



## **Publishable summary: 36-month periodic report (March 2015)**

### **1. Summary description of project context and objectives:**

Diabetes and obesity are multi-factorial diseases. Despite a strong genetic component, the rapidly rising prevalence of these disorders is thought to be due to adaptation to a changing environment. The epicentre of the 'diabetes epidemic' is in South Asia and, importantly, this is reflected in migrant populations across Europe, where the prevalence of diabetes in South Asians is 3-6 fold higher than the European average. Current prevention strategies are focused towards adults and target over-nutrition in high-risk groups; however for many populations across the globe, these strategies ignore the principle causes that underlie the increasing prevalence of these diseases.

A substantial portion of South Asians living in their home countries experience nutritional deprivation, while after migration to Europe, they may encounter nutritional abundance. This results in an imbalance during their life-course and it is thought these conditions may be of particular importance during foetal and early developmental stages, where environmental insults may interact with genetic risk to induce 'foetal programming' of adult metabolic disease.

Few groups have targeted early life programming as an opportunity for the prevention of diabetes/obesity in childhood and subsequent adult life and there are limited guidelines on this topic. The GIFTS programme, which brings together investigators from South Asia and Europe with wide-ranging expertise, has been established to improve diabetes prevention through an enhanced understanding of early life programming.

Three key objectives of the program, which will enable this ambition to be achieved, are outlined here:

- Use of results generated by GIFTS to inform public health policy via future guideline development in Europe and South Asia.
- Dissemination of key outputs to stake holders in diabetes prevention, including healthcare professionals and South Asian communities.
- Use of the results and expertise gained from GIFTS to design a large-scale pragmatic intervention for diabetes prevention in people of South Asian origin.

The GIFTS programme comprises 11 work packages, which can be divided into four groups:

1. Co-ordination and management (WP 1)
2. Lifestyle and nutrition from pre-conception to early childhood (WP 2-4)
3. Characterisation of gene and environment interactions (WP 5-7)
4. Clinical translation of the findings of GIFTS programme (WP 8-11)

### **2. Description of work performed since the beginning of the project and the main results achieved so far:**

Although there have been some delays and deviations from the original plan, the GIFTS programme work has progressed well. In December 2014 the European Community has granted us a 12 month non paid extension taking the end date of the project to 31<sup>st</sup> of January 2016.

#### **WP2: Baseline studies of lifestyle and nutrition**

Novel cohorts of pregnant South Asian women have been established in Bangladesh and Pakistan and are almost completed in Norway (April 2015) and the UK (May 2015). Baseline data has been collected on women and their newborns including: anthropometry, blood tests and health, lifestyle and dietary questionnaires. Establishing these cohorts has not only resulted in a unique, comprehensive dataset, it has also provided an in-depth insight into the

practicality of conducting clinical research in these communities/environments and the challenges which may be encountered.

Data from the Bangladeshi and Pakistani cohort of pregnant mothers were already analysed in the first reporting period while only preliminary data are available from the London site as the collection is ongoing. BMI resulted higher in London (25.5) compared to Bangladesh (21.3) and Pakistan (22.5) and percentage of overweight women (BMI>23kg/m<sup>2</sup>) is much higher (75%) than in Bangladesh (22%) and Pakistan (36%). Levels of Vitamin D deficiencies are high at 36% but even higher in Bangladesh (50%) and in Pakistan (44%). Vitamin B12 deficiency at 17% is similar to Bangladesh while Pakistan reported much higher values (44%). Publications are being prepared focusing on the differences in populations.

### **WP3: Pilot Interventions**

A complex, individualised intervention trial (ISRCTN register: 83599025 <http://www.isrctn.com/ISRCTN83599025>) has started in Bangladesh in July 2014.

Pregnant women in the first trimester are randomised to intervention or usual care. In the intervention arm they are offered lifestyle advice based on their BMI and diabetes status and/or administered vitamin B12 and vitamin D supplements according to their nutritional status. The primary endpoint for this pilot intervention is a composite based on maternal micronutrients at term.

1. Increasing total vitamin D repletion (>80nmol/l) to 40% (compared to an estimated 10% repletion in the usual care)
2. Decreasing vitamin B12 deficiency (<200pg/ml) to 5% (compared to an estimated 15% in usual care).

Secondary endpoints include a range of maternal and fetal outcomes. Recruitment stopped in January 2015 with 915 mothers consented and deliveries started in January 2014 and will be completed in July 2015. In March 2015, 72 deliveries have been recorded and only 1 sample was missed. Vitamin D insufficiency (<80nmol/l) was found in 82% of the women and 15% were low in B12 (<200pg/ml). At 24-28 weeks, 16% of the women developed gestational diabetes.

GIFTS is also funding a sub-study of the Pune Intervention Study, investigating the mechanisms by which 1-C metabolism may be linked to nutritional foetal programming. Samples resulting from these studies are also being stored, forming a biobank. Following a pilot study to standardize the methodology and better understand the 1-C metabolism in young Indian women, 40 young women were selected with low B12 levels (<100 pmol/L) and randomized into two groups to receive B12 alone or B12 plus multiple micronutrients plus protein and administered a methionine challenge test before and after at least six months of supplementation. This study is now completed with 35 women who completed the second test after 6 months.

### **WP4: Childhood Outcomes**

The delays in starting the intervention study in Bangladesh (WP3) means that it will not be possible (in the timeline of the GIFTS Project) to follow up the children at 1year. Follow up of children from the mothers in WP2 has started in Pakistan with measures of anthropometry and biochemical analysis collected in 53 children. Collection might be limited due to the available funds.

The Perinatal Care Project (PCP) Survey carried out in 3 areas of rural Bangladesh is completed. The study collected data on anthropometry (n=2588) and buccal swabs (n=2566) from 24-48 months children born from mothers who participated in the Perinatal Care Project (PCP), compared with children born to women in control areas, who did not receive the intervention (participatory women's group meetings).

Preliminary statistical analyses look very promising showing interesting differences in children metabolic outcomes depending when stratified by maternal BMI. Publication is currently under preparation.

#### **WP5: Development of Nutritional and DNA Assays**

The team in India has established a highly cost-effective low-tech genetics laboratory, in which they were able to extract DNA from blood (frozen EDTA and room temp biometrika tubes), saliva (using Oragene kits) and dried blood spots (DBS) and standardized DNA isolation from these samples stored for different time durations (3 months, 6 months and 1 year). Assays for the determination of homocysteine, Vitamin D and Fatty acid have been developed and will be standardized and validated in the next few months. In addition, GIFTS is funding expansion of the Andhra Pradesh Study of Parents and Children (APCAPS) biobank, which currently holds samples on >7,000 individuals.

#### **WP6/7: Genetic and Epigenetic Studies**

Samples from the Pune Maternal Nutrition Study (n=650) have been prepared and are awaiting analysis. DNA is being extracted from the blood samples already collected as part of WP2 and WP3 and analysis will start soon after all samples are ready. Partners are planning the experiments on the Illumina Human CoreExome BeadChip and for epigenotyping the Illumina Human Methylation 450k BeadChip and staff has been trained on how to analyse the data resulting from these platforms so to limit the time following data generation.

#### **WP8: Health Economic Analysis**

Some deviations to the planned work has occurred due to the delays in providing datasets for health economic analysis and unavoidable delays in starting the intervention trial in Bangladesh (WP3) which will provide the majority of data to develop the model for economic analysis. Recent changes in the company who was contracted to carry out the work might lead to small changes in the way data are analysed but the consortium is working hard to limit the effect on the final results and to make sure work is carried out as planned in the available timeframe.

#### **WP9: Qualitative Studies and Systematic Review**

The review submitted in the first reporting period looking at pregnancy outcomes in obese pregnant women following diet and lifestyle interventions has contributed to 2 publications:

1. Nutritional Manipulation for the Primary Prevention of Gestational Diabetes Mellitus: A Meta-Analysis of Randomised Studies. Ewelina Rogozińska, Monica Chamillard, Graham A. Hitman, Khalid S. Khan, Shakila Thangaratinam  
Published: February 26, 2015, DOI: 10.1371/journal.pone.0115526
2. Predictors of progression to type 2 diabetes in women with gestational diabetes: A systematic review of 93,461 women. Girish Rayanagoudar Research Fellow, Amal Abdirahim Hashi, Javier Zamora, Graham A Hitman, Shakila Thangaratinam, *In submission*

The qualitative studies carried out in east London exploring the illness experience and cultural perspectives in Asian women with current or past diabetes in pregnancy are completed and provided the researchers with interesting insights in this population. The studies included a first pilot group discussion with 17 women taking part in two Bengali, one Urdu and one Tamil story sharing groups, followed by a validation stage to make the model more patient centered, with a set of one on one narrative interviews conducted on 27 south Asian women. The experience of diabetic pregnancy was depicted as stressful, difficult to control and associated

with negative physical symptoms, especially tiredness. Taking exercise and restricting diet often though not always worsened these symptoms and conflicted with advice from relatives and peers. The results of the study will be disseminated through publication. A paper has been sent to BMC Medicine and we have been invited to make further modifications prior to a final decision.

#### **WP10: Equity and Access to Antenatal Care**

In-depth interviews and focus groups with pregnant or recently pregnant women of South Asian origin were conducted.

Key barriers and facilitators to emerge from the interviews and focus groups, which examined factors influencing women's uptake of services included: language and communication; acceptance of pregnancy/time to think; antenatal care not always a priority; lack of perceived urgency; beliefs around pregnancy as a natural process vs medical condition; service organisation and referral system; transience; sickness affecting ability to engage; seen as patient not person; and staff shortages and attitudes. The smaller pilot study carried out in Oslo reported some delays due to a difficult ethical approval and should be completed in the next few months. Publications are being prepared and findings will be included in the dissemination WP 11 by contributing to the e-learning portal being developed.

#### **WP11: Dissemination of Information**

A newsletter has been prepared and sent in November 2014 with most up to date progress. The project website [www.gifts-project.eu](http://www.gifts-project.eu) is up to date and reports pictures of recent meetings held in Bangladesh and a list of relevant events on diabetes prevention and fetal programming. To date the website has received 16500 hits.

An e-learning portal aimed at individuals with an interest in diabetes prevention is currently being developed, with the first few modules being prepared and tested by partners.

### **3. Description of the expected final results and their potential impact and use**

A comprehensive dataset describing the nutritional status of pregnant South Asian women from Asia and Europe and the effect this has on their offspring will be realised. This knowledge, when combined with that from the trial interventions, which are designed to assess whether it is possible to correct nutritional deficiencies during pregnancy and whether this has any effect on the offspring, will inform the design of a robust, pragmatic intervention aimed at diabetes prevention in pregnancy. The quantitative result of WP2 and WP3 will be used in the context of qualitative results from WP9 and WP10. These work packages will provide an insight into the views of South Asian women in relation to accessing antenatal care in Europe and diabetes in pregnancy. Incorporating what is learnt from this qualitative research will give the intervention the maximum possibility of being not only effective, but also meeting the needs of the target population, and being successful in a real-world environment. The planned health economic analysis will assess the affordability of this intervention, in both Europe and South Asia. This will facilitate influencing public health policy to introduce recommendations arising from this research. The genetic and epigenetic information gained will improve understanding in the field of gene-environment interaction and may give rise to the possibility of this being used in a clinical setting. Stakeholders in diabetes prevention will be able to learn about results of the GIFTS programme through dissemination of information. This will take the form of the website, peer-reviewed publications and the development of an e-learning portal. In addition, existing diabetes prevention curriculums will be revised.