Diabesity
A world-wide challenge

Towards a global initiative on gene-environment interactions in diabetes/obesity in specific populations
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Conference report

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The following report is an overview of the presentations and discussions during the conference *Diabesity – a world-wide challenge: towards a global initiative on gene environment interactions in diabetes/obesity in specific populations*, organised by the Health Directorate of DG Research and Innovation on 9-10 February 2012, Charlemagne Building, Brussels. It does not attempt to provide a word for word record or actual minutes of the meeting and considerable detail is omitted for brevity. It rather summarises the presentations and points discussed, to highlight the key issues, challenges, and recommendations.

The intention has been to summarise the main outcomes of the meeting, the recommendations and proposals made to allow them to be taken into account during any policy discussions within the European Commission and for future shaping of European policy and research funding with respect to diabetes, obesity and related causes and complications.

Details of the various presentations and participants involved can be found by accessing the conference website at: [http://ec.europa.eu/research/health/events-12_en.html](http://ec.europa.eu/research/health/events-12_en.html)

Further information about the health directorate can be found at: [http://ec.europa.eu/research/health/medical-research/intro_en.html](http://ec.europa.eu/research/health/medical-research/intro_en.html).

The Health Research Directorate of the European Commission's Directorate General for Research and Innovation DGRTD would like to thank all contributors to the event, in particular the session moderators and the rapporteurs and co-rapporteurs of each of the four parallel workshops.
Foreword

The conference *Diabesity – A World-Wide Challenge: Towards a global initiative on gene-environment interactions in diabetes/obesity in specific populations* was organised by the Health Research Directorate of the European Commission's Directorate General for Research and Innovation, and took place on 9 and 10 February 2012 in Brussels.

High-level scientists and national funding agencies took part from different world regions to identify key issues in the area. It built on four new EU-funded projects stemming from the FP7 HEALTH 2011 call that involves international cooperation with several other partner countries; and this event intended to build on this cooperation, define how it would work and seek input for future cooperation.

On Day 1 there was a roundtable when the main agencies voiced their interest in joining the programme level cooperation and gave a short overview on the challenges of the current research landscape and future trends for collaboration in their home countries; a session with presentations of EU-funded and non-EU funded projects from Europe and beyond with leading researchers defining key questions in the field.

On Day 2 scientific workshops further explored and identified potential for international collaboration according to the following themes:
- Genetics aspects in diabetes/obesity
- Lifestyle and diabetes prevention programmes for minorities
- Diabetes diagnosis and management in primary care in specific populations
- Challenges in diabetes/obesity for pregnant women

Background and rationale

In the EU, 32 million people suffer from the diabetes, with about a further 6 million unaware that they are living with it. This figure is set to rise by 25 per cent to about 40 million by 2030. Worldwide, around 350 million people have diabetes according to the World Health Organization, and more than 900 million are expected to be diagnosed with, or as having high risk of developing, type 2 diabetes within the next two decades.

In Europe, type 2 diabetes is likely to reduce life expectancy by up to 10 years. The disease contributes to coronary heart disease, stroke, peripheral vascular disease and end-stage renal disease, making it the fifth leading cause of death worldwide. It is even worse for type 1 suffers whose lifespan can be cut by over 20 years.

The costs linked to diabetes are spiralling upwards and are estimated to account for 8 to up to 18 per cent of total healthcare costs in European countries. They include the costs for treatment when diabetes is diagnosed, but more importantly also those caused by side effects and complications such as blindness, limb amputation, or kidney and heart diseases. At present, most of the resources are dedicated to diabetes treatment and care. Yet, further investment in diabetes research and prevention is needed if we are to drive down the economic burden associated with diabetes in the long term.
There are two types of diabetes: type 1 is not linked to obesity and it occurs when the body fails to produce insulin, requiring regular insulin injections to regulate blood sugar. Type 2 is a common metabolic disorder, often linked to an unhealthy lifestyle, which occurs when the body's insulin is not used or produced effectively. Once called adult-onset diabetes, type 2 is now a serious health condition for young adults and children.

**Executive summary**

The conference *Diabesity - A World-Wide Challenge* took place in Brussels on 9 and 10 February 2012. Organised by the European Commission Health Directorate of DG Research this event brought together more than 200 leading scientists, funding agencies, policymakers and other key players from across the globe.

Diabetes currently kills 4.6 million people worldwide a year and there are more than 346 million people with this disease, which is expected to increase by 2030 to 552 million. Because of this health imperative, also linked to increasing obesity, participants explored opportunities for greater international cooperation and new partnerships in research.

The event began with views from a MEP from Denmark and from an official from the Danish National Board of Health with the example of government policies such as sugar and fat tax to curb unhealthy eating. A global historical perspective for the evolution of the diabesity epidemic ended with the stark warning that "By 2020, diabesity is set to bankrupt the economies of many nations unless action is taken now".

The diabetes and obesity scenarios of different countries and corresponding research programmes were presented from New Zealand, Australia, Mexico, South Africa, USA and Canada showing an escalating epidemic, increased risk of morbidity and unsustainable projected public health expenditures. As an example of possible response to similar threats an international research collaboration between major health research funders the Global Alliance against Chronic Diseases had been set up to collect evidence to guide policy and help address these public health challenges. International funding agencies had the opportunity to present examples of research funding programmes and projects from their own countries in order to explore potential areas of collaboration.

Four research projects, funded under the EU FP7 programme, intended to contribute to defusing the 'ticking time bomb' of diabetes and obesity were presented. EPI-MIGRANT, MEDIGENE, RODAM, and GIFTS, bring together about 50 leading European and international research organisations. Each project investigates genetic, environmental and lifestyle factors from different populations around the world and their influence on the seriousness and impact of the disease. The four projects will also work in collaboration, in a cluster, and share some data and results. This will allow the researchers to discover new ways to curb the epidemic growth of diabetes and obesity more rapidly. Presentations summarised the projects and were followed by discussion. A fifth EU funded project (EARLYNUTRITION) was also presented on long-term effects of early nutrition on later health.

On Day 2 four workgroups of conference participants looked at different aspects of diabesity research: genetic aspects; lifestyle and diabetes prevention programmes; diagnosis and management in primary care; and diabetes and obesity in pregnant women. The consensus was that better measured and more detailed study of phenotypes and environment was needed across the lifespan starting before conception. International collaborations were advocated, long-term studies and clinical trials, along with a strong desire to increase sharing of databases, biobanks, operating procedures and ideas.
Key findings and recommendations

**Genetic aspects of type 1 and type 2 diabetes and obesity in specific populations**

*Type 1 diabetes*
- Continue approach of detailed studies in high-risk populations and individuals to identify environmental determinants and triggers prior to multi-population disease endpoint studies
- Birth cohorts to study commonality of pathways to type 1 diabetes, type 2 diabetes and other autoimmune diseases
- Consider preventive randomised controlled trials for low-risk interventions

*Obesity*
- Cohorts with emphasis on precise characterisation of environmental factors and obesity phenotypes
- International collaborations for evaluation of extreme phenotypes

*Type 2 diabetes*
- International collaboration in medium-sized cohorts with precise phenotyping of both environmental exposure and disease-related outcomes

**Lifestyle and diabetes prevention programmes for minorities**
- Develop better understanding of the policymaking dilemma
- Involve sectors outside health care: transportation; food industry; infrastructure
- Link experiences from different researchers and countries (start task force to increase cross-sectoral communication and share experience)
- Undertake more research on costs of lifestyle programmes
- Join up experiences of studies/projects in ethnic minorities to plan future research

**Diabetes diagnosis and management in primary care in specific populations**
- Develop optimum tools for screening using non-invasive methods
- Develop risk prediction engines for diabetes screening
- Identify barriers to screening
- Develop population-based educational modules to raise awareness

**Challenges of diabetes/obesity in pregnant women**
- Set up expert reference groups with global representation (Non-Communicable Disease Alliance), for worldwide standardisation; link with other groups. Promotion of importance of developmental origins
- Agreed action platform for exchange of data, samples and knowledge. Link with existing groups and platforms to create a uniform structure
- Develop and validate biomarkers; link with other studies across life course
GENE-ENVIRONMENT INTERACTIONS IN DIABETES/OBESITY IN SPECIFIC POPULATIONS: SCENE SETTING

Ruxandra Draghia-Akli
Director for Health, DG Research & Innovation, European Commission

Dr Draghia-Akli opened the meeting welcoming the international audience gathered and warmly thanked the European Parliament and the Danish Presidency of the EU for supporting this initiative. She noted that now that infectious diseases are for many parts of the world not the same threat they once were: non-communicable and chronic diseases are becoming the main worldwide public health challenge.

The problem of diabetes, obesity and cardiovascular disease (CVD) is growing especially when combined with an ageing population, contributing lifestyle and diet. Diabetes currently kills 4.6 million people worldwide a year and there are more than 346 million people with this disease, a number expected to double by 2030 to 552 million. The scale of this problem demands international action. Other compelling reasons are the complex, multifactorial nature of diabetes that needs a global approach and understanding by the best competencies. A global approach would also allow to take into account a diversity of genetic backgrounds, dietary preferences and lifestyles, all of which interacting in the development of diabetes.

The European Commission (EC) has recently adopted its proposal to provide support to research and innovation for the period 2014 to 2020. This proposal is called Horizon 2020 and it forms one of the elements of the Innovation Union, a key part of the Europe 2020 strategy – the EU's policy for growth and jobs for the next 10 years. Health, ageing and wellbeing is one of the grand challenges to be addressed in Horizon 2020.

Dr Draghia-Akli noted that the cluster of four international European Union (EU) funded projects presented at the Conference take a global approach to fight diabetes and obesity, already somehow bridging the Seventh Framework Research Programme (FP7) to Horizon 2020. These and other international projects and approaches will be discussed and this hopefully will lead to further cooperation, as such international cooperation is the way forward in tackling the ‘time bomb’ of the diabetes and obesity scourge.
Christel Schaldemose  Member of the European Parliament, Co-chair of the European Parliament’s EU Diabetes Working Group (EUDWG)

Reducing the burden of diabetes and obesity – views from the European Parliament

Ms Schaldemose said she was pleased to put the spotlight on diabetes and obesity and asked, “do each of us know someone with diabetes? Of course we do!” The numbers are increasing with an estimated 32 million in the EU with diabetes, another 30 million with pre-diabetes and 346 million worldwide as diabetes associated with obesity is a global problem. There are one billion people overweight and one in seven who are obese. This will become 900 million in 2030 if nothing is done and it is clear there is a pandemic. Alongside this there is a lack of political will.

It is important to act now. Good diet and access to medical treatment are costly but the alternative is a dramatic reduction in quality of life and life expectancy, with associated social costs of sick days, loss of salary, and discrimination as a consequence.

Although this is the pattern of the problem in the EU it is also characteristic of other countries worldwide. Around 70 per cent of the population in low- and middle-income countries develop type 2 diabetes and the human cost is even higher with difficult or no access healthy food and medication. Health systems cannot cope with chronic diseases and there is no doubt about the cost to individuals and society.

Ms Schaldemose referred to a study conducted by the London School of Economics on the economic burden of diabetes across five European countries, amounting to 188 billion euro in 2010 [1]. This stressed the importance of diabetes to Europe and the world. There is a fast return for investment and the European Parliament could also play a role with political leadership. She gave the example of towns in Denmark, which had increased sport in school and healthy eating, and is part of a study showing a reduced risk of developing type 2 diabetes.

Ms Schaldemose underlined that more research into diabetes and obesity is needed within a global research strategy, as well as with national action plans. The EU should coordinate this by insisting on national governments acting together. There should be better access to cheaper medicines. Research should be better coordinated with a greater global reach. Of great importance is standardisation of data collection in the EU. Ms Schaldemose concluded by mentioning the blue circle as a symbol – a link to bring people together to act in better global cooperation.
Increase in obesity and diabetes – a challenge for the individual, the health care system and the society

Ms Hansen-Thrige presented an overview of the challenges in Denmark. Many people have lives characterised by diabetes or other chronic illness, which is increasing partly due to people living longer. Not all people with chronic disease are incapacitated and worsening of the disease can be prevented or postponed by healthier lifestyles.

In Denmark it is estimated that in 2040 about 25 per cent of the population will be older than 65 years compared with 16 per cent today. About one third of the Danish population is diagnosed with one or more chronic disease, which reduces quality of life and forces early retirement. The implications are a mounting pressure on the health sector, 10 per cent of gross domestic product (GDP) is spent on health, and on social services.

There will be fewer young people in the labour market to pay for these rising costs, luckily early detection and treatment have developed rapidly, meaning fewer people die as a result of diabetic complications. However, the number of people with the highest risk of developing type 2 diabetes is increasing especially among children and young people because of diet and lack of physical activity.

The second challenge is that the health system is not adapted to demands of chronic disease; it is more adapted to acute diseases focused on cure rather than long-term care. We need to improve cross-sectoral cooperation between primary health care, general practitioners, and hospitals, and focus on complex needs while ensuring the best clinical results.

In Denmark there are awareness-raising campaigns against smoking, alcohol and to promote physical activity. The national board of health advise the public as well as health professionals by using evidence base if possible, or systematic and standardised best practices. Early detection of risk factors is seen as essential for prevention for chronic disease including diabetes.

Ms Hansen-Thrige described the responsibilities for health provision in Denmark, local authorities have responsibility for children and young people within the municipality health service, together with the general practitioner. Cooperation between primary and secondary sectors is central to prevention, treatment and control of chronic diseases. A model of prevention and integrated care was described with specialised care at the top through assisted care for multiple risk factor management, patients with chronic diseases that are difficult to manage, community health care including prevention, treatment and rehabilitation, to patients with well-managed or newly diagnosed chronic disease with no significant complications. Chronic disease management programmes including patient education cost about Euro 80 million. Patient groups must be defined and patients identified and registered. Treatment should be described in evidence-based medical guidelines.
Obesity in Denmark costs at least Euro 2 billion with 46.7 per cent of the adult Danish population overweight with body mass index (BMI) of 25 or more; more men (54.2%) than women (39.4%); 13.4 per cent are obese (BMI≥30). Some of the causes of obesity are only suspected and there is a complex interaction between factors; individual lifestyle, heredity, living and working conditions, socioeconomic, cultural and environmental factors all play a role.

Structures to support a healthy lifestyle should be available in childhood and can also be regulated by government. Type 2 diabetes has more than doubled in Denmark since 1997 and is primarily due to factors such as obesity and physical inactivity and a growing elderly population. 4.7 percent of the Danish population has diabetes (256,000), of which approximately 10 per cent is type 1, and this is not evenly distributed across Denmark, nor is it related to areas of low education.

Denmark has increased taxes on fat, sugar, chocolate, alcohol and cigarettes, and further regulations are planned in other areas such as smoking. This is supported by the reflection process on chronic disease in the European Commission and in Member States. Ms Hansen-Thrige looked forward to closer links between EU and the World Health Organization (WHO) and noted the needs and urgency of handling the challenges from diabetes and obesity.
DIABESITY: Potentially the greatest epidemic in the history of the world

Professor Zimmet gave a historical perspective on diabesity and noted that the term had originally been coined by Prof Eleazar Shafrir about 15 years ago, although it had hit the headlines more recently. The European Commission was to be congratulated on highlighting the combined problem of diabetes and obesity and this presentation would be used to illustrate, with data from comparative studies in migrated populations, that this is the largest epidemic in human history.

Such studies indicate genetic and environmental determinants in the causation of diabetes in different ethnic groups in the same location, with data on demographics, diet, physical activity, socio-cultural issues, genetic and epigenetic determinants along with recent interest in environmental pollution as a trigger to diabetes and obesity.

In September 2011 a major United Nations (UN) meeting took place, which highlighted the problem of non-communicable diseases (with International Diabetes Federation [IDF] involvement). The UN Director General called the diabetes epidemic ‘an epidemic in slow motion’. One of the major drivers of diabetes is obesity (OECD predictions for overweight to 2020 were shown (Fig. 1)). Global projections for the diabetes epidemic are 366 million in 2011 and 552 million in 2030 (revised figures, IDF Atlas, 4th edn 2009 [2]).

Initial studies had been undertaken by Dr I Prior (New Zealand), who showed higher rates of diabetes in Maori populations compared to those of European origin, also the case for people migrating to the outer Pacific Islands, an urbanized environment. Later, Dr P Bennett (Phoenix, AZ) described this in the Pima Indians. Subsequently, it was shown in Nauru that three of every four adults had diabetes. Studies by Dr Peter White in Australia also showed high rates of diabetes in the indigenous community.

Predictions indicate the top 10 countries for diabetes prevalence in 2010, with Nauru at the top; six of these nations are in the Middle East, the epicentre of the epidemic. China and India have the highest numbers of people with diabetes in the world.

The epidemic has a historical background in Asia with the Indian diaspora providing the model. William Wilberforce got the bill against slavery passed at which point Mauritians no longer had slaves to undertake the work and they began importing labour from India, this mirrored what was happening in other places such as the Caribbean. This provides the historical background to studies such as EPI-MIGRANT looking at Asian-Indian populations around the world.

There are three ethnic groups in Mauritius: Asian Indians, Blacks (Creoles) and Chinese, who constitute 66 per cent (two-thirds) of the world’s population so anything that happens in these groups reflects what happens in Europe.
Studies were carried out in 1987, 1992, 1998, 2004 and 2009 and Mauritius has seen a 62 percent increase in diabetes over the 22 years since the first study in 1987. This is mirrored in studies of Asian Indians in South Africa, Fiji and other nations where the diaspora occurs.

The physical side of diabesity is known but there are other factors that may be driving the epidemic. In China, between 2000 to 2002, one per cent had diabetes and in 2009 it is nearly 10 per cent, which may be an underestimate. The term cocacolonisation applies to the westernization of traditional lifestyle. India has been crippled by ‘sugar disease’ and around 15 per cent of all the people with diabetes in the world are in the Asian region where there has been a very rapid 40 per cent increase.

Prof Zimmet quoted the former Prime Minister of Australia as stating that diabetes would be the “leading cause of disease for men and the second leading cause for women” (after breast cancer). An indication of what was happening in Australia showed an age-specific prevalence of diabetes in indigenous Australians, the falloff in higher age ranges reflects the high mortality from diabetes. The research centre in Alice Springs has the largest renal dialysis unit in the Southern Hemisphere with the highest death rate from renal disease in the world. The epicentre with high rates of diabetes and massive rates of obesity is in the Middle East.

The idea that type 2 diabetes is due to lack of physical activity and poor nutrition had been seductive, but there is also the low birth weight hypothesis (Dr D Barker, UK). The first 9 months shape the rest of your life and early life ‘programmes’ diseases such as diabetes and obesity (as recently reported in Time [3]). What the mother eats, drinks or smokes during pregnancy may alter the DNA of the child.
The process whereby a stimulus applied in utero establishes a permanent response in the foetus leading to enhanced susceptibility to later disease, e.g. type 2 diabetes and CVD, is termed ‘developmental plasticity’ (Fig. 2). Epigenetics is a hot area of research with important implications for prevention, and can have intergenerational effects.

An example is the Dutch Winter Famine at the end of World War 2 in the Netherlands. Allocated rations were 400 to 800 calories/day and women exposed to this during the 2nd and 3rd trimester of pregnancy delivered small babies. As adults, these babies had a higher prevalence of type 2 diabetes, CVD, hypertension, obesity and schizophrenia.

Another example is Cambodia, where 30 years after the Pol Pot regime, although there was virtually no diabetes 30 years ago the rates published 10 years ago were similar to those in Australia and New Zealand.

In conclusion, the need for better data collection is essential (the IDF is considering better direction of international studies documenting diabetes in different populations). Meanwhile, diabesity continues to rise exponentially globally; ageing, lifestyle change and urbanisation are targeted as drivers but in developing nations and indigenous communities the story may be different. A greater focus on epigenetics and early life risk factors e.g. maternal nutrition may lead to more effective strategies to halt this global ‘perfect storm’ of diabesity. By 2020, diabesity is set to bankrupt the economies of many nations unless action is taken now.
**The Global Alliance against Chronic Diseases: A model for international cooperation**

In low-income countries, communicable diseases are still equal with non-communicable diseases (NCDs) as causes of death, but in low- and middle-income countries NCDs are far ahead. The impact of NCDs comes from the tremendous advances made in fighting communicable diseases, resulting in people live longer. Nearly three-quarters of the deaths from chronic diseases (CVD, pulmonary disease, diabetes and cancer) occur in low- and middle-income countries. Diabetes is definitely a part of the concern at the NHLBI because many of the diabetes deaths are related to CVD. Health and economic impacts are an underappreciated cause of poverty hindering economic development of countries, communities and families (Fig. 3).

The NHLBI supports the Framingham Study (FHS), which is a model of how epidemiology research can be identify crucial areas for basic and clinical research, leading to long-term population-level health benefits. The FHS was started in 1948 and continues (renewed every 5 years with more emphasis now on genetics). It originally identified that hypertension, cholesterol and smoking were major risk factors for later development of CVD in people who were asymptomatic. The NHLBI supported that work including the basic science on blood pressure and cholesterol. The pharmaceutical industry then picked up the costs to develop statins, anti-hypertensive drugs etc. NHLBI was then part of implementing that knowledge, and the result was a dramatic decrease in heart disease in the USA between 1960-2000, prior to the impact of the current diabetes epidemic. The impact is global on CVD death, with later studies performed in Finland (the North Karelia Project), where data have been used to inform implementation of major changes of diet and smoking.

The NIH is the largest public funder of biomedical research in the world. Many public funders of research have a major focus on public health issues. Other public funders have been working to coordinate better evolution of the world public health agenda. Both the contributing factors to the NCD pandemic and potential solutions have economic, political, diplomatic, ethical and humanitarian components.

The problems are complex, with the population, cultural, economic and environmental issues, none of which is easily modifiable. Challenges include finding evidence that decision makers can use to implement policy knowing there is a reasonable chance of success. Asking policy makers to make changes that have economic and business impact requires great justification and it is our scientific obligation to pull this information together.

Environmental issues are crucial. Many things change when people move from one place to another. BMI of South Asians increases as they move from rural to urban environments. Many of these issues are modifiable, but complex and multisectoral. The problems manifest in the health sector, but the solutions probably lie elsewhere.
Key issues in prevention are likely to be transportation, housing, education, agriculture, urban planning, local ownership, and policy makers. For policy makers to take leadership they must have data and evidence. Policy has had big impact in some areas (e.g. impact of smoking, control of lead in the environment). The UN summit came with a number of interventions to tackle some of the risk factors (tobacco, alcohol, diet, physical activity); all have a major impact on diabetes.

The Global Health Initiative (www.ghi.gov) launched in the USA does not yet have chronic disease on the agenda. Its core principles are gender equality; strategic coordination and integration; strengthen and leverage key multilaterals and other partners; country ownership; sustainability through health systems strengthening; improve metrics, monitoring, and evaluation; promote research and innovation. The Global Alliance for Chronic Disease (www.ga-cd.org), a virtual organisation created 4 years ago by the large public funders of biomedical research in Australia, Canada, China, India, South Africa, UK and USA, aims to address these issues. Its goals are to coordinate implementation of research activities; seek common approaches to guide policy; develop and share best practices; and build research/economic capacity. It aims to identify high priority items and research questions to develop funding opportunities.

The GACD plans to engage partners, especially in the southern hemisphere -- non-profit organisations, industry, and sectors often not involved in biomedical research e.g. transport, agriculture. Key areas are CVD, pulmonary disease, diabetes, cancer, but research may not necessarily be disease-specific. As there are overlapping and separate missions, and bilateral relationships among members, a common study will allow results to be interpretable. A request for funding applications will soon be funded on hypertension. All the issues common in low-income countries are also a problem within vulnerable groups in high-income countries (e.g. Pima Indians in the USA). Thus, it is necessary to collect evidence to guide policy and help address the severe problems that come from diseases including diabetes and obesity across all nations.

![Health and Economic Impacts are Huge](image)

**Figure 3.** Health and economic impact of non-communicable (chronic) disease
A video had been sent by Sir Peter, who was an obesity and diabetes researcher. New Zealand and the EU have a strong research relationship and he was delighted to see a meeting focused on the important subject of diabesity. New Zealand has particular concerns about diabesity, reflected in the UN Summit especially regarding maternal and child health. Some populations are more at risk especially the indigenous Maori people and the Pacific Island peoples.

An interesting question was why some people in some populations are more at risk in a given obesogenic environment. The focus has mainly been on genes and lifestyle and less on development. The focus of his institute, with worldwide collaborations especially in the UK, has been on the developmental/epigenetic contribution to the pathway to obesity and diabetes. Data indicate that epigenetics in early infant life played a role and contributed to individual and population-based insulin sensitivity.

New Zealand was active with centres across Europe (e.g. Southampton), and was a good example of the opportunities to identify research questions with the potential to lead to a productive road map, a move away from identifying the problem to identifying methods of prevention. He looked forward to seeing the research questions identified in this meeting. New Zealand was committed to joint research, to increasing the density of the relationship with other countries, bringing expertise that together with others can make a real difference.
From a research perspective diabetes/obesity is a number one issue in New Zealand. The broadness of the health problems also includes unique features of the incidence in the Maori people. Defining culturally appropriate ways to do research driven by the needs of the community tailored to specific communities are on the radar. One driver is the health economics changes and demographics of New Zealand.

Until a few years ago about 3-4 per cent of public health expenditure was on diabetes and obesity, but in 2030 it will be around 15 per cent and unsustainable. This is the near-term and thus gives a huge impetus to participate in research collaboration.

**Discussion**

There was a question of whether the concept of measuring obesity by BMI should be revised to rather using adiposity, especially in different ethnic groups where BMI does not work in an appropriate way? There is much evidence that the ‘correct’ BMI for someone of Asian origin is 21 or 22 and above that is probably at risk, rather than the current 30. This point was also made for waist circumference as a measure of abdominal adiposity, as a major risk factor for South Asians who have greater subcutaneous fat, liver and ectopic fat. There was general agreement that there is uncertainty when using traditional BMI in different populations.
Dr Brendan Nelson  Australian Ambassador to the European Union, Belgium, Luxembourg and NATO, Brussels

Dr Nelson presented stark figures from Australia, where reducing the diabetes time bomb was a priority. Around 61 per cent of Australians were overweight/obese, an increase from 56 per cent since 1995. Four per cent of Australians were diagnosed with diabetes (87% type 2) an increase from 3.5 per cent in 2004 (and probably higher). Aboriginal peoples and Torres Strait Islanders had a three-times greater risk of diabetes (with chronic renal disease four-times higher).

Type 2 diabetes would be the leading cause of disease burden by 2023 and was the seventh leading cause of death.

The National Partnership on Preventative Health (with benchmarks being a healthy body weight) prioritises education in early childhood, workplace and industry agreements on food content, local government to undertake and implement physical activity and diet programmes.

In 1996 diabetes had become a national health priority, others including an Indigenous Chronic Disease Package, development assistance for NCDs and monitoring, surveillance and research.

For Australia, which is only 0.3 percent of world population but 3% of the world’s intellectual output and has a global outreach in some disciplines, the best way to further improve quality of research is to collaborate more internationally e.g. through the Global Alliance for Chronic Diseases and also through the National Health and Medical Research Council-European Union Collaborative Research Grants scheme, project twinning and prevention, research and development assistance.

Discussion
Dr Nelson gave a further comment on Australian funding activity in primary care. Funding was being provided to primary care physicians to allow remuneration for providing preventive health.

Another practical element was that every school in the country was required to provide a minimal level of physical activity, in addition lessons were being provided on how to grow and to cook vegetables to encourage the present generation of Australians.
MSc Héctor Sámano Rocha  Director,  Bureau for Mexico-European Union Science, Technology and Innovation Cooperation (CONACYT), Mexico

MSc Sámano began by stating that the major health problem being faced by Mexico is diabetes and obesity. In a population of 112.3 million, 49.1 per cent men and 50.9 per cent women, 78 per cent urban, 22 per cent rural, the GDP per capita is 10,311 US dollars (year 2011). Life expectancy is 77.8 years for women and 73.1 years for men.

Health problems 70 years ago were mainly transmissible diseases such as parasites and infection of digestive and respiratory systems.

These were replaced between 1960 to 2000 by an increase in cancer, accidents and violence. Since 2005 leading causes of death have been CVD, malignant tumours and diabetes.

In 2010 the leading cause of death in Mexico was diabetes, where the prevalence is estimated at 7 percent of the total population (between 6.5 and 10 million), 10.7 per cent of Mexicans between 20 and 69 years have the disease and approximately 2 million are undiagnosed. 13 of each 100 deaths are caused by diabetes with Mexico being tenth in the world for diabetes, and at the present trend will likely occupy the seventh place by 2030.

Approximately two of every three Mexicans are overweight or obese (national prevalence of obesity is 24.4%). Mexico occupies the second place in the world for obesity, consequently the number with diabetes has increased. It occupies the first place for childhood obesity and if such tendencies continue 65 per cent of the population could be obese with more children with type 2 diabetes (30% overweight and 16% obese), with one out of three with diabetes. The cost to Mexico is nearly 6 billion US dollars a year, in addition to the impact on the family and the individual.

Research funds available in Mexico for health projects come from the scientific and technological sector through the investment of financial resources in the Sectorial Fund for Health Research and Social Security established by the National Council of Science and Technology (CONACYT), the Ministry of Health and two National Institutes of Social Security (IMSS and ISSSTETE), with the objectives of supporting science, technology and innovation projects.

A research call for proposals was issued in December 2010 by CONACYT through its Sectorial Fund for Health Research and Social Security for proposals in diabetes and obesity following the program level cooperation agreed. Thirteen projects were selected to start in 2011.

CONACYT has links between Mexican and European Health projects, access to and exchange of new methodologies and data in diabetes/obesity, promotes the visibility of Mexican research and innovation and generates future potential international collaborations. It is proposed to establish collaborative mechanisms.

**Discussion**

There was a question about whether education on lifestyle for children was being addressed in Mexico. In reply, Msc Samano said there was a campaign on obesity for children and parents and a specific campaign in schools to make children aware of the consequences of diet.
There is also a campaign on physical activity, along with measurement of the effectiveness of these campaigns. In addition, there were ongoing research projects in obesity.

A question was asked whether there were any projects looking at ethnic minorities in Mexico. In reply, yes, there is work being done with a Mayan population with a high prevalence of diabetes (28%) in family groups.

There was a comment about data from USA Mexicans showing they have the highest rates of diabetes and metabolic syndrome (and next highest BMI apart from African-Americans), but mortality does not appear correspondingly high. Is this because they return to Mexico and die there, or is there is some protective mechanism? In reply, there is evidence of genetic variance that may cause/favour the development of diabetes/obesity but at the same time protect from other diseases but it is not the only factor. The ‘Hispanic paradox’, of higher risk factors, high BMI, high cholesterol, high blood pressure but lower risk for CVD is evidence of genetic protective factors or generational factors.

**Dr Daan Du Toit**  *Minister Counsellor (Science and Technology), South African Mission to the European Union, Brussels*

South Africa has a longstanding scientific partnership with the EU and has participated in successive framework programmes. The European Commission commitment to harness global partnerships to address the shared global challenges is appreciated. Dr Du Toit focused on the research and innovation response to diabetes within the South African 10-year innovation plan, the grand challenge was to harness biosciences to address the disease burden and follows the approach to improve health and reduce health inequality.

To avoid fragmentation and duplication and to carry out comprehensive health product development the approach is to take priority diseases and evaluate current national and international efforts, then analyse available capabilities. By combining the abilities and equipment at the various research institutions it is hoped to develop or improve therapeutics, vaccines, diagnostics and also to understand better human health behaviour and impact of the environment on disease incidence.

A series of horizontal interventions supports the innovation product development cycle. South Africa is known for health programmes in poverty-related communicable diseases such as HIV AIDS and malaria, which continue to remain an important priority, while increasingly more attention has been given to chronic diseases, specifically diabetes.
For the UN summit on NCDs, South Africa prepared a policy briefing warning of the *Race against time*, to reduce risk factors, improve detection and management of CVD, diabetes, cancer, chronic respiratory disease and mental illness. NCDs are increasing in rural communities, poor people are more affected, and there is an increased demand for care.

Heart disease, diabetes and stroke are the second leading cause death. In the 1990s there was high prevalence of diabetes at 6 percent, the current incidence is up to 6 million. Recent data show an increase of 38 percent in death from diabetes.

Complications of type 2 diabetes, e.g. CVD, blindness, kidney disease, have significant socioeconomic impact on an often-fragile environment. South Africa has extremely high levels of overweight and obesity in 70 percent of women over 35 years and 45 percent of men over 35 years, especially in urban populations due to diet and lack of physical activity.

There has been a call for concerted research commitment and in response the main funder of research in South Africa; the Medical Research Council (SA MRC) has several dedicated research platforms. Major research avenues are effect of lifestyle, especially diet, from in utero to adult on the development of type 2 diabetes, while the cardiovascular team is investigating the pathophysiology of the myocardium in ischaemia and in type 2 diabetes.

The South African research and innovation response is to develop an NCD research and innovation initiative including diabetes, CVD, respiratory diseases and mental health with interdisciplinary and inter-institutional collaboration (including interactions between diabetes, HIV AIDS and tuberculosis). Diabetes is seen as the primary NCD priority for intervention. Current research focus areas are: biomarkers for early detection of diabetes; drug development; longitudinal studies (especially in rural areas with extensive data sets available for more than 15 years); research chair specialising in better understanding of the disease; population dynamics, e.g. South Africans of Indian origin being more insulin resistant; information technology.

South Africa is developing a Health Innovation model to encourage co-investment in the global research agenda. Research institutions are encouraged to work with industry, with government providing seed funding to initiate projects. There is a strong focus on international partnerships with traditional partners like EU, but also pan-African context, e.g. African Network for Drug and Diagnostics Innovation. Committed initiatives are addressing global challenges such as capacity building (GACD).

**Discussion**

The development of obesity gender differences were important with women more obese than men, this was noted as a typical finding. Dr Du Toit added that women and children become obese faster than men with urbanization, this was being investigated.
Dr Griffin Rodgers  Director, The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH), USA

The NIDDK is dedicated to diagnosis, prevention and treatment of diabetes; however, many other institutes also contribute. Currently 26 million Americans have clinical diabetes and some 79 million are in the pre-clinical state. The natural progression from normal to frank type 2 diabetes and its associated complications, diabetes management and long-term disability, and short life expectancy is the subject of efforts to try to stem disease progression.

Dr Rodgers reviewed some of the research projects in the area: HEALTHY study, attempting to reduce risk factors; TODAY study, in adolescents and youth with type 2 diabetes; LOOK AHEAD study, involving established diabetes to lower risk factors for complications by intense lifestyle modification; ACCORD trial, with modification of blood pressure, lipids, and glycaemia.

The Diabetes and Prevention Program (DPP) in pre-diabetes/obese individuals showed the benefit of lifestyle intervention with low calorie /low fat intake and exercise (compared with metformin and placebo), and found this to be durable over a 10-year follow up (Fig. 4). If the programme is to be expanded to all those at risk it cannot be under research conditions because of cost, but translational research has brought in the Young Men’s Christian Association (YMCA), with accessible locations and an infrastructure able to deliver intervention in a cost-effective manner.

![Clinical Research: Lifestyle Intervention Prevents Type 2 Diabetes and Achieves Weight Loss in High-risk Individuals](image)

**Figure 4.** Diabetes prevention program (DPP): long-term effects

There have been studies looking at genetics, large-scale genome wide association studies (GWAS), databases and investigation of gene environment interaction.
The intermural programme in Phoenix AZ studies groups with the highest prevalence of diabetes and obesity and their cousins who emigrated to Mexico where the prevalence is about one fifth of those residing in the USA.

Lifestyle interventions were ongoing in overweight and obese pregnant women, studying genetic differences and the vicious cycle with development of type 2 diabetes at an earlier age. From the HAPO study (Hyperglycemia and Adverse Pregnancy Outcomes), showing that almost all non-normal levels of blood glucose can contribute to perinatal complications, has emerged a new initiative to improve metabolic outcomes of mothers and babies.

Although it was in type 1 diabetes, and around 60 per cent of attributable risk was understood, the ongoing TEDDY study has the primary goal of identifying the triggers that cause the disease in genetically at-risk children. A secondary goal is to establish a central repository of data and biologic samples.

Other current efforts of NIH were noted including an agreement with India to begin collaboration on stem cell research as well as diabetes. The NIH was also developing a twin project with China, along with research efforts with Russia and Brazil.

Discussion
It was asked how findings on lifestyle would be translated into systematic education and information campaigns and programmes. In reply, Dr Rodgers said there are a number of ongoing efforts, with durable effects. Employers and companies for example are developing effective and cost saving programmes. One insurance company offers to those insured a 12-week educational effort with physical activity. In addition, there is the example of Mrs Obama who is interested in promoting physical activity. Translation of results is important and although it is a complex area, we must move beyond the science and medical model into city planning, transport etc.

A comment was made from the audience on the problem with illegal immigrants who leave Mexico healthy and return with chronic diseases. Lifestyle is important as is access to medical and prevention services. Mexico has a joint research programme with the University of California to look at health problems in Mexican immigrants, genetics are studied, but also lifestyle and it would be good to see industry support this issue. Dr Rodgers agreed that this was very important.

A further comment was on the term pre-diabetes, which the American Diabetes Association (ADA) had now pulled, although a useful term, as the term diabetes was very artificial, blood glucose should be considered as a continuum. Dr Rodgers said the ADA was now looking at HbA1C to diagnose diabetes.

The point was raised that DPP was called a prevention programme but most would agree that it is delaying rather than preventing diabetes by 2-3 years. We need to move even earlier than just looking at those patients who present at high risk. Dr Rodgers agreed, and although it does seem to prevent diabetes and in some patients the biochemical profile is normalised, this suggested that intervening earlier would allow a rest and regeneration for the remaining beta cells and this is under study. But patients who currently have the disease also require treatment.
Taxation of sugar and its removal from foods for 10-15 year olds was mentioned [4] in the management of obesity and diabetes and Dr Rodgers was asked what was the opinion of the NIH?

Dr Rodgers said, that on the issue of sugar and tax NIH can only provide research data, this is ultimately a policy decision; however, he co-chairs an obesity task force with Dr Shurin that will address sugar and sugar substitutes and will bring in expert advice.

A question was asked about breast-feeding as a way to prevent type 1 and type 2 diabetes and obesity. Formula contains sugar and generates addiction to sugar at an early age. In reply, Dr Rodgers said they were looking at this specifically among Pima Indians to demonstrate the benefit and reduced risk with breast milk. A comment was made about lifestyle interventions that had a dramatic 66 per cent decrease in diabetes; however, this had not been found in India or in Bangladesh where the effect was around 50 per cent. It maybe that such intervention does not work in all populations. Dr Rodgers said that this had been multiethnic study and the effects of intervention were quite pronounced and similar in all ethnicities, with the best effect seen on the over 60 years, who showed a 75 per cent reduction. The results seem effective and durable.

**Dr Philip Sherman**  
*Scientific Director of the Institute of Nutrition, Metabolism and Diabetes (INMD), Canadian Institutes of Health Research (CIHR), Canada*

Dr Sherman began with some background on CIHR. It was 11 years old and had the mandate to excel, according to internationally accepted standards of scientific excellence, in the creation of new knowledge and its translation into improved health for Canadians, more effective health services and products and a strengthened Canadian health care system. It has 13 virtual institutes and Canadians collaborate with researchers internationally.

The INMD supports research to enhance health in relation to diet, digestion, excretion, and metabolism; and to address causes, prevention, screening, diagnosis, treatment, support systems, and palliation of conditions and problems associated with hormone, digestive system, kidney, and liver function.

In 2008 approximately one-quarter of Canadian adults were obese (BMI of 30 or above), and 62 per cent were classified as either overweight or obese. Canada ranked fourth in prevalence of obesity in OECD Countries, 2004-2008, behind the USA, Mexico, and New Zealand, (Organisation for Economic Co-operation and Development Health Data, 2009). The prevalence of obesity was 2.5 times higher in 2004 than in 1978/79 among Canadian children and youth aged 2 to 17 years; obesity had tripled, from 3 to 9 per cent, among youth aged 12 to 17 years.

There is no one data source on obesity among First Nations, Inuit, and Métis peoples in Canada, but in 2004 an estimated 38 per cent of Aboriginal adults living off-reserves were obese (diabetes discussed in Fig. 5).
At its inception, the INMD distinguished itself from the other institutes within CIHR by choosing a single strategic priority: obesity and healthy body weight. Between 2000 and 2008, the annual number of Canadian obesity research publications tripled: from 93 in 2000 to 283 in 2008, Canada ranked fifth in the world for total number of publications in obesity between 2000 and 2008; thus increasing awareness. Research priorities were: obesity and healthy body weight; environment; genes and chronic disease (and the epigenome); food and health and continuum of care.

There was a need to intervene to improve quality of life and to seek solutions to the problem of obesity and body weight and INMD aims to support research on solution-focused interventions at the clinical, policy, and population health levels; foster research on priority populations including: children, Aboriginal peoples, and morbidly obese persons; emphasise knowledge translation to improve prevention approaches and enhance weight management strategies.

The aims are also to advance knowledge about environmental and genetic influence on development of chronic disease; increase knowledge on the phenotypic variation of diseases; understand better the interactions with the human microbiome and support research in the health consequences of changes in the natural and built environments.

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**Figure 5.** Diabetes in Canada: the challenge
Workshop Objectives:

1. Define strengths, gaps, and opportunities for targeted research to identify the interactions and roles of natural and built environments, human behaviour, and genes on the pathogenesis and pathobiology of chronic non-communicable diseases.

2. Identify strengths, gaps, and opportunities for increasing research capacity in Canada in the area of natural and built environments and their impacts on genes and chronic non-communicable diseases.

3. Identify Canadian research priorities for an environments, genes and chronic disease targeted research initiative.

Figure 6. Objectives of INMD workshop held on February 7-8 2012

Finally, Dr Sherman concluded by mentioning Banting and Best who along with Macleod had received the Nobel Prize for the discovery of insulin, and 90 years ago (in January) the first human subject had been treated with insulin, which was the legacy of diabetes research in Canada.

Discussion

There was a question on CIHR initiatives in primary care and the likely contribution to diabetes. In reply, Dr Sherman mentioned strategic funding initiatives, including one on primary care in community health interventions.
LEADING RESEARCHERS HELP TO DEFINE KEY QUESTIONS

PRESENTATION OF EU-FUNDED PROJECT EXAMPLES

Moderator: Prof Thorkild I.A. Sorensen  Director, Danish Obesity Research Centre (DanORC), Copenhagen, Denmark

Prof Graham Hitman  Barts and The London School of Medicine and Dentistry, Queen Mary? University of London, UK

Genomic and lifestyle predictors of foetal outcome relevant to diabetes and obesity and their relevance to prevention strategies in South Asian peoples (GIFTS)

Professor Hitman began by showing the world map re-drawn according to the prevalence of diabetes, with South East Asia highlighted. He then showed a map of North-East London with hot spots indicating high prevalence of diabetes perfectly matching locations of ethnic minorities. Prof Hitman noted that this was not a harmless observation and showed a league table in London indicating 7 years of life lost due to diabetes in inner city areas, compared with the suburbs where it was 2 years.

Diabetes is multifactorial, has a genetic predisposition and there are influences in utero, during child and adulthood. Great progress has been made in elucidating the genetic predisposition with over 42 genes identified through GWAS and a new clutch of genes will be identified using whole genome sequencing, but this currently only explains 10-15 percent of susceptibility. Although the onset of diabetes can be delayed with lifestyle, Prof Hitman suggested that that such strategies needed evidence that they delayed the onset of CVD and looked forward to trials addressing this issue.

![Image of epigenome diagram]

**Figure 7.** The epigenome: the missing link between genome and environment?
Early life programming of metabolic disease has been targeted as an opportunity for prevention and this is the focus of the GIFTS project. The gene environment interaction is familiar, but what is now emerging is another link, which happens at the epigenome where the environment can also make changes on the genome (Fig. 7). It does not change the base structure, but it is hypothesised that environment can lead to secondary changes (for example by methylation) that affects gene function. He suggested that in the presence of genetic susceptibility and together with a diabetogenic environment this could have an amplification effect. The horrific part is that it can be cross generational.

Regarding evidence of foetal programming, in the Hertfordshire birth cohort (in seminal studies first described by Drs D Barker and N Hales) a low birth weight followed by high catch up growth in the first year was found to be a potent risk factor for diabetes and metabolic disease. This was also the case with the Dutch Winter famine. Differences in nutrition and over nutrition can also programme towards diabetes development. Prof Hitman described a study by colleagues in India looking at folate and vitamin B12 levels during pregnancy and studying the offspring at the age of 6 years for indicators of insulin resistance. This was especially important as vitamin B12 is one of the feeders into methylation so B12 deficiency could have a direct effect on gene function.

Themes and organisation
The overall programme of GIFTS concentrates in South Asians with three themes and 11 workpackages combining prevention strategies, state-of-the-art genomics, social sciences and public health, which focus on these early life predictors of disease.
1. Lifestyle and nutrition from pre-conception to early childhood
2. Characterisation of gene and environment interactions
3. The preparatory steps required for the clinical translation of the findings of the GIFTS project.

GIFTS has 16 partners and is targeting early life programming as an opportunity for prevention of diabetes and obesity in people from South Asia living either in their home countries or Europe. To make a significant impact we need to explore opportunities for greater international cooperation and a willingness to share data, resources and expertise to the common good.

Discussion
A question was asked about why only measure folate and vitamin B12 and not tryptophan and other metabolites? The response was that this was important and other micronutrients would also be studied such as vitamin D but the budget was restrictive. However, as samples are being biobanked this provided an opportunity to collaborate with different groups to study different hypotheses.
It was asked that as epigenomics will be done in the future what were the current thoughts on relevant tissues and should this be pre- or post conception. In reply, Prof Hitman said current experiments would be proof-of-principle, but if it is pre-conception it should not matter which material, if it is post-conception then likely to only apply to certain tissues. Placenta samples would be saved.

There was some discussion around the word interaction and it was suggested that *interplay* between genes and lifestyle would create better understanding and be more appropriate.

A related study, ‘Born in Bradford’ was about to begin, with material being biobanked. Much of what will be done in GIFTS (including qualitative research) would also be done in this study and perhaps there was an opportunity for collaboration.

**Prof Florin Grigorescu INSERM, France**

**New genetic approaches in understanding susceptibility for metabolic syndrome in Mediterranean populations (MEDIGENE)**

Professor Grigorescu explained that MEDIGENE would explore new genetic approaches in understanding susceptibility to the metabolic syndrome in Mediterranean populations by examining the way of life of different people in their native countries. The project will consider the way of life, natural (ancestral) ecological niche and consequences of migration as a potential factor for the global increase in diabetes/obesity, including the impact of deregulation of food supplies in modern times. Human genetic diversity is a source of persistence and increase in the differences in health as seen in people across the EU disadvantaged by inequalities and low-income. Understanding and accepting human genetic diversity, as opposed to biological egalitarianism represents a major advance in current thinking. Group differences will help to understand how genetic and environmental factors produce biological outcomes. Genetic diversity should be considered a virtue of mankind not a defect, and a source of evolutionary resilience and adaptation assuring survival and health with potential positive economic consequences on agriculture and environment.

**Aims and organisation**

MEDIGENE is a consortium of 13 partners in the Mediterranean area comprising clinical endocrinologists, geneticists, anthropologists and archeologists. It has eight workpackages and looks at modern migrations (immigration) and comprises vulnerable groups, with low health status and low income.

1. *Explore the insulin resistance syndrome* (metabolic syndrome) in immigrant populations in Europe (in host and home countries)
2. *Unravel new susceptibility genes* for the metabolic syndrome considering genetic variability (stratification) in case-control GWAS and gene environment interaction.
3. *Improve genetic markers*; to explain heritability better by complex haplotypes of SNPs and their phylogeny in populations; and to offer a new basis for personalized medicine. There is a relationship between migration and health, which would be examined with information on historical migrations in the Mediterranean (the antique Romans) along with archeo-genetics of Europe (Paleolithic).

The methodology used in the study includes next generation sequencing, GWAS, bioinformatics and statistics, and data integration.
Expected value of results
- New genes or allele variants specific to populations may help prediction, diagnosis, and treatment.
- Alternative for classical GWAS - considering rare variants (SNP), ethnic specific and better explanation of association and heritability in populations.
- May help to explain a series of epidemiological paradoxes, e.g. lower mortality in immigrants from Maghreb in France (men but not women), differences in metabolic syndrome between North and South France, low cardiovascular mortality in first generation Greeks, and the role of the Mediterranean diet.
- May provide an alternative explanation for insulin resistance, energy allocation mechanism versus adaptation of humans in relation to fertility, population density, social competitiveness, and rural to urban transition.

Discussion
It was noted that MEDIGENE looks at a very diverse population. North Africa for example offers a huge diversity: how will the results be extrapolated? Or, will more homogeneous subsets be examined to help interpret results? Prof Grigorescu agreed that the population of Africa is divergent, but the DNA and chromosome Y would be genotyped by recomposition from a large mixture in the GWAS, separated and stratified according to function of the mitochondrial DNA and chromosome Y.

There was a comment that from experience of studies with people of European descent tens of thousands of samples are needed to detect even modest effects of fasting glucose, lipids, or obesity. Does this study expect to find novel genes and why use the metabolic syndrome as a phenotype? In reply Prof Grigorescu said there would be around 2-3,000 samples, which should be sufficient. The project would try to produce the data by putting together in another way, to increase the power. For the components of the metabolic syndrome, all the components will be examined to locate a gene. Even if the same genes are found, the combination in each specific population will be of interest as different populations respond by adaptation.

There was a question on the role of SNPs in disease, when it has been said that atherosclerosis and metabolic disease is a postprandial phenomena and dietary influence is much higher. Is it useful to look at the SNPs, rather perhaps do metabolic studies to treat the phenotype? Prof Grigorescu in reply said that he felt it was important to look at the SNPs.

Dr John Chambers Imperial College London, UK

Identification of epigenetic markers underlying increased risk of type 2 diabetes in South Asians (EPI-MIGRANT)

Dr Chambers began by explaining that when compared with the global burden of disease there is an increased burden of cardiovascular and metabolic disease in South Asians. The prevalence of type 2 diabetes has been compared in South Asians and Europeans living in the UK (LOLIPOP study) and showed the risk to be increased in South Asians and the known environmental and genetic factors do not explain this increased risk. The hypothesis of EPI-MIGRANT is that epigenetic modification may predict and/or mediate the increased risk for type 2 diabetes among South Asians.
Heritable changes in gene expression are not determined by changes in DNA sequence, rather they are mediated by DNA methylation at cytosine residues. DNA methylation is altered by environmental challenges including maternal under-nutrition and low birth weight. Rural Indian mothers are shorter and thinner and their neonates are lighter, compared with Europeans. Maternal under-nutrition and low birth weight are associated with future type 2 diabetes in South Asians.

**Aims and organisation**
EPI-MIGRANT aims to test the hypothesis that epigenetic modification contributes to the increased type 2 diabetes risk among South Asians; to quantify the contribution of lifestyle, environmental, genetic, and epigenetic risk factors to type 2 diabetes among South Asians in diverse regional settings; and to use the results to develop new risk tools for prediction of type 2 diabetes among South Asians.

The project will be carried out in five workpackages:
WP 1 Project coordination and management
WP 2 Epigenome-wide scans
WP 3 Replication testing of 384 epigenetic markers
WP 4 Data analysis
WP 5 Risk factors for type 2 diabetes in South Asians

**Expected value of results**
- Improve understanding of epigenetic mechanisms underlying type 2 diabetes.
- Describe the contribution of lifestyle, environmental, genetic and epigenetic risk factors to type 2 diabetes among South Asians in diverse settings.
- Enable development of new tools for prediction of type 2 diabetes in South Asians.
- Highlight therapeutic strategies to reduce the global burden of type 2 diabetes.

**Discussion**
It was asked under what conditions metabolomics would be carried out. Dr Chambers said it would be peripheral blood in the fasting state. It was then asked if there was existing literature or would there be a pilot study on what is found at the transcription level in peripheral blood and correlate this to what happens in liver, beta cells or fat cells for example. In reply, Dr Chambers said that so far there was no published study of transcriptomics in South Asians and so this was at early stages of reporting, such questions would be pursued during the study.

A comment was made about risk allele frequency correlates between South Asians and Europeans, although valuable at the population genetic level is this what happens at the disease level? It is assumed that there may be different gene-environment interactions in South Asians and so it would be interested to see a similar graph of odds ratios. Dr Chambers said these have been published but omitted for simplicity, and if anything were rather weaker than in Europeans. (Cross-tissue epigenetics is the focus of the EU project BLUEPRINT.)

There was a question about the age cut-off for the control group. Dr Chambers noted that the age range in the study was between 30-70 years (wide distribution); however, if there is genetic susceptibility it should be evident at all ages. He accepted that the project does not have early life exposure, but the fact that there is a 10 percent rate of diabetes at age 40 is dramatic, which must indicate genetic susceptibility or early life exposure.
A question was asked about how the study samples were obtained. Dr Chambers said the biosamples already exist in the freezer and came from prospective cohort studies, which means there would be incident cases of diabetes and will reduce confounding effects by DNA methylation resulting from diabetes treatment.

Several questions were asked about measures of central obesity, adiposity and BMI in the study cohort of South Asians. Dr Chambers said that South Asians are more adipose than European counterparts; however, mean levels of central obesity among South Asians had not been shown, compared with Europeans, if anything they were about half a SD greater, which does account for some of the excess risk and reduced the odds ratio from 4 to 3.8 (only a small amount). There was a question about whether the waist/hip ratio was a proper measure of whole body adipose, Dr Chambers agreed and said that ideally what was needed was quantitative imaging data.
Diabetes and obesity among Ghanaian native and Ghanaian migrants (RODAM)

Higher rates of obesity and diabetes in ethnic minority groups in European countries are not fully explained by traditional risk factors (obesity, adiposity, diet and physical activity cannot explain this risk of diabetes). A better understanding of why this risk is increased is imperative in order to develop interventions and policies specifically in those populations.

The key questions are: why does the risk of obesity and diabetes change due to changes in environment following migration? How do environmental and genetic factors interact/interplay? One example is the increased risk of obesity and overweight after migration in people from Ghana migrating to urban areas and to high income countries, such as the UK, the Netherlands and Germany.

RODAM wants to measure the environment very precisely because in previous studies factors have been overlooked such as psychosocial stressors and possibly previous analyses have been too simple, for example related to socioeconomic status.

Aims of RODAM
To understand changes in risk of obesity and diabetes among migrants in relation to environmental changes and gene-environmental interactions, Ghanaian migrants migrating to London, Amsterdam, and Berlin will be compared with their compatriots in rural and urban Ghana. Previous work also inspired this project, when the risk of diabetes in migrants was examined it differs between countries. The prevalence of diabetes between English and Dutch ‘white’ populations was reflected in migrant populations, which are genetically or geographically related.

For the risk of diabetes, when we looked into the differences between ‘white’ people in the UK and ‘white’ people in the Netherlands the prevalence of diabetes is higher in the Netherlands and these same differences were reflected in the migrant populations both the black population and the South East Asian population. This shows that the location of migration matters. It is expected that higher rates of diabetes will be seen in the Ghanian populations in the Netherlands and in Germany compared with the UK.

Methods of RODAM
In four countries, Ghana, Netherlands, Germany and the UK and including the IDF and a small-medium enterprise (SME) (seven partners) the study will look at five random, population-based samples among two sites in Ghana, and Ghanaian migrants in London, Amsterdam and Berlin in each sample 1,250 respondents at each site (6,250 in total). Interview data: (socioeconomic) background, environmental factors, health behaviours, dietary pattern, psychosocial stressors. Physical examination: anthropometric measurements, blood pressure, fasting blood samples (HbA1c, glucose, etc.), DNA. Qualitative data: used to supplement the study (focus groups, individual interviews) to gain insight into perception and knowledge of obesity and diabetes.
Interaction between genes and environment

*Case-control design:* obese, impaired fasting glucose/diabetes, healthy respondents (1000 each).

*Identification of known SNPs:* associated with obesity and/or diabetes.

*Epigenetic printing:* changes in the expression of specific genes due to environmental changes (e.g. dietary fatty acids).

**Discussion**

It was asked whether there was an inherent bias because the migrating group may be more affluent and may be going to another country based on money? There is a socioeconomic or behavioural difference and how will this be resolved? In reply, Dr Stronks said selection mechanisms are very important and this was one justification to set up a database to measure precisely the exposures people had, and to ask questions such as where do you come from and about job status so there should be a precise measure of all the factors which might play a role, measured on each site in as standardised a way as possible.

There was a question of why the ‘white’ population was not studied as this may provide some genetic information. In reply Dr Stronks said that limited resources means making choices, but the ‘white’ population would be examined as this is part of a much larger study looking at other groups. The study would try to draw a sample in Ghana in a specific region because it is known from previous studies that most migrating people are from that region, this is also a way to get as representative a sample as possible. Dr Stronks said there was a focus on the precise standardisation of the protocol and data collection.
**PRESENTATION OF PROJECT EXAMPLES FROM INTERNATIONAL FUNDING AGENCIES**

**Moderator:**  Prof Gernot Desoye  Department of Obstetrics and Gynaecology, Medical University of Graz, Austria

**Dr Robin Olds**  CEO, Health Research Council, New Zealand

**Diabetes and obesity the New Zealand perspective**

Dr Olds spoke about the situation in New Zealand for research into diabetes and obesity. A unique opportunity exists in New Zealand, there is a slowly growing population currently 4.4 million – will be 5.55 million by 2026. 86 per cent are urban, 14 per cent are rural, and it is ethnically diverse, the largest ethnic group is European, with Maori, Asian and Pacific Islanders. These are young populations, especially Maori and Pacific, and 23 per cent were born overseas. There is a free high quality health system with national datasets and ethnicity records and good integration of clinicians working with basic scientists.

Obesity, as found on one of the national surveys, has increased at a frightening rate over the space of 10 years. Rates in the Maori and Pacific populations are much higher than in Europeans and it is already present in youth. Dr Olds then showed a slide of the relation between affluence and obesity, with the most deprived having the highest prevalence of obesity. The same kinds of figures are reflected in the high rates of diabetes and the cost of type 2 diabetes was (2007) about 3 per cent of health budget, which will rise to 15 per cent by 2021 if nothing is done.

**Collaboration opportunities**
- *Longitudinal and cross sectional research cohorts:* e.g. Dunedin multidisciplinary health and development study, Pacific Island family study
- *Primary healthcare records*
- *Application of e-health modalities*
- *Early life nutrition:* epigenetics
- *Dietary/exercise intervention:* National Centre for Diabetes and Obesity Research
- *Cultural-specific contexts and interventions*

**Discussion**

There was a question on the prevalence given for diabetes on the Pacific islands as about 10 per cent; was this information from a questionnaire, or blood testing, as most other studies show 15-20 per cent. In response, Dr Olds said it was questionnaire information and likely to be unreliable, the prevalence was likely to be at least 50 per cent higher.

It was asked if there were sub-groups within the larger ethnic groups mentioned? Dr Olds said that yes, Pacific Islanders are a very diverse group, at least in New Zealand, they are Polynesian as opposed to Melanesian, but with a great degree of diversity.

A point was raised about thinking about new strategies in looking for individuals with greater longevity and genes protective against other diseases.

In reply to a question Dr Olds said that in New Zealand a lot of thought was given to prevention. Some examples of public health campaigns were noted, and for example ENERGISE was a randomised trial in schools showing reduction of obesity.
A family based intervention to study genetic and environmental factors related to type 2 diabetes oral treatment failure

In Mexico type 2 diabetes is the first cause of mortality and prevalence is 7 per cent with 8 million Mexicans with diabetes. In Yucatan the Mayan contribution is the ancestral Amerindian component and there is a diabetes prevalence of 11.8 per cent. Sisal is a rural fishing community on the northeast coast of Yucatan with a prevalence of 28 per cent, co-morbidities of 51 per cent, with 78 per cent in poor glycaemic control.

Factors involved in oral hypoglycaemia failure

Environmental: diet, physical activity, obesity, lack of adherence to treatment, and lipotoxicity.

Genetic: a decreased beta cell activity, increased insulin resistance, ethnicity admixture population. (It had been reported that CAPN10-SNP43 variant may influence the response to treatment with sulphonylurea and metformin, being dependent on obesity in the Yucatan Mestizo population. Garcia-Escalante. Invest Clin 2009, 50;1:65).

Objectives

To evaluate the genetic and environmental contribution to oral hypoglycaemic treatment failure by a prospective design based intervention in affected type 2 diabetes families in a Yucatan, Mexico population.

Materials and methods

Genograms: family-based association

Intervention: nutrition, lifestyle and adherence treatment

Candidate genes (found in other populations), PPARG2 etc and Candidate gene analysis: ancestry estimation

Ancestry informative markers (AIM) SNP markers, short tandem repeat (STR) markers, variable number tandem repeat (VNTR) marker, mitochondrial (mt)DNA hypervariable regions.

Co-morbidities: obesity, hypertension, metabolic syndrome, dyslipidaemia

Treatment: combined, monotherapy and insulin (78% were in poor glycaemic control)

Challenges

The challenge was to obtain an epidemiological diagnosis of diabetes in the described population. The identification of environmental and genetic factors modifying type 2 diabetes treatment will provide a basis for diagnosis and improved treatment along with implementation of tailored public health intervention programmes. A future challenge was to be able to apply the findings as genetic risk markers for other populations with similar genetic stratification. It was intended to develop a comprehensive care model for families with diabetes. To develop strategies for population characterisation and to identify type 2 diabetes susceptibility genes through a GWAS approach.

Perspectives

It was aimed to have a reference population with little mixture and a high prevalence of type 2 diabetes to enable a comparison with the findings of risk factors. This is a population with low migration and extended families with type 2 diabetes, which could be monitored long-term to evaluate the treatment response.
It is hoped to undertake a genome screen to identify potential additional risk genes and epigenetic changes to diet, and environmental factors different to those to which the European population is exposed.

**Discussion**
It was noted that this was a comprehensive and interesting project from a special population. Perhaps there was a more complicated genetic background and it may be also useful to study different genetic markers and subgroups.

There was a comment that the population, being fishermen, presumably eat mostly fish, in which case why are Japanese protected from diabetes and CVD and this population is not? In response, it was noted that they did eat fish but it was fried and there was the influence of the American diet and lack of physical activity.

The level of dyslipidaemia was surprisingly low in such a population considering the level of obesity. Dra Valadez said that this was likely due to a lack of regular lipid measurement and checks. At the start of the study there was a metabolic and biochemical characterisation.

A question was asked whether the diet was evaluated with a food frequency questionnaire, as it was important to obtain information on nutrients? In response, Dra Valadez said that there will be a quantitative and qualitative dietary assessment and that in the process individual diets were being designed for individual families with evaluation after 3 months.

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**Prof Kerin O’Dea** Director, Sansom Institute of Health Research, University of South Australia in Adelaide, Australia

**Prevention of diabesity among Indigenous Australians: challenges and opportunities**

Professor O’Dea began with noting the extreme social disadvantage of Aborigines with high unemployment, welfare dependency, poor education and overcrowded living conditions. They suffer poor health with a heavy burden of infectious diseases, particularly among children, and heavy burden of lifestyle-related chronic diseases among adults. There was a poor quality diet with high cost and limited availability of fresh vegetables and fruit in rural and remote Australia, along with a high consumption of sugar and fat. For many individuals it is much cheaper to consume sugar, flour, white bread, and this is the main source of protein. Fresh fruit, vegetables and lean meats are too expensive although many would like to eat such a diet, especially the fruit and meat.

**Chronic diseases in Indigenous Australians: an escalating epidemic**

In both men and women there is obesity with centralised fat distribution and an early onset of type 2 diabetes, about 10 times higher in those aged 20-50 years. Premature CVD of approximately 10 times higher in the 25-45 year age group with dyslipidaemia (high triglycerides and low high-density lipoprotein (HDL)-cholesterol), hypertension, microalbuminuria and a heavy burden of infectious diseases, which may amplify the inflammatory and oxidative burden. Kidney failure is up to 100 times higher in the worst affected communities than in Australia generally.
The challenges
Extreme social disadvantage and associated problems start in early life: with maternal stress, smoking, substance abuse, leading to low birth weight, failure-to-thrive and infectious disease. An escalating risk of early onset obesity (especially in young women) and unknown burden of diabetes in pregnancy - which is an indicator of future risk of diabetes in both mothers and offspring. The challenge of poor nutrition is evident across the lifespan.

The opportunities: early intervention in life and in disease pathways
Opportunities were provided by the rigorous evaluations of existing interventions, which Dr O'Dea said could be better: the nurse home visiting programmes, school breakfast and lunch programmes (popular in Australia), and implementation of clinical guidelines are obvious examples that should be evaluated.

Examples of NHMRC-funded research
- Diabetes and vascular disease in Indigenous Australians: causes, interventions and system change
- Nutrition interventions: improving the quality of the food supply in remote communities
- Subsidies/taxes/culturally specific education: targeted nutrition programmes (pregnant and lactating women, young children and school gardens and healthy food preparation)
- Diabetes in Pregnancy Register (Northern Territory Health); early diagnosis and management; follow up of mothers and offspring (interventions to reduce future diabetes/obesity risk and strongly promote breast-feeding for first 6 months)
- eGFR program: early detection and treatment of kidney disease
- Improved systems of care for diabetes: early diagnosis and treatment of diabetes and related conditions in North Queensland; reduction in complications and hospitalisations; exercise and diet to reduce rapid weight gain in young women
- Depression and increased risk of CVD
- Interventions to improve pregnancy outcomes, Aboriginal Birth Cohort
- Pre-pregnancy interventions (nutrition, substance abuse, social support), smoking cessation, breast-feeding, nurse home visiting
- Long-term follow-up through data linkage.

In conclusion Dr O'Dea said she was very keen to share protocols and to develop international collaborations.

Discussion
A comment was made about the importance of pregnancy and the issues of pre-pregnancy care, pregnancy and breast-feeding. Intergenerational effects, also of pregnancy and maternal health on the mother's long-term health in e.g. later CVD such as maternal hypertension and delivery of small for gestational age babies.

The issue was raised about underlying cause of disease from socioeconomic determinants and treatment with medical interventions. Without social intervention the medical interventions would lead to failure. Dr O'Dea agreed but said that disease cannot be left unresearched. and better ways were being sought, for example breakfast and lunch programmes for children. She commented that it will be interesting to see the results of Danish tax interventions on highly processed and refined foods. System-level change is difficult, especially in relation to food supply, given the powerful vested interests.

A question was asked about collecting more physical information, for example on insulin resistance, metabolic syndrome. In all Indigenous communities for which data are available there are high levels of insulin resistance and metabolic syndrome.
In relation to the food supply Dr O’Dea noted that population-level data is collected, not individual intakes. However, this is valuable in evaluating the quality of the food supply. For example, recently it had been found in three of six remote communities that white bread was the major source of protein. Such a poor quality of protein in the diet could be a driver of over consumption of cheap calories ‘hunger foods’. Dr O’Dea referred to past work with reintroduction of traditional diet and lifestyle which demonstrated that all of the metabolic abnormalities of diabetes and risk markers for cardiovascular disease can be greatly reduced, and even reversed, in about 7 weeks.

It was asked how the influence of the pre-conception environment on future health could be investigated epidemiologically and biologically, were there suggestions as to what kind of influences would be worth looking at? In response Dr O’Dea said the focus of most work was not on the genomic influence, but rather studying areas of health promoting behaviours such as smoking cessation, social support, substance abuse. One particular peer-support programme, Strong Women, Strong Babies, Strong Culture, which was implemented in a number of regions, but had only been evaluated in the Northern Territory and in that region demonstrated a 30 percent reduction in the prevalence of low birth weight. Unfortunately this program has ceased due to lack of funding.

A comment was made that the role of inflammation had been mentioned as an indicator of metabolic stress in type 1 and 2 diabetes and should there be more effort to look at the inflammazome, which may explain the link between diabetes and obesity. In reply Dr O’Dea agreed - she saw this as an inflammatory and an oxidative environment, exacerbated by poor quality diet resulting in low protection. High levels of C-reactive protein (CRP) were associated with weight gain - particularly in women. Clearly inflammation is important and was being examined.

A question was asked on the best way to capture information on early life factors, in migrant populations. Dr O’Dea said early life is important and is the reason behind the Diabetes in Pregnancy Study and the Aboriginal Birth Cohort. A particularly important question is what is the long term health impact of low birth weight and ‘failure-to-thrive’ on those infants who survived...
This type of information is very hard to get from standard health data, and rigorous cohort studies are needed. The preservation and sharing of data is critical. There are many small studies, which it is hoped could be shared as this was a way of working together to find solutions.
Conclusions to Day 1

In conclusion Dr Desoye noted the distinct population groups that had been presented with similar problems to those in Europe, but more accentuated. There are links between social economic environment and health, this was a most important point to communicate to politicians and care providers, that resources were necessary for health care and especially for education.

There had been some really very interesting presentations from very different studies. There was a good overview of existing cohorts with distinct phenotypes and genetic backgrounds offering great research opportunities and possible collaborations.
Professor Godfrey explained that increasing evidence demonstrates that early nutrition and lifestyle have long-term effects on later health and risk of disease into old age, even across generations (metabolic programming). The most convincing evidence is for obesity and associated disorders, e.g. metabolic syndrome, hypertension, diabetes and CVD. Therefore, the focus of EARLYNUTRITION is obesity and associated disorders due to its major public health importance and transgenerational nature.

At issue is where in the lifecourse will intervention have most impact and what the intervention should be. This had been considered by the UK Foresight group when it looked at global environmental change and took into account potential governmental policies across built, health, fiscal, research, educational, regulatory, social structure and family domains. In conclusion, the only policy with significant impact on obesity was ‘to promote/implement a programme of early interventions at birth or early infancy’.

On later consideration it was found that there is a critical window during pregnancy, and probably pre-conception, but intervention in early life generated the highest impact across all scenarios and greatest success was achieved with a long-term approach. It was concluded that society should be prepared to measure success over a long timeframe.

**Figure 8.** Early intervention reduces lifecourse risk of NCDs
This policy and the systematic review led to a conceptual framework to understand how early intervention reduces lifecourse risk of NCDs. As people age the risk of developing NCDs increases, also as they get older their ‘plasticity’ decreases and they show inadequate responses to new health challenges. Therefore, late interventions can be impactful for vulnerable groups but they do not fundamentally change the risk trajectory of NCDs. Early intervention is thought to fundamentally change these trajectories and ultimately produce a greater reduced risk (Fig. 8).

Epigenetics is thought to underlie plasticity and is the mechanism behind an important set of processes. Over the past 5 years some progress has been made in the field of perinatal and epigenetic biomarkers of later NCDs, and this field is the subject of one of the EARLYNUTRITION workpackages. However, the technology is new and commercial arrays do not measure exactly what investigators would like and there are many pitfalls; increasing knowledge may increase the risk of erroneous conclusions.

Themes and hypotheses
EARLYNUTRITION would test three hypotheses leading to metabolic changes (obesity, visceral adiposity, metabolic syndrome, diabetes, hypertension, CVD). Foetal overnutrition hypothesis: transgenerational acceleration of obesity (e.g. maternal obesity, high pregnancy weight gain, diet in pregnancy, gestational diabetes), which will be examined in a combination of cohorts and intervention studies across the globe (in parallel with animal studies and sample analysis of placental, epigenetics, and metabolomics studies). Mismatch hypothesis: foetal undernutrition (e.g. maternal nutritional imbalances, placental dysfunction) and postnatal overnutrition (high nutrition/low physical activity postnatal environment, which may be particularly important in migrants and in areas of the world where there is rapid nutritional transition. The Accelerated postnatal growth hypothesis, looking at postnatal nutrition and growth (short duration breast feeding, overfeeding with excessive protein in infancy) thought to be linked with metabolic endocrine changes and increased adipogenesis altering risk, which will be studied in a combination of intervention and observational studies.

Study organisation
Human data (and data from animal and genetic studies) will come from 11 observational cohorts and 9 interventional cohorts comprising more than 470,000 individuals studied in 21 workpackages. The studies will allow examination of exposures in four groups: pre-pregnancy, during pregnancy, infants and children, with the aim of developing recommendations to improve health in these four target groups.

This 5-year project is an international collaboration of a multi-disciplinary team of scientists (36 partners in 13 European countries, USA and Australia) working across academia, industry and SMEs to develop recommendations and disseminate new evidence in the field with the aim of informing government policies and public health practices.
IDENTIFYING SCIENCE POTENTIAL FOR INTERNATIONAL COLLABORATION – WRAP-UP SESSION

CHAIRS REPORT ON THE OUTCOME OF THE WORKSHOPS

Moderators:

Prof Jean-Michel Oppert  Chairman of the European Association of the Study of Obesity (EASO)
Prof Philippe Halban  Chairman of the Alliance for European Diabetes Research (EURADIA)

Professor Halban introduced the final session saying this had been an extraordinary meeting with more than 200 delegates from more than 40 countries representing all sectors from national governments, policy makers, funding agencies, academics, health professionals, industry, and SMEs. However, despite broad participation there was still a need to reach out to other sectors beyond our immediate expertise while keeping the focus on diabetes and obesity. Following presentation of the projects on Day 1 the aims of Day 2 were to inform the European Commission and other potential partners of opportunities for collaboration towards a global initiative on gene-environment interactions in diabetes and obesity in specific populations. He invited the chairs of the working groups to highlight opportunities and identify areas ripe for cross-fertilisation.

Genetic aspects of type 1 and type 2 diabetes and obesity in specific populations

Chair: Prof Nick Wareham  Institute of Metabolic Science, University of Cambridge, UK

The workgroup had considered some initial questions to guide the discussions.

Type 1 diabetes
• How can we study gene-environment interaction on the incidence of type 1 diabetes?
• Do we have sufficient knowledge of the separate genetic and environmental aetiological factors in type 1 diabetes to make this a realistic proposition?
• Should we study the effects of this interaction on the incidence of type 1 diabetes itself or on intermediate endpoints?

Type 2 diabetes
• How can gene-lifestyle interactions be studied further in type 2 diabetes?
• Are there novel environmental aetiological hypotheses that are potentially under investigated?
• Can existing studies/capacities address these questions in type 2 diabetes, or are new initiatives required?

Obesity
• What study designs are required to study the interaction between genetic predisposition and lifestyle behavioural factors on the development of obesity?
• Do we have sufficiently precise and unbiased tools for measuring the key determinants of weight gain to make the study of gene-lifestyle interaction a realistic proposition?
• Are there novel environmental aetiological hypotheses for obesity that are potentially under-investigated?
Professor Wareham commented that progress in understanding the genetic basis of type 2 diabetes, obesity, and type 1 diabetes has been principally driven by technology and a changing culture of closer collaboration between scientists. In genetic epidemiology less work is done by individual groups and more in larger collaborations across countries where scientists accept they play a smaller part in a bigger endeavour. This has consequences for funders and how they reward such contributions. However, progress would not be made if scientists revert to a culture of working in small groups. Collaboration must go forward, working across countries, the question was how this should be done.

Progress in understanding interaction, or interplay, between genetic factors and the environment has been limited perhaps because studies that have been useful for genetics have usually been cross-sectional, and when they measure environmental exposure, those measurements have tended to be relatively imprecise. Thus a different approach must be considered.

**General obstacles/challenges**

- Missing heritability
- Imperfect nosology/classification of disease (fundamental)
- Limited progress in identifying causal variants that underlie the genetic associations
- Limited evaluation of less common variants
- Few intervention studies (to search for differential response in gene-environment interaction) and a paucity of intervention trials funded by the EU in diabetes
- No similarly sized efforts in non-European populations as most information has been found in European populations
- Imprecise measures of environmental factors (diet, activity, toxins, vitamin D and beyond). This is a problem for studies within populations, but is a major problem when comparing between different populations and socio-cultural groups
- Lack of adequate biomarkers: e.g. metabolomics
- Only basic analyses of GWAS data (additive model, main effect)

**Type 1 diabetes (specific issues)**

As the disease has a relatively low incidence, traditional cohort studies are difficult. Conversely case-control studies are not a good strategy because of recall bias of exposures assessed after disease has been diagnosed and a lack of clarity about plausible environmental factors.

- **Major problems:**
  - Low incidence/recall bias (most studies go for high-risk groups)
  - Unclear environmental trigger or determinants
- Quite heterogeneous: needs better characterisation
- Integrate with other autoimmune diseases
- Address the combination of both type 1 and type 2/obesity in individuals who later develop insulin resistance
- Address cohorts of type 2 diabetes for latent autoimmunity
- Continue to focus on populations with high incidence (e.g. Finland, Sardinia)
- Examine the differing incidence of T1D in the same group across country borders
- Develop the hygiene, vitamin D and growth hypotheses (birth cohorts)
- Key population for the study of complications
Obesity

- **Major problems:**
  - Weight, BMI, or weight gain are not sufficiently precise outcome phenotypes; need to study body composition, storage capacity, dynamic tests of fat tolerance
  - Differences across various ethnic groups
  - Phenotype affects ability of participants to engage in intervention (positive feedback loop),
- Must expand conceptual framework beyond energy balance: focus on brain/behaviour, anticipation of energy needs, socioeconomics
- Will need collaboration with other fields
- Invest in large-scale precise phenotyping
- Investigate ectopic fat, lipidomics, inflammatory markers
- Explore how obesity and diabetes interact in different ethnic groups
- Extremes of obesity, early onset of diabetes in youth across populations

Opportunities

- Smaller studies with greater detail in other populations (need 1,000’s)
- Metabolomics
- Integration of genetics to investigate causality (Mendelian randomisation)
- Genomic studies in people of African, Native American or Asian descent with appropriate cosmopolitan arrays
- Global collaboration on monogenic diabetes and extreme phenotypes
- Integrate with clinical databanks (which need to improve precision on capturing items such as diet and physical activity)
- Study of migrants
- Broader capture of environmental markers (e.g. toxins, microbiome)
- Pharmacogenetics
- Harmonisation of protocols

Recommendations for future action

**Type 1 diabetes**

- Continue approach of detailed studies in high-risk populations and individuals to identify environmental determinants and triggers prior to multi-population disease endpoint studies
- Birth cohorts to study commonality of pathways to type 1 diabetes, type 2 diabetes and other autoimmune diseases
- Consider preventive randomised controlled trials for low-risk interventions

**Obesity**

- cohorts with emphasis on precise characterisation of environmental factors and obesity phenotypes
- International collaborations for evaluation of extreme phenotypes

**Type 2 diabetes**

- International collaboration in medium-sized cohorts with precise phenotyping of both environmental exposure and disease-related outcomes
Discussion

Given the classification issues in diabetes, it was suggested that it may be preferable to study pre-diabetes as a phenotype. Prof Wareham agreed that studying the pathways leading to diabetes, i.e. insulin resistance and secretion could be a profitable approach to studying the aetiology of type 2 diabetes.

Bariatric surgery shows that weight loss is critical in treating type 2 and should there be more emphasis on obesity genetics in type 2 diabetes. Prof Wareham said the point was well made; obesity is certainly a dominant factor in the aetiology of Type 2 diabetes and Mendelian Randomisation studies of obesity variants have shown that this is a causal relationship.

It was pointed out that it takes around 3-5 years to develop new instrumentation to measure metabolomic and genomic variables; this was also an area needing support. Prof Wareham agreed that high technology instrumentation was essential and also required investment.

Lifestyle and diabetes prevention programmes for minorities

Chair: Prof Eric Ding Harvard Medical School, USA

The workgroup had considered some initial questions to guide the discussions.
• What variations in diabetes prevalence and incidence exist in different minority and immigrant communities in various countries, and between minority groups and mainstream local populations?
• How can changing lifestyle risk factors of diabetes in minority groups be better monitored?
• What is the extent and rate of acculturation to Western diet and lifestyle factors in various minority groups?
• How do racial and ethnic backgrounds affect effectiveness of conventional lifestyle intervention programmes?
• How can lifestyle intervention programmes in difficult-to-reach minority groups be better targeted and managed?
• Given social cohesiveness of minority population, how can minority social networks be leveraged for more effective diabetes prevention and control?

Prof Ding reported that this group worked less specifically on the medical model of diabetes, and rather focused on prevention approaches, with different strategies being discussed from micro-community based intervention to the macro national policy level.

Main challenges
• Minority groups are often more vulnerable to health inequalities and poor healthcare
• Reaching minority groups for lifestyle education is challenging, given barriers in language, culture, and neighbourhoods
• Effectiveness and generalisability of traditional diabetes prevention programmes is uncertain in minorities and immigrants
• Given the social cohesiveness of minority populations, need of social-network targeted interventions for obesity and diabetes prevention for leveraging social network influences
• Optimising interventions for social networks may be important to managing diabetes; hence, To identify specific risk factors; effective behavioural approaches
• Interventions are developed in populations different to the minorities in question and this limits the applicability
• Need for basic awareness of link between lifestyle and diabetes in minorities
• Need to understand diversity within broadly defined minority populations (e.g. recent migrants compared with longer integrated populations)
• Micro-community level (combine scientific and community expertise) based, tailor-made interventions to leverage culture and cohesiveness
• Finance for lifestyle primary prevention, health education council, health vascular check (UK National Health Service [NHS]), insurance companies (pay for success)
• Macro-national level policy (sugar, fat tax) dual benefit to raise finances, decrease consumption
• Impacting social networks: how to tap into the cultures of minority/vulnerable populations? Probably not scientists, but people within the community
• Need to convince policymakers of benefits of lifestyle programmes, consider safety of environment, urban planning, transport, agriculture and other non-health sectors
• Not just more research on cost of lifestyle programs, but more importantly more research on cost-effective and cost-saving lifestyle prevention programs for obesity and diabetes, and future development of economic models and financial incentive instruments for targeting lifestyle prevention programs.

Obstacles
• Not sufficient collaboration between investigators and experts in different fields
• Interplay between policymakers, scientists, community workers
• Perception of body image and other cultural barriers
• Difficulty to reach ethnic minority groups

Benefits and opportunities
• Lifestyle intervention: cost effective for health systems
• Societal costs are decreased
• Economic productivity is increased

To keep in mind
• Need to involve policy makers, community workers in the scientific process
• Need to ask policy makers what they need to make or change policy
• How to convince EU politicians (justification)? Consider health inequalities, disease prevention, cost savings

Recommendations for future action
• Develop better understanding of the policymaking dilemma
• Involve sectors outside health care: transportation; food industry; infrastructure
• Link experiences from different researchers and countries (start task force to increase cross-sectoral communication and share experience)
• Undertake more research on costs of lifestyle programmes
• Join up experiences of studies/projects in ethnic minorities to plan future research
**Discussion**

It was asked whether the populations were indigenous or migrant populations. Prof Ding responded that it was any minority and vulnerable group significantly under served (also included homeless indigenous peoples). But it would also be good to study in populations back in their home countries, who were also more susceptible to diabetes in general.

The comment was made that this may be an opportunity to mirror what was of interest in minorities with majorities. People who come to Europe from various Asian countries for example represent more than half of the world’s population. Studying the minority may be beneficial although differences may be more related to gene environment interaction.

Prof Ding said this was important and was the basis of the four cluster projects. Linking projects to learn from minorities to take to larger populations and vice versa. Prof Ding said that this would be a useful indicator of social network dynamics and interventions.

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**Diabetes diagnosis and management in primary care in specific populations**

**Chair: Prof Anoop Misra**  
*Fortis-C-DOC Centre of Excellence for Diabetes, Metabolic Diseases and Endocrinology, New Delhi, India*

The workgroup had considered some initial questions to guide the discussions:

- How can research identify appropriate low-cost and convenient strategies to detect diabetes: random blood glucose, HbA1C, clinical risk prediction, or non-invasive assessment of glucose?
- How can research establish the most cost-effective ways to increase awareness and education about diabetes and its complications in deprived populations: mobile telecommunication technology (mobile phones) or more conventional methods?
- What are the key aetiological factors of diabetes in lean and deprived populations: under nutrition, nutrition during pregnancy, micronutrient deficiencies, beta cell defect, genetics, and how to study this effectively?
- What are the key aetiological factors for development of complications (renal disease, coronary artery disease), poor management, non-compliance, unbalanced nutrition, other lifestyle factors or genetics? What is the most effective way to study this?
Main challenges
- Need for simple, cost-effective and validated tools for diagnosis, two-step process?
  Ethnic-specific clinical risk prediction. Fasting blood glucose, HbA1C?
- Cost effective ways to optimise education and awareness of patients
- Identifying barriers for effective screening for diabetes (social, economic, cultural, gender), specific groups would benefit from screening

Lower priority
- Initial management of hyperglycaemia
- Factors leading to non-adherence to treatment (e.g. culture)
- Prediction of cardiovascular and renal risk

Obstacles
- Inadequate research particularly in primary care
- Multiple diagnosis and management guidelines/diagnostic methods not validated in heterogeneous populations
- Sub-optimal education and sensitisation of patients at diagnosis

Benefits
- Increasing uptake of screening programmes
- Early detection of diabetes
- Education leading to improved risk factor control

To keep in mind
- Cost-effectiveness of strategy
- Local-regional and socio-cultural issues

- Studies should include multiple population groups with adequate representation from developing countries

Recommendations for future action
- Develop optimum tools for screening using non-invasive methods
- Develop risk prediction engines for diabetes screening
- Identify barriers to screening
- Develop population-based educational modules to raise awareness

Discussion
A technical question was asked about use of HbA1c as a measure of glycaemia in locations where thalassaemia and sickle cell anaemia were present. Prof Misra responded that this test may not be sufficiently ready for use as a diagnostic tool for diabetes, it measures differently in different populations, e.g. in children.

It was noted that more non-invasive screening tools were needed, for example microvascular screening.

Prof Misra said that there were already a number of non-invasive methods using e.g. tears, saliva, infrared, but most are physical and therefore can be affected by environment, temperature, skin thickness and others.
Challenges of diabetes/obesity in pregnant women

Chair: Prof Gernot Desoye Department of Obstetrics and Gynaecology, Medical University of Graz, Austria

The workgroup had considered some initial questions to guide the discussions.

- What is needed at the global level to address this gene-environment interaction in diabetic/obese pregnancies (networks, infrastructure, studies)?
- Can we identify specific risk factors and/or biomarkers for the transmission of obesity and type 2 diabetes in an individual?
- What do we know about the long-term consequences of moving to an affluent environment before, during or after pregnancy for mothers and children in migrant populations?

Main challenges

- Definitions of exposures prior to conception and prior to and during pregnancy (e.g. to maternal adiposity/glycaemia, nutrient quality, physical activity, environmental pollutants, maternal hormones) and outcomes (e.g. relative adiposity, metabolic status of neonate). Potential importance of foetal gender (placental tissue and differences in gene expression) and paternal contribution.
- Need to share knowledge and resources (database, biosamples from cohorts) and protocols of intervention studies across regions and countries. Awareness of existing cohorts.
- Identify biomarkers for body composition, metabolic status and epigenetic status (define methods and normal ranges in mother and offspring that allow prediction of disease risk later in life

Obstacles

- Existing scientific, medical, organisational culture
- Regulatory requirements, intellectual property, legal and ethical limitations, competing pressures for funding and publications
- Sufficient samples needed to achieve statistical power relating biomarkers to definite clinical outcomes

Benefits

- Possibility to combine study results, e.g. prospective meta-analysis; confirmation of biomarkers across ethnically and geographically diverse cohorts
- Identification and confirmation of relevance of biomarkers; facilitation of joint studies
- Link biomarkers with disease mechanisms and therapeutic options

To keep in mind

- Difficulty in achieving worldwide consensus and underlying biological differences between populations, e.g. fasting compared with postprandial glucose
- Relation to existing biobanks and infrastructure
- Specificity of signal (compared with ‘noise’) with multiple measurements, e.g. –omics

Recommendations for future action

- Set up expert reference groups with global representation (Non-Communicable Disease Alliance), for worldwide standardisation; link with other groups. Promotion importance of developmental origins
- Agreed action platform for exchange of data, samples and knowledge. Link with existing groups and platforms to create a uniform structure
- Develop and validate biomarkers; link with other studies across life course
Discussion
A comment was made on the need to collect data on pollutants from across different countries to compare between countries based on samples of urine and blood toxicology. In response, Prof Desoye said that pollutants should first be identified and linked to end results and then further study would be required within different environments and countries to be able to draw conclusions.

A question was asked about biomarkers and the need to collect information over long time periods in relation to development of chronic diseases.

Biomarkers are of no use unless they are predictive of disease and the challenge was to ascertain how this historical information could be used to prove relationships. In response, Dr Desoye said he was optimistic as there are already established relationships between interuterine events, e.g. obesity in childhood and development of type 2 diabetes around age 10 (in Pima Indians). Already biomarkers can be validated for such time spans.

General final discussion
The issue of sharing knowledge, common databases, and biobanks was raised and how this could be set up in the context of international collaboration. Suggestions were that links with influential individuals were important in national organisations in different countries, along with common goals. The comment was made that it may be better to develop commonalities of structures in the context of research questions.

Sources of funding were addressed and participants were urged to look beyond the usual sources of funding to e.g. mobility funding to exchange and share knowledge and this was extended to third countries. Also to look at funding programmes such as COST actions and Infrastructure grants. Private finance was also mentioned; the challenge was to bring together people and projects and to find potential funders. European Commission peer-reviewed funding provides clout and legitimacy and makes it easier to obtain additional funding from the private sector.

There was a need for more global studies, but the quality should be improved, in about 40 per cent of datasets data is incomplete, inconsistent or missing. This is a challenge, from the low level of data acquisition, to sampling of materials, and to data analysis. Before developing the studies or the physical support framework, however, was the need to develop ideas and hypotheses. There was a need for intellectual investment and this conference was a positive step.

The issue of bioethics and an ethical component to research (not issues of consent) was raised in the context of the magnitude of the diabesity epidemic. Re-distribution of resources was needed in the question of chronic vs acute diseases. Population health ethics covers the scientific areas identified in this meeting and a plea was made to include bioethics in ongoing discussions.

It was mentioned that an independent council of bioethics in UK had identified this issue of undertaking global studies and how to ensure population ethics is a key area in research.

Close bilateral dialogue between participating countries should be maintained.
There was the need to ensure that information obtained through scientific research is translated quickly into policy measures, even if lacking in detail. Policy measures can then be developed to reduce overweight and promote physical activity, which should help to cut the scourge of diabesity.

**Prof Jean-Michel Oppert** Chairman of the European Association of the Study of Obesity (EASO)

**Conclusions**

Professor Oppert concluded that the meeting had focused on the powerful concept of ‘diabesity’, which had brought together participants from different fields. The title referred to genes and environment; thus, genetics and genomics, and improvements in technology had been central to discussions but there was still much research to undertake into detailed phenotyping and environment and these areas needed investment.

Much had been heard about international collaborations, there were strong suggestions to increase collaboration, exchange and share biobanks, operating procedures, databases, and ideas; this means a huge challenge for research in Europe and for the other parts of world as diabesity has no frontier. Prof Oppert concluded that he hoped these suggestions would be useful in gathering support for further international collaboration in diabesity.

**Ruxandra Draghia-Akli** Director for Health, DG Research and Innovation, European Commission

**Closing comments**

What we have learned in this meeting is that diabesity is a huge scientific challenge for a global effort and that local, regional, social, cultural, issues should be taken into account in the various populations in order to understand and coordinate better. The current issues are of particular importance for a global approach. It includes urgent measures some of which have already been implemented to face the rise in number of populations affected by diabetes and obesity.

It is obvious we should aim to work better, to find modalities to get results more quickly to the policy makers and to the people with diabetes and obesity, in order to curb this epidemic. We cannot do this alone, we need international cooperation and need to be organised in simple things such as sharing data and biosamples, improving knowledge standards and implementing or adapting existing measures.

New international partnerships and synergies are the only way forward to diffuse the ticking time bomb of diabetes and obesity.
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Acknowledgments

I would like to express my sincere thanks to you, and extend them to your collaborators from DG Research, for inviting me to the *Diabesity* conference, on behalf of the European Association for the Study of Obesity (EASO). The European obesity research community, that EASO represents, cannot agree more on the importance of the development of international collaboration in this field. I would like to add that EASO will be extremely interested in the follow-up of the *Diabesity* event, whatever form it will take.

*Prof Jean-Michel Oppert*, MD, PhD, Institute of Cardiometabolism and nutrition (ICAN)
University Pierre et Marie Curie-Paris 6, Paris, France
President European Association for the Study of Obesity (EASO)

Thank you for allowing me to participate in the recent *Diabesity* meeting organised by the European Commission. This was a landmark meeting from many points of view. Diabetes and obesity have reached pandemic levels, with devastating consequences for society in both developed and less developed countries. A united research effort will be critical to prevent further increases in the number of people affected across the globe, and Europe is particularly well placed to take the lead. This meeting was a unique occasion for researchers, health professionals, politicians and administrators from all regions of the world to discuss this challenge at the highest level, with exceptional opportunity for free discussion and networking. The reports from the working groups present an exciting new platform for future international collaboration, with several areas of research identified as ripe for immediate action. Congratulations!

*Prof Philippe Halban*, Department of Genetic Medicine and Development, CMU, Geneva, Switzerland.
Chairman of the Alliance for European Diabetes research (EURADIA)

This was an excellent conference, which brought together high-level representatives of funding organisations, other stakeholders as well as scientists. The organisation went smoothly and was up to the highest standards. Thank you for all the hard work put into it and for allowing me to be part of this conference. Hope more will come in the future.

*Prof Gernot Desoye*, Department of Obstetrics and Gynaecology, Medical University of Graz, Austria

Thank you very much for the very worthwhile meeting you organised last week. I can only imagine what planning it has entailed bringing so many excellent persons together in one place and time. Going beyond EU-related projects and bringing persons and research bodies from the Americas, Australia and Africa widened the perspectives in a very stimulating way. A true scientific event with lots of new, interesting persons and interactions.

*Prof Peter Bergsten*, Department of Medical Cell Biology, Uppsala University, Sweden
Meaningful debate, great and adequate food. First diabetes and obesity conference where fruits and salads, as well as fish - and not junk food - , are served, and thoughtful arrangements for the programme with lots of time for interactions. This is the best networking conference that I attended in the last ten years!

**Prof Paul Zimmet**, Director of International Research, Baker IDI Heart and Diabetes Institute, WHO Collaborating Centre for the Epidemiology of Diabetes Mellitus, Australia

I wanted to thank you for the invitation to attend the Diabesity meeting last week. It was a very valuable experience and I believe has placed Europe in a leadership position with respect to the global prevention and treatment of diabetes. From a personal perspective it was equally rewarding, not only to play a part in advancing diabetes research but also to create further EU and inter-continental links. I am meeting the Irish Minister for Research and Innovation today to draw further attention to the importance of research in diabetes, the approach of the EC and to show him the value of European collaboration to Irish research, the economy and people with diabetes.

**Donal O’Gorman, MSc, PhD**, Dublin City University, Ireland
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Diabetes causes severe health complications and is the fifth leading cause of death world-wide. The number of people suffering from type 2 diabetes is set to rise to some 900 million globally by 2030, with devastating health and economic implications.

To counter this scenario, increasing attention is given to research into environmental and genetic risk factors for diabetes and obesity in specific populations. Under its current Research Framework Programme, the European Union supports a series of major scientific projects to better understand and combat type 2 diabetes.

The Health Directorate of the European Commission’s DG Research and Innovation organised the conference DIABESITY-A World-Wide Challenge, in Brussels on 9-10 February 2012.

This conference brought together, leading scientists in the field, national funding agencies from different parts of the world, national, European and international policy-makers, other key players in the field. The conference took this approach further by presenting the state of play and exploring opportunities for even greater international cooperation and new partnerships.

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