

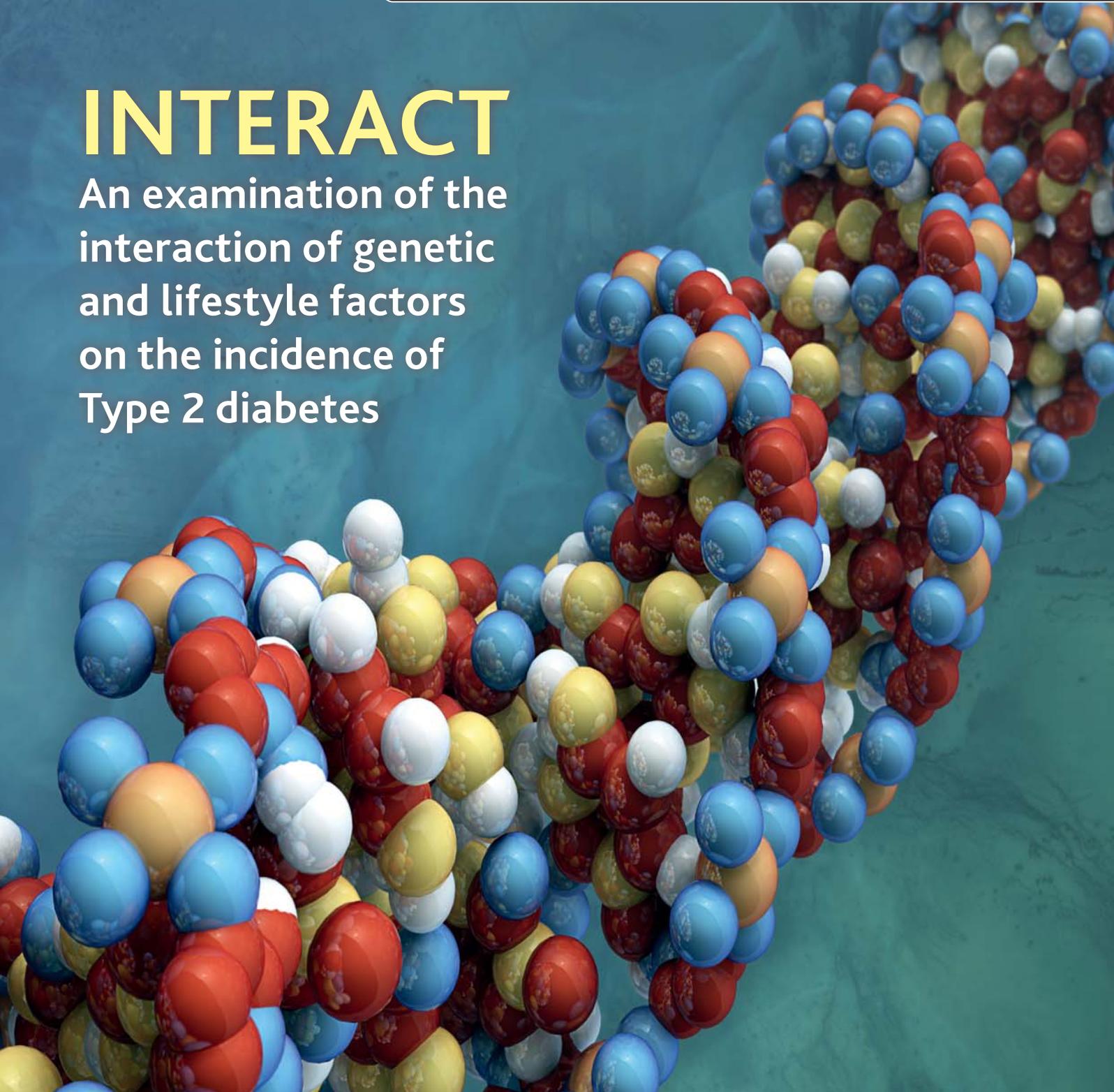
International Innovation

Disseminating science, research and technology



INTERACT

An examination of the
interaction of genetic
and lifestyle factors
on the incidence of
Type 2 diabetes



Talking about Type 2

Professor Nick Wareham outlines the progress of a major research project he is leading, examining the interaction of genetic and lifestyle factors on the incidence of Type 2 diabetes in European countries



Firstly, could you detail the focus and core objectives of the InterAct project?

InterAct was designed to investigate how genetic and lifestyle factors operate together to lead to increased risk of diabetes in European countries. The variation in the risk of diabetes between people, between countries and over time, suggests that the disease originates from the interplay between innate susceptibility and lifestyle behavioural factors. However, the molecular basis of such interactions is unknown.

It is projected that deaths related to diabetes could double between 2005 and 2030. What are the main factors behind this and who is at greatest risk?

It is clear that there is a marked and continuing rise in the prevalence of Type 2 diabetes in most countries around the world. This rise in prevalence is driven partly by the change in age distribution in many countries, with many people living to old age. This has a major impact on Type 2 diabetes, which is strongly age-dependent. The prevalence also rises because care for people with diabetes has improved and thus people live with the condition for longer. However, it is also true that more people living with diabetes into older age will mean that the

total number of deaths attributable to diabetes will increase.

Furthermore, why is the incidence rate of diabetes rising so sharply in developing countries?

One additional important driver for the increasing prevalence of Type 2 diabetes is the rising incidence of newly diagnosed cases. This has two explanations. In the past, many people had diabetes but were unaware of it. Improved awareness of this issue has led to earlier detection in many countries and a rise in the rate of new cases. The second reason for increased clinical incidence is a true increase in the rate of disease occurrence largely driven by obesity, physical inactivity and unhealthy diets.

Have you drawn on data from previous studies? How have you overcome the lack of standardisation that has so limited previous studies of gene-lifestyle interaction?

As part of InterAct we undertook a review of the possibility of synthesising evidence of interaction from published literature. The review showed that this approach is highly unlikely to be successful because of problems of standardisation between studies and issues of publication bias. Some of these issues can be dealt with by ad hoc consortia, but the problems of standardisation are difficult to resolve. InterAct is fundamentally different because it was set up at the beginning as a multi-centre study in which the measurement of important but difficult to quantify behaviours has been standardised.

Can you elaborate on the importance of collaboration in this project and offer an insight into the strengths of the consortium?

The InterAct project builds on many years of work to establish the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study in 10 different European countries. InterAct would not be possible without the

long and dedicated work of the consortium of researchers who had the foresight and perseverance to set up and maintain this large scale study. InterAct is itself run by a consortium of researchers representing the EPIC centres but also bringing in additional experts in diet and physical activity epidemiology, genetics and intervention studies. Measuring biochemical and genetic markers on such a large scale has also required an enormous investment in the robotic infrastructure to undertake measurements efficiently.

What progress have you made in your studies into biological plausibility for interaction and how did you select which polymorphisms to investigate?

We have focused initially on genetic variants that have previously been shown to be associated with diabetes. We have not started with an approach based solely on biological plausibility because this approach has not been very successful when considering main genetic effects and there is no real reason to think it would be more successful in this context. Our approach is first to determine whether genes are truly associated, and whether interactions are likely to be real rather than a statistical artefact, and only then to consider biological explanations.

What is the greatest success of your research to date?

InterAct is a large and complex study and is only now beginning to realise its huge potential. Some of its findings may be undramatic but may generate much stronger evidence than was available previously. Other findings may provide evidence that previous claims about the association of lifestyle factors with diabetes risk in smaller studies may have been exaggerated. We believe that the value of InterAct is likely to come not from a single report, but rather from the production of a body of work outlining with confidence how genetic and lifestyle factors work together to lead to diabetes.

Size matters

The EU-funded **InterAct** project is the largest and most ambitious study of the effects of gene and lifestyle factors on Type 2 diabetes ever undertaken and is based on 28,000 participants from eight European countries

DIABETES IS A CHRONIC disorder of glucose metabolism and is a major cause of heart disease and premature death. Globally the number of people with diabetes is rising and World Health Organization (WHO) figures project that the number of deaths related to the condition could double between 2005 and 2030. It is estimated that 35 to 40 per cent of people in Europe will develop diabetes over their lifetime. The incidence of diabetes is also increasing rapidly in developing countries and the WHO estimates that 80 per cent of people living with diabetes are in low to middle income countries. Recent figures from the International Diabetes Federation estimate that there are 366 million adults living with diabetes globally.

Encouragingly, it is already known that Type 2 diabetes, which typically develops during adulthood, can be prevented or delayed by maintaining a healthy weight, being more physically active and eating a healthy diet. It has been suggested that Type 2 diabetes originates from an interaction between genetic and lifestyle behaviour factors, such as physical activity and diet. Identifying how genetic and environmental factors influence the risk of Type 2 diabetes is therefore crucial for understanding how diabetes develops and how it may be prevented in the future.

A UNIQUE STUDY

InterAct is an ambitious EU-funded study at the forefront of ongoing efforts to understand these interactions, and is formed of a consortium that brings together 35 partners in nine European countries and in India. The project brings together experts in clinical epidemiology, prevention, human genetics, diabetes research, endocrinology, bioinformatics, physical activity, nutrition, and genotyping technology, with the aim of investigating how genes interact with potentially modifiable lifestyle and behavioural factors in Type 2 diabetes.

Until now, adequately powered studies with prospective, unbiased, standardised assessment of key behavioural factors for gene-lifestyle studies have been lacking. Professor Nick Wareham, who is leading the InterAct study, explains what makes the project unique: "Most previous studies of gene and lifestyle factors on Type 2 diabetes risk have been too small to observe the combined impact of lifestyle factors and the relatively weak effects of the genes that we know about already," he comments. "InterAct is also different because it uses a prospective design and assesses

the lifestyle factors well before people become diabetic. It is large, including 4 million person years of follow-up and more than 12,000 incident cases of diabetes. The advantage of a study this size is that investigating cases from different European countries affords the opportunity to ascertain the varying impact of the highly distinct dietary patterns in this spread of locations.

THE STUDY COHORT

InterAct is built around a case-cohort study nested within an existing multinational cohort – the European Prospective Investigation into Cancer and Nutrition (EPIC) study. The cohort for the EPIC investigation is large, comprising 350,000 participants from eight European countries. As part of EPIC, standardised information was collected at baseline on lifestyle exposures, and information on socioeconomic status, education and occupation was collected by questionnaire. In addition, biological samples (blood plasma, blood serum, white blood cells and erythrocytes) were collected.

The InterAct Type 2 diabetes case-cohort study includes 28,000 participants, the largest project of its kind in the world. This group is comprised of 12,403 people with verified Type 2 diabetes and 16,154 non cases. These occurred during 3.99 million person years of follow-up of the 340,234 EPIC participants who were eligible for InterAct. A centre-stratified sub-cohort of 16,154 individuals was defined for comparative analyses; individuals with incident diabetes who were randomly selected into the sub-cohort were included as cases, while all prevalent diabetes cases were excluded. InterAct cases are followed up for an average of 6.9 years.



.....
30,000 DNA SAMPLES ARE BEING ANALYSED IN INTERACT

The project brings together experts in clinical epidemiology, prevention, human genetics, diabetes research, endocrinology, bioinformatics, physical activity, nutrition, and genotyping technology, with the aim of investigating how genes interact with potentially modifiable lifestyle and behavioural factors in Type 2 diabetes

INTELLIGENCE

INTERACT: AN EXAMINATION OF THE INTERACTION OF GENETIC AND LIFESTYLE FACTORS ON THE INCIDENCE OF TYPE 2 DIABETES

OBJECTIVES

To discover how genetic and lifestyle behavioural factors interact in their influence on development of Type 2 diabetes.

PARTNERS

Danish Cancer Society; Steno Diabetes Center; Aalborg Hospital, Denmark • University of Helsinki; University of Kuopio, Finland • International Agency for Research on Cancer; Inserm, France • Germany Cancer Research Center; German Institute of Human Nutrition, Germany • India Diabetes Research Foundation, India • Cancer Research and Prevention Centre; National Cancer Institute – Milan; Federico II University of Naples; Fondazione ISI; Ragusa Cancer Registry, Italy • Wageningen University; University Medical Center Utrecht; National Institute of Public Health and the Environment, The Netherlands • Andalusian School of Public Health; Public Health Department of Gipuzkoa, Basque Government; Catalan Institute of Oncology; Murcia Health Council; Institute of Public Health Navarra; Public Health and Health Planning Directorate, Asturias, Spain • Umeå University Hospital; Lund University, Sweden, MRC Epidemiology Unit; Oxford Centre for Diabetes, Endocrinology and Metabolism; University of Oxford; Imperial College London; The Wellcome Trust Sanger Institute, UK

FUNDING

InterAct (LSHM-CT-2006-037197) is a European-Community funded project under Framework Programme 6

CONTACT

Professor Nick Wareham

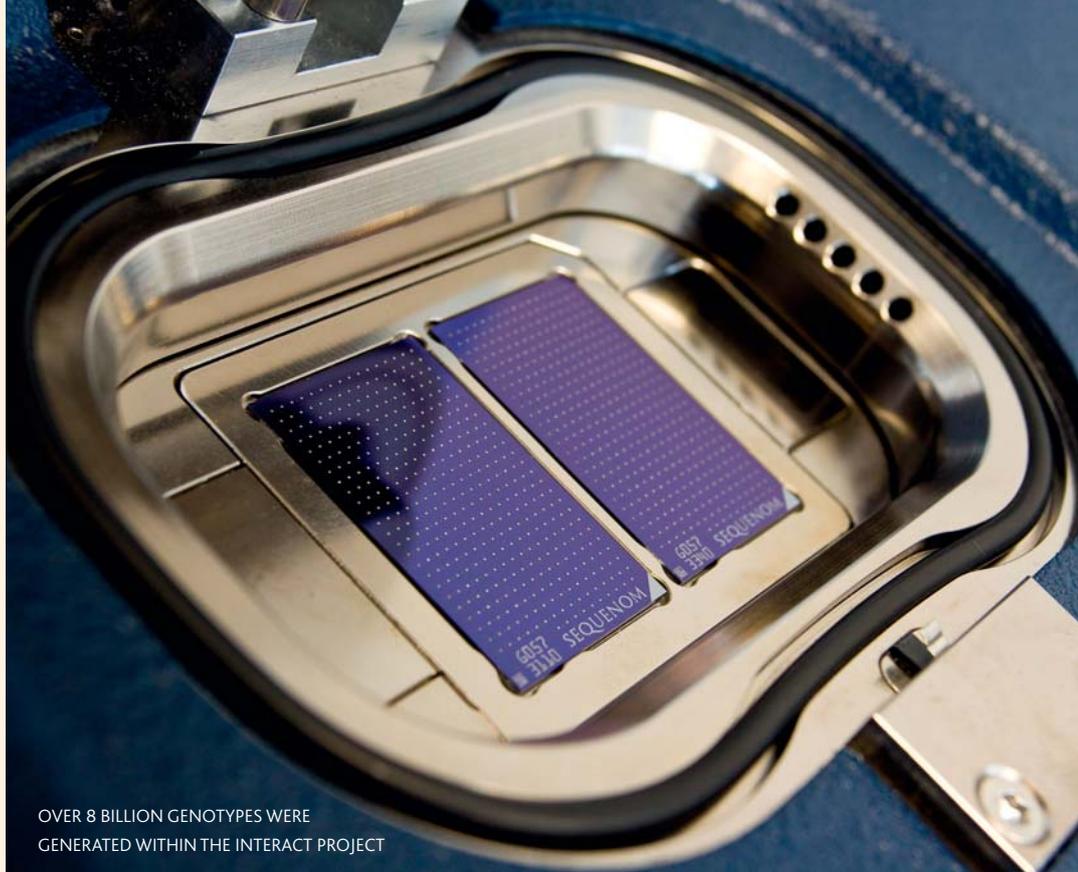
MRC Epidemiology Unit, Institute of Metabolic Science, Box 285, Addenbrooke's Hospital, Hills Road, Cambridge, CB2 0QQ, UK

T +44 (0) 1233 330315

E nick.wareham@mrc-epid.cam.ac.uk

www.inter-act.eu

PROFESSOR NICK WAREHAM is Director of the MRC Epidemiology Unit in Cambridge and an Honorary Consultant at Addenbrooke's Hospital, Cambridge.



OVER 8 BILLION GENOTYPES WERE GENERATED WITHIN THE INTERACT PROJECT

GENETIC INVESTIGATION

To ensure efficient and high quality data can be gathered, DNA extraction and genotyping from the collected biological samples has been undertaken using centralised high throughput methods: "The baseline samples in EPIC have been stored over many years in liquid nitrogen," outlines Wareham. "Although this is expensive to set up, it does provide the best approach to protecting samples over time from degradation. We have set up robotic short-term storage and re-array facilities in order to efficiently prepare samples for measurement without risk of human error."

Wareham outlines the approach his team has taken in investigating the relationship between genetic and lifestyle factors: "We have examined how variants in the 30 to 40 established genes for diabetes interact with lifestyle behavioural factors to influence risk of progressing to diabetes," he says: "However, such an approach might miss novel genetic loci that interact with lifestyles but which haven't been detected in studies that only looked at genes. Therefore, we have also undertaken a discovery approach using a genome-wide association study for interaction in which we directly type 500,000 genetic markers and impute a further 2 million variants in each individual."

DIABETES, DIET AND EXERCISE

The independent role of dietary and nutritional factors in Type 2 diabetes over and above obesity is a contentious subject and this is an area in which Wareham hopes InterAct will play a major role. The study is making significant progress: "To date,

we have studied the association with diabetes for overall patterns of diet, specific foods and food group and nutritional factors," he explains: "In the case of nutritional factors, we have not only studied estimated nutrients derived from reported food consumption but also objective measures of intake as assessed by biological markers such as the pattern of phospholipid fatty acids in blood." One example of the study's dietary findings so far is the discovery that individuals who adhere to a Mediterranean dietary pattern are at lower risk of developing Type 2 diabetes.

InterAct has also made progress in highlighting the association between physical activity and future risk of Type 2 diabetes, first completing a validation in 2,000 people in 10 different European countries of the simple global index of physical activity used in EPIC. The results were enlightening: "We have shown that the benefits of physical activity on risk of diabetes are strong and consistent across countries," recalls Wareham. "They are also the same independently of the level of obesity, suggesting that all individuals could benefit from increasing activity levels."

Unpicking the relationships between diet, exercise and diabetes is clearly a complex and extensive task and the results of the InterAct study are being disseminated widely as they emerge. Wareham is hopeful about the influence the project will have on the prevalence of Type 2 diabetes in the future: "We think findings will have relevance to how we think about strategies for the prevention of diabetes," he concludes, "including the balance between individual and whole population approaches and the specification of the nature of preventive interventions".