

Publishable summary: 18-month periodic report (September 2013)

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 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, during the first 18 months of the GIFTS programme work has progressed well and significant progress has been made.

WP2: Baseline studies of lifestyle and nutrition

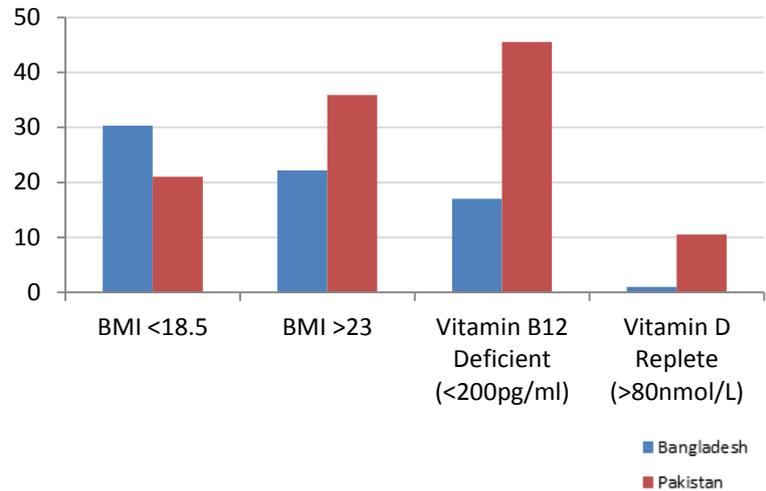
Novel cohorts of pregnant South Asian women have been established in Bangladesh and Pakistan and are in progress in Norway and the UK. Baseline data has been collected on women and their newborns including: anthropometry, blood tests and health, lifestyle and dietary questionnaires. Establishing these 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.

Preliminary data analysis from the Bangladeshi and Pakistani cohort of pregnant mothers shows that nutritional deficiency is high with 30% and 21% respectively of the population having a BMI <math><18.5\text{kg/m}^2</math>. Nonetheless, overweight pregnant mothers in Bangladesh (22%) or Pakistan (36%) are still common. Vitamin D insufficiency (<math><80\text{nmol/L}</math>) is almost universal, including in the UK, while low levels of Vitamin B12 are found in 17% of the Bangladeshi and 44.5% of the Pakistani pregnant mothers at booking.



The data collection environment and study team in Bangladesh (top row) and Pakistan (bottom row).

Nutritional Deficiencies in Pregnant Women



A literature review has been prepared, bringing together current knowledge on lifestyle and genetic factors which have been investigated during pregnancy and early childhood in South Asians living in Europe. South Asians were found to have a higher risk of developing gestational diabetes than their European counterparts and, additionally, intrauterine growth retardation was found to be more common. There was also found to be a higher incidence of vitamin D deficiency, hypocalcaemia, hyperinsulinaemia and dyslipidaemia in the newborns of South Asian women. Together, these factors contributed to poorer birth outcomes for these newborns.

The design of a preliminary economic model has been delayed; it is expected this work will be completed in the next year and will have no impact on downstream tasks.

WP3: Pilot Interventions

A complex, individualised intervention has been designed and is due to start recruitment in Bangladesh in late 2013 once ethical approval has been obtained; this is imminent. Study participants in the intervention arm will be offered lifestyle advice 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 (>math>>80\text{nmol/l}</math>) to 40% (compared to an estimated 10% repletion in the usual care)
2. Decreasing vitamin B12 deficiency (<math><200\text{pg/ml}</math>) to 5% (compared to an estimated 15% in usual care).

Secondary endpoints include a range of maternal and fetal outcomes.

In addition to the intervention planned for Bangladesh, GIFTS is funding a sub-study of the Pune Intervention Study. This study is 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.

To date, 39 women have completed baseline methionine challenge tests. All were found to be hyperhomocysteinaemic (>15 µM/L). Homocysteine was inversely related to B12, while cysteine was directly related to B12. Folate deficiency was rare and folate was unrelated to homocysteine, as were B2 and B6.

WP4: Childhood Outcomes

Participants in the Perinatal Care Project (PCP) are being followed up in relation to metabolic outcomes aged 3yr. The sample size has been increased from 100 in each of the control and intervention arms to 1,487 and 1,347 respectively to enable this to be an adequately powered study rather than a study of feasibility of measurements. Buccal smear samples are being taken on all children as well as anthropometric measurements.

Following the introduction of measures to make the data collection environment more child-friendly, recruitment has been progressing well. 40% of samples have been collected thus far and we anticipate recruitment will conclude in September 2013.



Data collection environment PCP follow-up study.

W5: Development of Nutritional and DNA Assays

A protocol for the determination of homocysteine levels from dried blood spots has been developed and the team are moving on to method development for folic acid and vitamins A and D. The development of high throughput, affordable DNA extraction assays is currently underway and different sample types are being explored.

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. All other experiments are dependent on samples generated from the pilot intervention and will be analysed in the last year of the study. The genotyping platform to be used is the Illumina Human CoreExome BeadChip and for epigenotyping the Illumina Human Methylation 450k BeadChip.

WP8: Health Economic Analysis

Health economic analysis, modelling the cost/benefit of the introduction of diabetes prevention strategies is planned. This cannot be completed until further data is generated by upstream work packages and is planned for the latter part of the grant.

WP9: Qualitative Studies and Systematic Review

A systematic review of diet and lifestyle interventions in obese pregnant women on pregnancy outcomes has been prepared. This review concluded that weight management interventions in obese pregnant women are effective in reducing gestational weight gain. Those interventions based on diet are successful in reducing adverse outcome in mothers but no effect is observed on foetal outcomes.

Qualitative research, in the form of story sharing groups, exploring the illness experience and cultural perspectives in Asian women with current or past diabetes in pregnancy is progressing well and feedback from participants has been positive. Data analysis is due to start shortly.

WP10: Equity and Access to Antenatal Care

This qualitative research, taking the form of in-depth interviews and focus groups started in July 2013. A systematic review, collating evidence from existing research on factors influencing access to pregnancy related services in urban areas of South Asia is being prepared.

WP11: Dissemination of Information

The project website was developed and launched within six months of the project start date. The website provides information regarding the overall GIFTS programme, as well as more in-depth information at a work package level. The website is available at: www.gifts-project.eu. To date the website has received 6,000 hits.

A project information sheet has been prepared and is available on the GIFTS website.

An e-learning portal aimed at individuals with an interest in diabetes prevention is currently being developed.

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 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, 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.