PETER THIEDEKE/ALAMY

HEALTH

Edible advice

Diet-related illnesses are some of the biggest killers today. Can we tailor our food intake to prevent these diseases? Large international projects are underway to find out.

BY FAROOQ AHMED

'Too much tea can treble cancer risk in women'. 'Tea could cut risk of ovarian cancer'. Just two examples of the frequent contradictory newspaper headlines that confuse the public about the health benefits — or risks — of food and confound genuine nutrition-related research.

For some diseases such as diabetes the link with food is subtle. "Although we know that dietary factors are related to the risk of diabetes, there are a lot of inconsistencies between studies in terms of what precise micronutrients or macronutrients associate with the disease. We're quite limited in terms of the data," explains Nick Wareham, head of the epidemiology unit at the UK's Medical Research Council.

Using new tools and methodologies, ambitious projects are underway to make up this shortfall. One such effort, which Wareham coordinates, is InterAct — a multinational study to define how diet and lifestyle influence risk of type 2 diabetes. This disorder of blood glucose regulation is a growing problem in Europe, afflicting nearly 40% of the population at some point in their lifetime. InterAct estimates that the diabetes accounts for as much as 10% of health care costs in Europe.

Through endeavours such as InterAct, researchers are starting to expose the complex interplay of genetics, diet and disease, and bring order to the confusing array of nutritional information.

InterAct began in 2006 as part of the European Community's sixth Framework Programme. It has a budget of €10 million and involves more than 12,000 patients recently diagnosed with diabetes across 10 countries — nine in Europe plus India. Such a broad cohort is important. "Sometimes variation within a country is not so great," says Wareham. "International efforts give you heterogeneity in the lifestyles of patients, especially in the diet, and that's a major advantage." This diversity provides scientists with more variables to study as they attempt to untangle what factors are responsible for causing disease.

THE BIGGER THE BETTER

This research is part of the largest diet and disease study ever undertaken: the European Prospective Investigation into Cancer and Nutrition (EPIC). Initiated in 1992, EPIC has recruited more than half a million people. Participants are physically examined at one of 23 centres, complete lifestyle surveys including detailed diet questionnaires, and have their blood tested. Their DNA is scanned for disease-related genes using techniques that can detect hundreds of thousands of genetic variants in large numbers of individuals.

"Large-scale projects can really be a catalyst to bring together multiple centres to share instruments," says Wareham. "InterAct has benefited greatly from the huge EPIC cohort and access to those technologies."

Another large-scale study, a parallel to InterAct though not part of EPIC, is Interheart — which examined the link between dietary patterns and heart-attack risk. Between 1999 and 2003, the Canadian-led study recruited 5,761 patients and 10,646 control subjects, living in 52 countries, across six continents. Using questionnaires, physical examinations, and blood analysis, the teams compiled data on people including demography, diet, anthropometric measurements such as body mass index and biomarker levels including cholesterol and lipoproteins.

Interheart researchers concluded that the globalization of a Western pattern diet — high in animal products, fried foods, and salty snacks — is responsible for a third of the risk of heart attack worldwide[1]. A 'prudent' diet rich in fruits and vegetables reduced risk regardless of location. Prior to Interheart, few epidemiological studies linked dietary patterns in ethnically diverse populations and cultures to disease. Research like this "is crucial if we truly want to understand these diseases, because they manifest differently in European and other populations," says nutritional geneticist Jim Kaput, who also serves as director of the Division of Personalized Nutrition and Medicine at the US Food and Drug Administration.

CROSSED PATHWAYS

InterAct and Interheart both demonstrate that the metabolic pathways at the epicentre of dietary-related illnesses, such as diabetes and cardiovascular disease, are strongly related. Research on one can uncover clues to the other. "Factors like blood pressure, cholesterol and triglyceride levels, which are predictive of coronary heart disease, are also associated with diabetes," notes Wareham.

Leafy vegetables, such as lettuce and spinach, are core components of the prudent diet as identified by the Interheart study. These vegetables are enriched in polyunsaturated fatty acids (PUFAs) — essential macronutrients also found in some types of fishes, nuts and cheese. Two types of PUFAs in particular, omega-3 and omega-6, are powerful dietary components because they can change gene expression, both directly and indirectly. PUFAs "act more like hormones than like typical food," says nutrition scientist Donald Jump of Oregon State University, who studies these macronutrients.

For example, PUFAs have two ways to

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modulate gene activity and lower the levels of fatty acids and triglycerides in the liver: they can bind and activate a family of transcription factors called peroxisome-proliferator-activated receptors (PPARs) to speed up the breakdown of fatty acids; PUFAs can also deplete another transcription factor, sterol regulatory element binding protein-1 — thereby curtailing fatty-acid synthesis. This two-pronged attack provides a significant health benefit. "Along with cholesterol," explains Jump, "elevated triglycerides are a common target for the management of atherosclerosis, cardiovascular disease and stroke."

Although most research on PUFAs has focused on their connection to cardiovascular disease, by manipulating an enzyme involved in fatty-acid metabolism Jump's team has demonstrated that PUFAs can also balance blood glucose levels, suggesting a potential treatment for type 2 diabetes[2].

"Dietary omega-3s are not usually thought of as a treatment for elevated blood sugar," says Jump. Yet by studying diet and its effect on metabolic pathways, these types of links are being uncovered.

After diet and metabolism, a third element in development of diet-related disease is the genome. "In humans, genetic background plays a role in either responding well, or not, to particular nutrients," says Jump. Adding global genetic diversity to the mix greatly increases the complexity of the research.

The International HapMap Project, a database of genetic variation, began in 2002 and stores data from Canada, China, Japan, Nigeria, the United Kingdom and the United States. So far, the project has identified tens of millions of single nucleotide polymorphisms (SNPs) associated with both disease and drug response. SNPs in PPAR genes that are regulated by PUFAs affect, among other things, the ability to lose weight, a crucial step to controlling diabetes. One SNP in particular has been found to account for 7% of the variation in people's weight loss[3].

In 2010, InterAct recruited the ten-thousandth person to their search for markers that reveal the roles of obesity and exercise in the risk of developing diabetes. Analyses of their genomes will be published in 2011, and Wareham is confident this approach will uncover new interactions. "We're using a discovery approach on a mass scale," he says. "We don't focus so much on the expression of particular genes, but on the interplay between innate susceptibility and dietary and lifestyle factors."

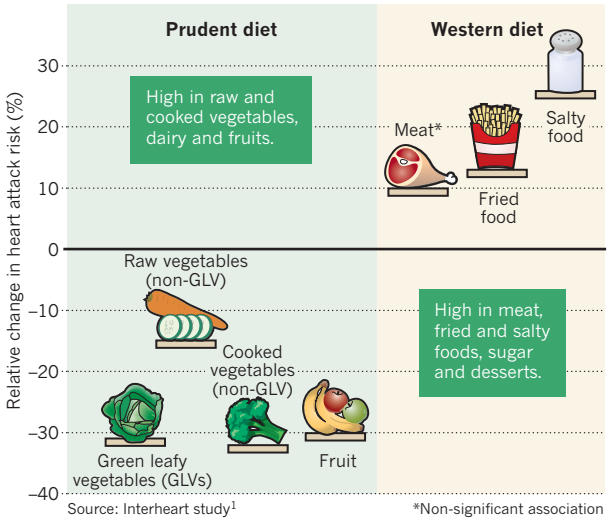
Such a link would fill a gap in our knowledge. "Hypothetically," muses Wareham, "the genome-wide influence of dietary and lifestyle factors may account for the heritability we have seen in diabetes that remains unaccounted for on the basis of simple genetic variation."

Subtle changes are lost in the background noise of standard single-gene studies. But they do have an impact — not least of all for our definition of disease and the way that clinical trials are designed. "Geneticists," says Kaput, "have been treating all of us like coins when it comes to deciding whether we have a disease: heads or tails — are you or are you not diabetic? That's how many studies are designed."

There is a need for new ways to interpret disease that recognize the contribution of genes

RISKY FOODS

Diets high in certain food types carry an elevated risk of heart attack.



Source: Interheart study[1] *Non-significant association

DEVELOPING WORLD NUTRIGENOMICS

Reversing the health and nutrition relationship.

As globalization is exporting fatty fast-food diets around the world, malnutrition is rampant in many developing countries. According to Médecins Sans Frontières, malnutrition causes 60% of deaths in children under the age of five in developing nations. New technologies that provide nourishment while treating diseases could save millions of lives.

That's the stark reality that led Raymond Rodriguez to launch the Global HealthShare Initiative (GHSI). "We started to look at health disparities in racial, ethnic and economically disadvantaged communities," explains Rodriguez, director of the Center of Excellence for Nutritional Genomics at the University of California, Davis. "Often the people who need food and drugs the most are the last to get them."

Lack of proper nutrition opens the door to disease. "Malnourished individuals have reduced immunity, and thus vaccines are less effective," says Somen Nandi of GHSI. Nandi is leading efforts to develop an international network of researchers, investors, non-governmental organizations and drug makers to combat diseases with nutrition-based therapeutics. "We're merging the concepts of nutrition and immunity," says Nandi.

AAMIR QURESHI/AFP/GETTY IMAGES

Malnutrition impairs vaccine efficacy.

One tangible benefit of this new way of thinking is a novel rice-based matrix in development as a delivery base for a vaccine against cholera and diarrhoea. This could help sustain the malnourished and bolster their immunity, while immunizing against the diseases.

GHSI's vaccine development projects also recognize the economic factors involved. Rodriguez's and Nandi's ambitious goal is to help create sustainable economies in countries where diarrhoeal diseases are prevalent, such as Bangladesh. They hope to identify and develop sites in resource-limited countries where therapeutics can be formulated, manufactured and distributed.

"We think that GHSI will create an opportunity for the four billion people who are not a part of the global economy to enjoy better health and a better standard of living," says Rodriguez. Thus the fruits of nutrigenomics research could not only help Westerners cope with a diet of excess, but also bring better lives to the impoverished people in developing nations.

and metabolic pathways. Metabolites are small molecules — amino acids, vitamins and other chemicals — in circulation and influenced by both genes and nutrient intake. Metabolomics, or the study of these metabolites, offers perhaps the best opportunity to observe these interactions in a minimally invasive manner.

Metabolic phenotypes can be very finely segregated, as demonstrated in an analysis of urinary metabolite patterns found in thousands of individuals in China, Japan, the United Kingdom and the United States. Not only did East Asians have a different pattern of metabolites from Western populations, but individuals from northern China could be differentiated from those in southern China. Both Chinese groups were distinct from Japanese, who were in turn different from Japanese Americans[4]. People who consumed a lot of meat, as is common in Western diets, had elevated levels of biomarkers indicative of high blood pressure compared with people who have a primarily vegetarian diet.

InterAct is also searching for novel biomarkers that accumulate as an individual's risk of diabetes rises. When combined with epidemiological studies, this type of metabolic phenotyping could lead to the identification of biological red flags for individuals, even before disease manifests. Biomarker metabolites might also be therapeutic targets one day.

BREAKING DOWN SILOS

While large-scale scientific projects such as InterAct and Interheart have had success, barriers still exist to international collaborations. Researchers occasionally encounter a lack of willingness or an inability to share information. "It has sometimes been a challenge to convince colleagues who run the individual centres that by working together we end up with better science," says Wareham.

Kaput agrees. He suggests that biologists take a page from the physicists' handbook. "They built the Large Hadron Collider, thereby working across disciplines", he says, "but we still haven't made the silos go away in the biological sciences community."

Wareham has faith in the technology-driven approach that encourages and facilitates collaboration. These major projects, he says, can bring different disciplines closer together — as they have in the genetic HapMap project. "The ability to measure multiple SNPs at very low cost on a mass scale revolutionized that field, and I think that's where we're headed for other risk factors such as diet and nutrition," contends Wareham.

Such a large-scale, system-wide approach is being used by Kaput and FDA chemist Carolyn Wise. They are considering early environmental influences, micronutrient availability, metabolic and regulatory pathways and genome-wide association maps as they try to define combined genetic–metabolic types for people in terms of obesity and type 2 diabetes[5]. This approach can be emulated and scaled in other studies to help researchers work together and share information as they try to make sense of huge amounts of data.

PREVENTION IS BETTER THAN CURE

As these nutrigenomic studies begin to classify individuals into specific groups based on the interplay of their lifestyle, metabolic pathways and genetic variants, tailored diets may become early therapeutic interventions. Personalized diets might even guide people genetically at risk for diabetes, but not yet in a pre-diabetic state, to help them avoid developing the disorder by fine-tuning what they eat. A well-regulated ounce of prevention could obviate the need for a cure.

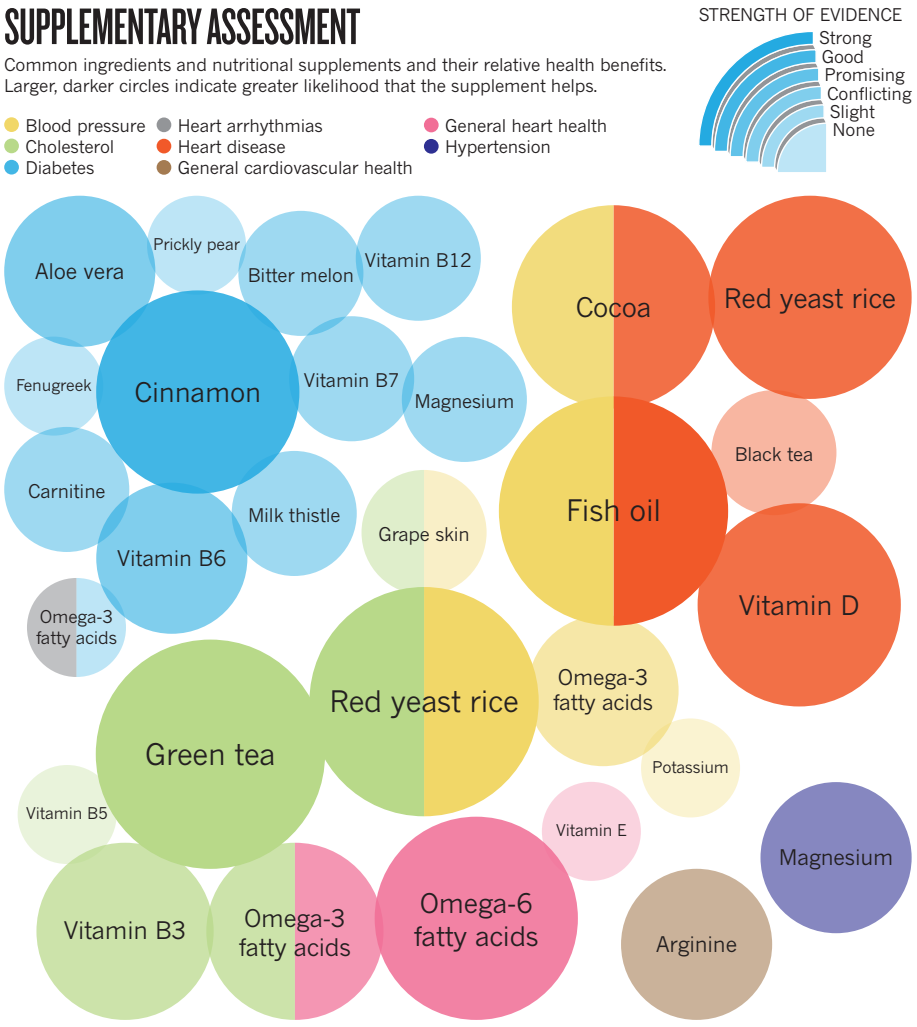
However, the development of personalized diets has been prematurely promised before. In the early 2000s, a slew of companies claimed to be able to provide personalized nutritional advice based on genetic tests. An investigation by the US Government Accountability Office in 2006 found that these companies "misled consumers" and provided only generalized advice. The US Senate Special Committee on Aging convened a hearing that further criticized these direct-to-consumer genetic tests. Unable to secure funding, several of these companies went bust.

Here, says Kaput, is where the FDA's Division of Personalized Nutrition and Medicine is ahead of the curve. "Right now, we don't have a product to regulate. We're not sure where the field is going necessarily, but when products come in for possible FDA regulatory activities, we will have the research background to help the regulatory centres make their evaluation."

Teasing out the relationship between food and disease is a tricky task, one that involves tens of thousands of people and encompasses hundreds of nutritional and genetic factors. It is not likely to provide simple or quick fixes either, meaning that for now at least the 'tea causes cancer' stories can safely be ignored. ■

SUPPLEMENTARY ASSESSMENT

Common ingredients and nutritional supplements and their relative health benefits. Larger, darker circles indicate greater likelihood that the supplement helps.



Adapted from www.informationisbeautiful.net/play/snake-oil-supplements/

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