cohorts of about 80 000 people with a few thousand deaths from heart disease – there was an absolutely clear difference that the vegetarians had lower mortality from heart disease. There is an effect but that was not the topic this morning.

Mediterranean diet and cancer risk

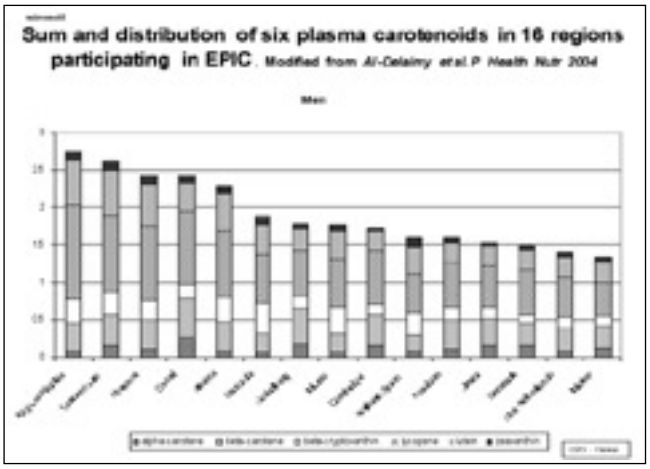
Domenico PALLI
Molecular and Nutritional Epidemiology Unit, Cancer Research and Prevention Centre (CSPO), Scientific Institute of Tuscany, Florence, Italy

I would like to thank the organisers for giving me the opportunity of giving this lecture.

Actually, the Mediterranean diet concept is not very well defined and we may find hundreds of definitions. In general, it has been associated with a reduced risk of cardiovascular disease. More recently, however, the possibility that this dietary model might protect from cancer has become more and more popular among researchers and in the lay press. We focus on this issue because a traditional Mediterranean dietary model might help to optimise the combination of protective dietary components, leaving out the detrimental ones or keeping these detrimental habits to a minimum.

Among the hundreds of definitions, I would like to focus on foods from plant sources and olive oil.

These results were published last year on the journal Public Health Nutrition (Al-Delaimy et al., 2004): this is a cross-sectional study. Each bar represents the average plasma levels of the 6 major carotenoids in a sample of 100 men across 15 different areas participating in the EPIC study. In first place, you see men from southern Italy, northern Italy, central Italy, Oxford (which has a high component of vegetarians), Greece, Granada (southern Spain), and so on. On the other side, you see the minimum levels found in Scandinavia and the Netherlands. The different components are basically alpha-carotene levels, which are greatly consumed in European countries, beta-carotene, beta-cryptoxanthin, which is at a very high level in Granada, southern Spain, because of orange and citrus fruit components, and then we have other carotenoids, particularly lycopene and lutein with high values in Italian participants.



This is the picture among women, again with each bar based on 100 women (in 16 local cohorts, including France where only women were enrolled), ranked according to the total sum of plasma carotenoids. Again, the highest levels are found in southern Italy, northern Italy, central Italy, Oxford, Greece, and then the other centres.

Irrespective of a very precise definition of a Mediterranean-style diet, when we measure some dietary components, we find some differences between populations living in different areas of Europe. Dr Riboli in his introduction on the first day mentioned the problem of decreasing age at menarche and increasing height. This slide is taken from another study, again across EPIC centres, and we see that women participating in EPIC in the three Mediterranean countries – Italy, Spain and Greece – were shorter in earlier cohorts. We see an increase in the adult height, but this increase is in parallel with the increase shown by northern and central European females (Onland-Moret et al., 2005).

There is no clear definition of the Mediterranean diet, you can either focus on some relevant component of a diet or you can use a Mediterranean diet score. Several projects have focused on cancer mortality and we also tried to carry out some analyses on cancer risk.

A paper recently published in the New England Journal by A. Trichopoulou reported that apart from a protective effect on the overall survival, a multivariate model showed that there was a reduced risk of mortality from cancer in the Greek component of the EPIC study, just applying the Mediterranean diet score proposed by that group.

Another study showed that if you count the number of protective factors, including a sort of Mediterranean score for diet, there was a significant protection from cancer-specific mortality in elderly Europeans.

On the other hand, when we think in terms of fruit and vegetables, we think of the natural and most relevant components of the Mediterranean diet. We were a little disappointed with the paper published recently by another group from the US because it came out that for fruit and vegetable consumption the strong benefits were restricted to cardiovascular disease but were not evident for cancer, which is our primary target.

Thus, we applied the Mediterranean index to the EPIC Italy cohorts (47,000 adults from 5 centres across the country) and also focus on the overall consumption of fruit and vegetables in this relatively large national series.

We have already seen this map of Italy. The interesting fact is that we have two centres in southern Italy with a very Mediterranean-style diet. We have Florence in between, and then we have two centres in northern Italy with more continental habits. The interesting fact is that because of socio-economic reasons in the 1950s and 1960s, a lot of people from southern Italy migrated to Turin and Milan and other industrialised areas in northern Italy. Approximately one third of current residents in these areas originated from southern Italy, so this is a nice mix.

Overall, we have approximately 47 000 adults participating in Italy – 15 000 men and 32 000 women (Palli et al., 2003). We have recently updated for 1 500 newly diagnosed cases of cancer which were diagnosed after enrolment. Women represent three quarters of our series and you see that there are 3 cancers in females for each case of cancer in men. There are two major types of cancer: more than 500 cases of breast cancer, and 150 cases of colorectal cancer. The other cases are evenly distributed among other sites.

Age at diagnosis is another relevant aspect: approximately 10% of our cases have been diagnosed in subjects older than 65 years of age, so the bulk of our cases were diagnosed before 65 years of age. This is the distribution according to the length of follow-up and you see that most of the cases have at least 3 or 4 years of follow-up.

This is the basic multivariate model. We adjusted for educational level, smoking history, and some basic anthropometric measurements, which were all taken by us at enrolment according to a standard protocol.

What comes out in this EPIC-Italy analysis is that the trend over the quintiles of total vegetable consumption is statistically significant, although the effect of moving from one quintile to another is quite small. Even more statistically significant is the inverse association between leafy vegetable consumption over the quintiles and total cancer risk. Root vegetables – mostly carrots – show a significant inverse association, while there is no effect for tomatoes and for another potentially interesting category, as cabbages.

Association between **quintiles of food consumption** and **total cancer risk** in the frame of the follow up of 44,865 volunteers enrolled in the EPIC-Italy study (1993-98) (1,488 incident cancer cases).

	EPIC – ITALY		
FOODS GROUPS / FOODS	RELATIVE RISK*	IC 95%	P for trend
Vegetables (all types)	0.95	0.91-0.99	**0.02**
- Leafy vegetables (total)	0.95	0.91-0.98	**0.005**
- Root vegetables	0.96	0.92-0.99	**0.04**
- Tomatoes	0.98	0.94-1.02	0.41
- Cabbages	0.97	0.94-1.01	0.19

*Relative risk estimated by Cox regression models stratified by centre, sex and birth cohort, including terms for smoking history, education level, weight, height, total calories (log) and each food separately (quintiles).

In terms of micro-nutrients, these are very preliminary results, but we can show that there was a stronger inverse association with the total fibre consumption. In terms of micro-nutrients with antioxidant capacity, the most relevant result was the inverse association with beta-carotene, although there was a limited association for folic acid. Leafy vegetables are a very good source of folic acid in this population which, at least at the moment, has a very low proportion of subjects taking vitamin supplements.

Association between the **intake of fiber and selected micronutrients** (in quintiles) and **total cancer risk** in the frame of the follow up of 44,865 volunteers enrolled in the EPIC-Italy study (1993-98) (1,488 incident cancer cases).

	EPIC – ITALY		
Nutrient	Relative Risk ^	IC 95%	p
Fiber	0.94	0.89-0.99	**0.02**
Folic acid	0.96	0.91-1.01	0.14
ß-carotene	0.95	0.92-0.99	**0.02**

* Relative risk estimated by Cox regression models stratified by centre, sex and birth cohort, including terms for smoking history, education level, weight, height, total calories (log) and each nutrient separately (quintiles). The RR shows the modification of the risk associated with the increase of one logarithmic unit.

We also used the Mediterranean score proposed by our Greek colleague. We substantially adopted their model and these are the results. Again, we have a statistically significant trend over the categories, although no single category is statistically different from the unit. But there is some suggestion that the highest category – those really adopting a Mediterranean-style diet – have an approximately 40% reduction in total cancer risk.

Association between the Mediterranean SCORE and **total cancer risk** in the frame of the follow up of 44,865 volunteers enrolled in the EPIC-Italy study (1993-98) (1,488 incident cancer).

	EPIC – ITALY		
Mediterranean SCORE	Relative Risk ^	IC 95%	p
0-1	1		
2-3	0.96	0.79-1.16	0.63
4-5	0.85	0.70-1.04	0.11
6-7	0.88	0.70-1.09	0.23
8-9	0.62	0.33-1.15	0.13
P for trend			**0.02**

^ Relative risk estimated by Cox regression models stratified by centre, sex and birth cohort, including terms for smoking history, education level, weight, height, total calories (log).

CSPO - Florence

Most of our cases were females and the most relevant type was breast cancer, so we focused on breast cancer. Recently, in the Journal of the American Medical Association, there was a negative meta-analysis concluding that fruit and vegetables consumption in adults was not significantly associated with a reduced breast cancer risk. More recently, the EPIC consortium published a negative study at the European level focused on breast cancer, which again was published by the Journal of the American Medical Association (van Gils et al., 2005). Here we focused on the updated series of breast cancer cases among the 32 000 women enrolled in EPIC-Italy. We present some data after exclusion of approximately 10% of the cases that were diagnosed immediately after enrolment in the cohort. We ended up with a series of 480 breast cancer cases. The age distribution is quite young – just 10% of all breast cancer cases were diagnosed at the age of 65 or older, so these are relevant cases in younger adults. According to menopausal status at enrolment, you see that we now have an equal balance between women who were enrolled in a pre-menopausal status or who were already post-menopausal, with a small group in between.

These are the person-years accumulated by our cohort and the distribution of the cases. You see that after excluding the first 6 months, most of the cases had a follow-up of at least 4 or 5 years.

This is the more complex model we used to adjust for dietary variables. We included terms for education level, reproductive history, age at menarche, menopausal status and anthropometry. Again, you see that height was a statistically significant predictor of breast cancer risk in our population.

These are the main results. We found a suggestion of a protective effect of the total consumption of vegetables in this Italian population, although that was particularly strong in terms of the leafy vegetables, either raw or cooked. There was no other association, in particular with tomatoes. You may have seen a negative paper published in the last few months on cancer aetiology by an American group. The paper also measured lycopene in blood and there was no association with breast cancer.

Association between **quintiles of food consumption** and **Breast Cancer risk** in the frame of the follow up of 30,133 volunteers enrolled in the EPIC-Italy study (1993-98) (477 incident breast cancer cases). (1)

	EPIC – ITALY		
FOODS GROUPS / FOODS	RELATIVE RISK*	IC 95%	P for trend
Vegetables (all types)	0.93	0.87-1.00	0.06
- Leafy vegetables (total)	0.92	0.86-0.98	**0.01**
- raw	0.93	0.87-0.99	**0.04**
- cooked	0.92	0.86-0.99	**0.02**
- Root vegetables	0.97	0.91-1.04	0.35
- Tomatoes	1.02	0.95-1.09	0.55
- Cabbages	0.96	0.90-1.03	0.25

*Relative risk estimated by Cox regression models stratified by centre and birth cohort, including terms for education level, age at menarche, number of children, menopausal status, weight, height, total calories (log) and each food separately (quintiles).

We also took into account other aspects of dietary habits in this female population, and the only relevant result we have is this borderline significant positive association with the consumption of potatoes. You may remember that there was some discussion yesterday on vegetables and potatoes (potatoes are not included in the category of vegetables).

The other key point of the Mediterranean diet is olive oil, but it is very difficult to measure the consumption of olive oil and that is why we think our results are inconclusive. On the other hand, seed oils, which mean all other vegetable oils, consumed in this female population have, if any, some positive association with breast cancer risk.

These results on the inverse association we have found between the consumption of vegetables and breast cancer are in substantial agreement with a recently published paper by the Milan group led by Franco Berrino. They had an approach based on dietary patterns and they found that patterns characterised by a high consumption of raw vegetables and olive oil was strongly inversely associated with the risk of breast cancer.

We have done some analysis in our local cohort in Florence evaluating the association between dietary habits and high mammographic breast density, which is a condition that is very frequent in adult women and which has been consistently associated with increased breast cancer risk. We again found an inverse association with the consumption of total vegetables, and particularly leafy vegetables (Masala et al., 2005).

Before finishing, I would like to mention that in terms of Mediterranean diets and cancer, there is a strong interest among researchers about intervention studies with specific food items and the use of biomarkers, particularly tomatoes and olive oil. This is a protocol of a study published by a group from Milan in the British Journal of Nutrition (Porrini et al., 2005). The size of the study is moderate because they have only 26 volunteers and they used a commercial drink based on tomatoes. The expectation was that the consumption of tomato components (mainly lycopene) by this drink would decrease the oxydative damage, and they found that there was a significant reduction.

Again, I would like to remind you of the particular distribution of lycopene levels across European countries: the highest levels are found in southern Italy and other Mediterranean areas.

Olive oil has repeatedly been reported to be inversely associated with the risk of cancer, and very recently we carried out a small cross-over intervention study in Florence. We assigned women to use extra-virgin olive oils with a very high concentration of hydroxytyrosol and natural phenolic compounds, in comparison to a similar extra-virgin olive oil with low levels of hydroxytyrosol and natural phenolic compounds.

We have been able to show that this population was compliant, and we can show that the urinary excretion of biomarkers of consumption of this metabolite increased during the consumption of high extra-virgin olive oil and decreased during the consumption of low extra-virgin olive oil (Salvini et al., submitted). So these interventions are feasible in the Italian population and other populations also. Also, in terms of oxidative damage, we found a statistically significant difference between the Comet assay results in the two study phases. The problem with this study is that it is quite small because it is very difficult to raise funds to run large intervention trials.

To conclude this presentation, we are convinced that components of a Mediterranean-style diet may play a role in cancer prevention and we urgently need well planned interventions trials. Thank you for your attention.

Questions

Member of the audience
How can you explain that in the Italian small sub-cohort you can see the inverse association and in the whole of EPIC you can not?

Domenico PALLI
This is a very relevant question because it is the same question we have asked ourselves. At some primary point in the analysis of the European data, we had this inverse association only in Italy. It was the only country where breast cancer was inversely associated with total vegetable consumption. Then we updated the central database. In different countries we use different tools to collect data, so some of the information detail is lost when we use the central database. We have recently updated the follow-up in Italy so we have a slightly larger series, and we find these results, which were already evident at the very beginning at the European level. However, I agree with you that we have to better investigate why there is this apparent contrast with the common analysis.

We focused on vegetables and it is possible that the quality, variety, the seasonal distribution system and conditions in which vegetables are on the market in Italy, and other areas with locally-grown products, are essentially different from what happens in other countries where the market provides you with vegetables grown far away. This is a possible explanation.

Also, vegetables in Italy tend to be consumed with olive oil, so it is not clear if we are measuring the effect of one or the other. What is strongly evident to me is that we are unable to capture the real food intake but we would need to understand better the details of olive oil consumption, because it is very difficult, and also the types of olive oil vary in different areas – it is not homogenous, even across Italy. We have to work more on these issues, but at least these results are promising.

The previous member of the audience
As I understand it, in this model you tried to adjust for olive oil.

Domenico PALLI
No. These are multivariate analyses with just one dietary component.

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Introduction

Lorelei DI SOGRA
Director of the 5 a Day Programme, National Cancer Institute, NIH, DHHS, Bethesda, USA

Welcome to this afternoon's session. This session will leap from the scientific evidence to health promotion and disease prevention actions taking place around the world. We will talk about what is happening in 5 different countries. We are talking about action: how do we take the science and move it into action to change and improve eating behaviour.

The subject of this afternoon's session will focus on ways and actions to increase fruit and vegetable consumption. As many of you know, we have 15 years of scientific literature telling us how important it is to increase our fruit and vegetable consumption. All populations around the world are eating many less fruits and vegetables than they need for good health. Many countries have national nutritional policies that recommend 5 servings of fruits and vegetables a day or to double fruit and vegetable consumption. We also have the WHO recommendations, again promoting increased fruit and vegetable consumption.

This afternoon, we will look at 5 actions that are taking place to try to increase fruit and vegetable consumption.

Our first speaker is Laurent Damiens from France. He is the Director of Aprifel in France, which is the agency for research and information on fruit and vegetables.