Proposal full title: **Vitamin D And Lifestyle Intervention for Gestational Diabetes Mellitus (GDM) Prevention**

Proposal acronym: **DALI**

Type of funding scheme: Small or medium-scale focused research project

Work programme topics addressed:
HEALTH-2009-2.4.3-1: Novel therapeutical approach to pregnancy-induced diabetes

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Abbreviations:

3BHB	3 Beta Hydroxy Butyrate
AC	Abdominal Circumference
ACHOIS	Australian Carbohydrate Intolerance in Pregnancy Study
ACOG	American College of Obstetricians and Gynaecologists
ALSPAC	Avon Study of Parents and Children
BBMRI	Pan-European Biobanking and Biological Resources Research Infrastructure
BMI	Body Mass Index
BPD	Biparietal Diameter
CA	Consortium Agreement
CGMS	Continuous Glucose Monitoring System
CSII	Continuous Subcontinuous Insulin Infusion
DAFNE	Does Adjustment for Normal Eating
DIAMAP	Road Map for Diabetes Research in Europe
DMEC	Data Monitoring and Ethics Committee
DMZ	Demilitarised Zone
DPP	Diabetes Prevention Project
DPSG	Diabetic Pregnancy Study Group Europe
DQM	Data Quality Management
EPO	Erythropoietin
EQ-5-D	A standardised instrument for use as a measure for health outcome
FDPS	Finish Diabetes Prevention Study
FEND	Federation of European Nurses in Diabetes
FL	Femur Length
GDM	Gestational diabetes mellitus
HAPA	Health Action Process Approach
HAPO	Hyperglycemia and Adverse Pregnanycy Outcome (Study)
HbA1c	Glycosylated haemoglobin A1
HC	Head Circumference
HDL-C	High Density Lipoprotein Cholesterol
HOMA	Homeostasis Model Assessment
HOR	Health Outcomes Research
HRQoL	Health Related Quality of Life
IDPP	Indian Diabetes Prevention Project
IFG	Impaired Fasting Glucose
IGT	Impaired Glucose Tolerance
IPR	Intellectual Property Right
IR	Insulin Resistance
IS	Insulin Sensitivity
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
LDL-C	Low Density Lipoprotein Cholesterol
MoBa	Norwegian Mother and Child Cohort
MRC	Medical Research Council UK
MRI	Magnetic Resonance Imaging
NICU	Neonatal Intensive Care Unit
OGIS	Oral Glucose Insulin Sensitivity
oGTT	Oral Glucose Tolerance test
OLAP	Online Analytical Processing
P3G	Public Population Project in Genomics
PA	Physical activity
PCOS	Polycystic Ovarian Syndrome
PDA	Personal Digital Assistant
PI	Principal Investigator
PI	Pulsatility Index
PM	Project Manager
QCS	Arterial stiffnes
QIMT	Blood vessel wall thickness
QUICKIE	Quantitative Insulin Sensitivity Check Index
RCT	Randomised Controlled Trial
RI	Resistance Index
ROC	Receiver Operator Curve
SD	Standard Deviation
SE	Socio-economic
SF12	A standardised instrument for use as a measure for health outcome
SOP	Standard Operating Procedure
SQL	Structured Query Language
T2D	Type 2 diabetes mellitus
US	Ultrasound

B1. Scientific and/or technical quality, relevant to the topics addressed by the call

B1.1 - Concept and objectives

B1.1.1 Aim

We will use an exploratory trial approach to develop the best intervention for preventing gestational diabetes mellitus (GDM). We will concurrently use the trial data, samples and cohorts to increase our understanding of the pathophysiological mechanisms leading to enhanced diabetes and obesity risk to mother and baby. Building upon the expertise of members of the Diabetes in Pregnancy Study Group Europe (DPSG) and joined by behavioural researchers and health economists, our study is designed to collate the evidence around the epidemiology of GDM in Europe, to promote pan-European standards and measures for GDM and identify suitable preventive measures against GDM.

B1.1.2 Background

Europe is facing an unprecedented threat from Type 2 diabetes (T2D) with associated human suffering and economic burden of enormous and rapidly growing proportions. While T2D is traditionally associated with sedentary lifestyle and unhealthy diet, the currently observed growth in developed countries is greater than expected from lifestyle changes alone. Evidence is accumulating that GDM is a more important contributor to these epidemics than previously recognised. Firstly, women with past GDM comprise up to 31% of parous women with T2D (1); secondly, intrauterine exposure to hyperglycaemia through GDM, predisposes for diabetes and obesity: so called "fuel mediated teratogenesis" (2). If GDM is acting as the "accumulator" behind the T2D epidemic, strategies to arrest this inter-generational transmission are urgently needed. However, there is a shortage of evidence about how to proceed, which the "Vitamin D and Lifestyle Intervention for GDM Prevention" (DALI) intends to address with the goal to pave the way for a pan-European strategy to prevent GDM.

Why is GDM a European problem?

Diabetes is a major and increasing health threat in Europe and throughout the world. More than 25 million people are estimated to be living with diabetes within the EU-25. The reported EU average prevalence rate is 7.5% among adults aged 20 or over. Moreover, there is an alarming rise in the number of children diagnosed with T2D. Evidence of the dramatic costs of treating diabetes and its complications were found in the CODE-2 study (3), which reported the total direct costs of T2D to be 29 billion Euros in 1998 for 10 million people with T2D in only eight EU countries: up to 15 % of national health care spending. Nevertheless an EC audit conducted in 2006 revealed the incompleteness of existing data regarding this problem, and moreover, the lack of specific programmes to address it. The rise in diabetes is generally attributed to obesity, sedentary life style and unhealthy diets. In several countries of the European Union more than half of the adult population is overweight, and 20-30 percent is obese (4). However, the epidemic rise in obesity can not be attributed to unhealthy life styles alone. An accumulator effect appears to be taking place, exacerbating the problem to dramatic proportions. In the next 20 years cases of diabetes are expected to increase by 21% in the European Region according to the World Health Organisation (WHO), largely driven by the growing prevalence of T2D. The personal, societal and economic burden of this epidemic will be dramatic in Europe, but affects developing nations even more with rates of T2D increasing by up to 80%. T2D is therefore a European and worldwide problem which needs our society’s immediate attention.

What is GDM?

Gestational Diabetes (GDM) is defined as 'carbohydrate intolerance resulting in hyperglycaemia of variable severity with onset or first recognition during pregnancy' (5). GDM is characterised by pancreatic beta cell function that is insufficient to meet the body's insulin needs, usually as a result of insulin resistance. There is no common unique pathogenomic complication of diabetic pregnancy and a continuous relationship exists between maternal glycaemia and perinatal outcomes (6). Like T2D in general, the prevalence of GDM in Europe is reported to vary considerably, in some populations GDM occurs already in up to 20 % of all pregnancies. However, there are no generally accepted diagnostic measures, making pan-European surveys of GDM currently very difficult. Policies which could address this, could fuel larger epidemiological and intervention programmes comparable to the global advances after the agreement on criteria for T2D. As members of the DPSG in Europe, we see our programme instrumental to promote such a shift.

The perinatal risks of GDM include intra-uterine death, macrosomia, shoulder dystocia, birth trauma and several neonatal metabolic abnormalities. The maternal risks include an increased risk of caesarian delivery, pregnancy induced hypertension and pre-eclampsia. In addition GDM has been linked to an increased prevalence of metabolic syndrome (7). GDM is therefore a significant public health concern of women and their babies across Europe in its own right.
However, GDM probably has a larger public health impact through its role in future diabetes in the mother and diabetes and obesity in the offspring. Several indicators point towards GDM promoting a vicious cycle of increasing obesity and diabetes in the offspring (8), leading to yet higher rates of GDM, T2D and obesity in subsequent generations, which is proven for rats (9). The increased risk is not confined to those infants who were overweight at birth and may even occur when GDM is treated adequately, indicating the strong need for prevention. Another concern is the observation of impaired intellectual achievement in offspring of women with GDM (10).

What is the prevalence of GDM in Europe?
In preparation for this application, the DPSG has performed a survey which indicated that the prevalence ranges from 0.9 to 21%. This wide range confirmed that differences in diagnosis make a European wide comparison of GDM prevalence impossible. Very different approaches for diagnosing GDM are being used throughout Europe: criteria, sensitivity of tests, and referral rates vary widely and in some countries all women are tested, while others used risk factor screening first, an approach associated with approximately 50% detection rates. As a result of these and other complexities, there are no comprehensive data relating to the prevalence of GDM across Europe, which lies at the root of one of the major public health threats for Europe.
DALI will address this major obstacle to GDM research, epidemiology and improved clinical practice, by initiating a European survey with unified measurements, definitions and thresholds on the basis of WHO or HAPO (Hyperglycaemia and Pregnancy Outcomes study) recommendations. This groundbreaking effort will result in the first meaningful pan-European epidemiological study of GDM and is expected to serve as a land mark to help induce other centres throughout Europe to adopt these standards. Due to the considerable variation in prevalence of diabetes this effort is expected to yield sofar unidentified risk factors for GDM, as currently 35 % of GDM are not associated with known risk factors and a proportion may therefore remain undetected and untreated.

Preventing Gestational diabetes mellitus - What solutions to the problem are available?
There are few published studies about preventing GDM (11). While GDM has its own additional pathophysiological processes, most of these, particularly relating to insulin secretory capacity and underlying insulin resistance are also contributors to the development of T2D. Strategies for preventing T2D could therefore also be useful for GDM prevention. There are obviously two approaches for preventing GDM: Prior to pregnancy and after pregnancy has occurred. Lifestyle change including the prevention of obesity in the general population is the focus of much research currently, which we do not wish to replicate. In our study, we will focus on prevention of GDM in the antenatal period. Pregnancy poses a specific problem, as any treatment might have an adverse effect on the foetus, therefore pharmacological or surgical intervention at a stage before GDM has developed is ethically and medically not feasible.

B1.1.3 Project objectives
DALI will mount a research programme to identify preventive measures and new risk factors for GDM through addressing the following objectives:

- To obtain information on GDM prevalence in Europe for the first pan-European epidemiological study (**Epidemiology**)
    - Description of national approaches to screening and diagnosing GDM across Europe
    - Assessment of the prevalence of GDM locally and in obese women
- To identify the best available measures to prevent GDM in an ongoing pregnancy (**Prevention**)
    - Evaluation of GDM diagnostic maternal measures and foetal measures
    - Comparison of the impact of increased physical activity, enhanced nutrition and Vitamin D supplementation either alone or in combination on maternal glucose tolerance, maternal weight gain and insulin sensitivity
    - Evaluation of barriers and promoters of uptake in life style changes
- To provide a cost-benefit calculation of GDM prevention for health care systems (**Societal impact**)

  - Completion of a cost and quality of life calculation for GDM
  - Completion of an economic evaluation of DALI preventive strategies
  - Development of a decision tree to estimate cost-effectiveness of prevention strategies
- To establish a pan-European cohort of mother-offspring pairs for future analyses with a central biobank and data base (**Sustainability**)
  - Creation of a comprehensive internet-based data base
  - Creation of a physical store of placental tissue, maternal and cord blood (serum, DNA)

These objectives will be realised by a consortium combining the necessary expertise and providing sufficient complementarity to achieve critical mass, which is a prerequisite for implementing an ambitious research plan to evaluate prevention measures of GDM comprehensively.

B1.1.4 Overall concept of this project

Adherence to both lifestyle change and medications are notoriously difficult. However, pregnant women at risk of GDM have the health of their babies as a major motive to make and maintain such changes. Furthermore, they do not have to maintain a healthy lifestyle for the prevention of a disease 20 years in the future, but pregnancy gives them a specific and limited time for a potentially immediate effect. Nevertheless, other behavioural and psycho-social factors may outweigh this "driver" of behavioural change and mitigate against adoption of interventions. Clearly, attempting to address prevention through a biomedical approach will not address these behavioural determinants. In view of this, when considering our approach to preventing GDM and reducing the impact on the foetus, based on the options for preventing GDM of lifestyle change and/or Vitamin D supplementation, we have defined the following causal model:

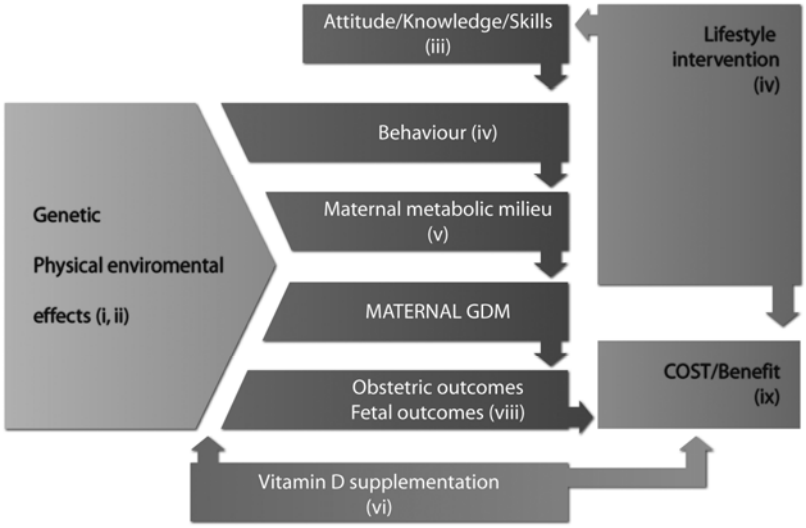

Figure 1: Schematic representation of the project concept.

This model allows the identification of important measures of the milieu in which the intervention operates (i), the maternal context in which the intervention is being delivered (ii-v), the nature and fidelity of the interventions (vi-vii), the impact of the intervention on obstetric and foetal outcomes and the balance between costs, risks and benefits (viii-ix).

This model proposes that adherence to either lifestyle intervention and/or vitamin D supplementation will be increased by modifying behaviour through enhancements to relevant attitudes, knowledge and skills. This change in behaviour would then allow the intervention to be implemented more completely, thereby altering the maternal metabolic milieu and progression to GDM. Several questions also remain to be answered around the safety of these interventions (include diet and exercise) during pregnancy. DALI will therefore include measurements of the cost, risks and benefits of the intervention to the foetus to identify the "best" approach to prevent GDM.

Is Lifestyle change in pregnancy really an option for preventing GDM?

Maternal obesity and the decrease in physical activity (12, 13) of the pregnant women are accepted as the by far most critical risk factors for GDM (14). However, implementing lifestyle programmes is fraught and requires

relatively intensive intervention and quality control. Any lifestyle messages themselves need to be delivered in a manner which is well grounded in behavioural theory. The transtheoretical (15) and Social Cognitive (16) theories underpin such delivery and have now been joined in the Health Action Process Approach (HAPA, 17), and the Self-Regulation Theory also known as Common sense Theory (18):We have previously used this approach in a pilot diabetes prevention programme among Maori in New Zealand, to good effect (19). The approach established in that study included the identification of a range of lifestyle changes from which participants began by choosing one or two which they felt they were ready and able to begin moving towards success with these activities, promoted uptake of other messages.

The use of "high level" interventions (ie simple messages such as "reduce sugar intake") and an intervention framework based upon cross cultural behavioural theory should allow the intervention to be tailored for use in each country while maintaining the integrity of the study itself.

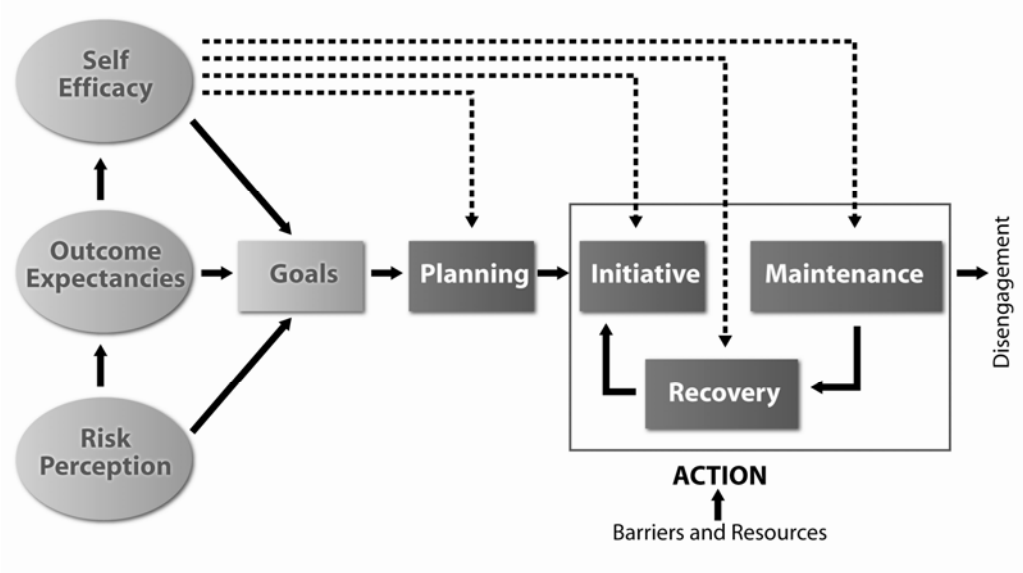

Figure 2: HAPA model.

Lifestyle interventions have successfully been used to prevent T2DM. They are thought generally safe and have collateral benefits on blood pressure, lipids and general well being. Studies of intensive lifestyle intervention such as the Diabetes Prevention Project (DPP) and Finnish Diabetes Prevention Study (FDPS) (20, 21) have been able to achieve a 58% reduction in incidence of Type 2 diabetes among non-pregnant adults. Less intensive interventions such as the Indian Diabetes Prevention Project (IDPP) have been associated with a <30% reduction in incidence. These studies have all promoted negative energy balance by increased physical activity and changes to diet. In the DPP and FDPS, the intervention included a large number of classes and very regular contact.

The importance of regular physical activity for glycaemic control in women with GDM has also been shown repeatedly. The increased insulin resistance normally occurring during pregnancy can be reduced by increased levels of moderate intensity daily physical activity (22,23). In a clinical trial back in 1989 glycaemic control in women with GDM was improved after treatment with an exercise program, similar to improvements obtained with pharmacological therapies (24). These results were confirmed later by others (25-27). However, no trials have yet been conducted studying the effect of physical activity in the prevention of GDM. In the absence of either medical or obstetric complications, the American College of Obstetricians and Gynaecologists (ACOG) recommended 30 minutes or more of moderate physical activity on most, if not all, days of the week for pregnant women. In a Finnish trial (28), a counselling intervention was successful in increasing the amount of leisure time physical activity during pregnancy among primiparas recruited from maternity clinics.

The evidence base of any nutritional intervention having a beneficial effect on the prevention of GDM is minimal (11). However, a number of nutritional lifestyle messages have been used that could be considered. Gestational weight gain is a risk factor for GDM and limiting energy intake should result in limited gestational weight gain, which is a cornerstone of management of GDM in the USA (29). Weight loss should not be aimed for, since there are concerns about weight loss in pregnancy and the potential for the associated ketonaemia to be

associated with reduced intellectual function in the offspring (30). Other options include lowering dietary fat intake (eg to 30% of total energy intake; 20,21); using a low glycaemic diet (shown to be associated with a reduction in the development of type 2 diabetes (31), a 0.43% reduction in HbA1c (32, 33) and greater glycaemic control (34) and increasing consumption of both dietary fibre and 3 portions of wholegrain cereal (11, 35). An intake of 15g/1000kcal dietary fibre was used in the Finnish diabetes prevention trial (20).

Is Vitamin D supplementation in pregnancy really an option for preventing GDM?

Vitamin D deficiency is associated with obesity (36) and reductions in insulin sensitivity (37) and insulin secretion (38). Cross-sectional and prospective studies from the MRC Epidemiology Unit (39) have shown an inverse association between vitamin D status and glucose tolerance. The prevalence of vitamin D deficiency is also increasing (40) in parallel with the growth in obesity and GDM. Vitamin D concentration and pre-pregnancy body mass index display the expected inverse association (41). There are few clinical studies involving vitamin D and glucose tolerance in pregnancy. In three of four studies, vitamin D levels were lowest in women with GDM (42-45). Furthermore, women with vitamin D deficiency in early pregnancy have a 2.66 risk of developing later GDM (45).

Studies of Vitamin D supplementation on glucose tolerance among Vitamin D-deficient subjects have been either too short, involved too small doses of vitamin D, were under powered (46, 47), or not designed to adequately test the benefits on glucose tolerance (48). There has been one two-week study of 1,25-dihydroxyvitamin D supplementation in 12 women with GDM which showed an improvement in glucose tolerance attributed to increased insulin sensitivity (49).

To date there have been no other intervention studies looking at vitamin D supplementation in women with GDM or in obese pregnant women with vitamin D deficiency who are at risk of developing GDM.

There is no unanimity on the definition of vitamin D sufficiency outside pregnancy, and various cut-off levels have been proposed (50,51); there is no indication that definition should be different in pregnancy. Current recommendation for the dietary allowances for vitamin D for pregnant women varies (200-2000 IU/day) and do not have a solid scientific basis. In pregnant women, several trials have used 1000 IU (25 µg) /day without untoward effects (NICE, 52) and a trial currently underway (not studying glucose tolerance) uses 2000 and 4000 IU per day (53).

Clearly, there are sufficient data to warrant a trial of vitamin D supplementation and this is one limb of our proposal. Our hypothesis is that vitamin D supplementation to obese pregnant women in early pregnancy can reduce the risk of developing GDM in later pregnancy.

Identifying the best intervention to enter a full trial for the prevention of GDM

Although a trial for the prevention of GDM is urgently required, we still do not have enough evidence as to how to undertake such a trial. Furthermore, we still do not have a pan-European agreement on the criteria for GDM, although the HAPO group is working with the DPSG and the other diabetes in pregnancy study groups to gain agreement on global criteria. Even after such an agreement, translation of such criteria into day to day practice is required. Overall DALI is designed as a 4 year study which will enable the progression of common criteria for GDM (across the participating centres at the very least), the development of different interventions for the prevention of GDM and the identification of the "best" intervention to enter into a full randomised controlled trial. Such a trial would be large (we estimate approximately 4,000 subjects for a comparison between intervention and control), and require greater resources than available under this FP7 programme. However, it could be initiated and completed quite quickly after DALI, in much shorter time than the T2D prevention trials which have been generally taken 3-4 years.Instead of GDM, we therefore propose to use three key surrogates of GDM and show that these can be improved before delivery through our interventions. The fasting blood glucose is a major risk factor for subsequent GDM, is part of the criteria for GDM and women with higher fasting blood glucose early in pregnancy are more likely to develop GDM. In HAPO (6) it was the major determinant of foetal hyperinsulinism and macrosomia, the key outcomes used for defining GDM. Reducing the mean fasting glucose is likely to translate into significant reductions in GDM development. A main predictor of developing diabetes in the FDPS and DPP was weight loss. In pregnancy, we can not strive for weight loss in view of the putative risks from maternal ketogenesis, but we can attempt to limit weight gain in our lifestyle intervention groups. This would serve as a measure of effectiveness of our lifestyle interventions and also as a surrogate for reduced GDM risk. The third surrogate, insulin sensitivity, is a key factor in the pathogenesis of GDM and should be modifiable through some but not all our interventions.

Understanding the effect of the intervention on the foetus

1. On foetal hypoxia
It has been clearly established that maternal hyperglycemia increases the delivery of glucose to the foetus, resulting in foetal hyperinsulinemia. Both foetal hyperglycemia and hyperinsulinemia lead to foetal hypoxemia (54-56). Thus, in diabetic pregnancies and as a consequence of chronic foetal hypoxia, foetal plasma and amniotic fluid erythropoietin (EPO) levels can be elevated (56, 57) and polycythemia and increased nucleated red blood cells are often observed. Foetal EPO levels correlate directly with maternal HbA1c and relative birth weight (macrosomia) (56, 58). In addition, EPO levels in cord blood display an inverse correlation with umbilical artery pH, base excess and pO2 and a direct one with pCO2 and lactate. In fact, intrauterine hypoxia may underlie some "unexplained" foetal deaths during the last weeks of diabetic pregnancies (59, 60). Our hypothesis is that those interventions effective in improving surrogate parameters of GDM will be associated with less foetal hypoxia and lower EPO levels in cord blood. To test this, we plan to measure EPO (as a measure of foetal hypoxia), C-peptide (as a measure of insulin, robust to hemolysis) and leptin (reflecting intrauterine growth patterns especially of adipose tissue (61, 62)) in the cord blood of newborns to obese pregnant women participating in the trial.

2. On foetal blood vessel characteristics
With the exception of ultrasound assessment of foetal growth, the impact of maternal hyperglycemia on the foetus is usually performed after delivery (measurement of anthropometrics, umbilical cord and clinical outcome parameters). Currently, early non-invasive markers during pregnancy for predicting adverse short and long-term outcomes in these pregnancies are lacking. Recently, non invasive means to assess blood vessel wall properties have been developed in a real time, and automated way (63). Arterial stiffness (QCS) and blood vessel wall thickness (QIMT) are the best validated parameters studied so far. The interest of these vessel wall properties originates from the fact that they affect the flow rate through the vessel and therefore the Doppler wave signal. And it is well established that uterine artery Doppler flow abnormalities are strong predictors of adverse outcome in pathologic pregnancies including foetal growth restriction, pregestational diabetes and GDM (64). Uterine and umbilical artery vascular impedance in pregnancies complicated by GDM is related to birthweight and placental weight, but not to maternal HbA1c levels (65). The influence of maternal obesity per se remains to be established. The ESAOTE arterial analyser (ART-LAB®) offers a technology for more refined assessment of the uterine artery properties in a real time, standardised, automated and easy way and could potentially be an early marker of adverse outcome in pregnancies of women with GDM and/or obesity. So far, however, the ART-LAB® application has not been studied in pregnancy and we aim at undertaking it.

3. On foetal growth, measured in utero
Foetal hyperinsulinemia mediates anabolic metabolism with increase of placenta, fat tissue and viscera such as liver, heart and adrenal glands. Under standard care, estimation of foetal weight and anthropometry is usually performed by ultrasound measurements. However, the accuracy of such measurements in predicting macrosomia is rather low with a false positive ratio of about 15% (66, 67). Ultrasound measurement of subcutaneous foetal fat, correlates with the postpartum measurements of neonatal fat mass but the results are scattered and thus the 95% confidence interval is rather wide (68,69). In foetal medicine, magnetic resonance imaging of the foetus is regarded as a safe and accurate imaging method when used after the first trimester (70, 71). It allows a better estimation of foetal weight than ultrasound measurements (72) and normal values for foetal subcutaneous fat have already been established (73). We plan to compare the performance of MRI and ultrasound in the assessment of foetal growth.

Understanding whether the trial worked
Undertaking these complex lifestyle trials and ensuring safety in pregnancy are essential components of a GDM prevention programme. We need to ensure that the trial is delivered as planned and to understand the wider impacts of the intervention on maternal physiology/pathophysiology and the foetus. Measuring any variance, rapidly addressing any deviation from the protocols and assessing the impact of such variance is essential. Pregnancy is associated with a range of psychological changes. For example the ACHOIS (Australian Carbohydrate Intolerance in Pregnancy Study) intervention was associated with a reduction in postnatal depression. These changes also need to be considered in terms of causality, intervention uptake and impact on outcomes. The proposed trial qualifies as a Phase II study: defining trial and intervention design using the MRC framework for the evaluation of 'complex

interventions' (74). This involves testing different versions of an intervention in an exploratory trial, and testing feasibility and acceptability of the intervention. Such an exploratory trial also offers the opportunity to test the consistency with which an intervention is delivered, which is very important since the intervention will be provided across different countries. Using intermediate outcomes (ie our primary outcomes) instead of the ultimate health outcome is acceptable and indeed recommended in this Phase. Based on the results, along with a range of secondary outcomes, including process measures and patient-reported outcomes, a Phase III definitive RCT should be designed, in which the effects of a fully defined intervention on the actual incidence of GDM are evaluated.
The extent to which an intervention is implemented as intended by the program developers is known as fidelity (75). Fidelity is an important methodological concept, central in process-evaluations, and indispensable in the comparison between and dissemination of effective interventions (76-78). A high fidelity can be seen as an assurance that the intervention implemented during the study will be the same as implemented in practice (79). In this trial, fidelity of the intervention will be assessed extensively. An intervention meets fidelity requirements if each of its components is delivered in a similar way to all participants, and if it is true to the theory and objectives underlying the program (80).

Health economics of the interventions
From the above it has become obvious that GDM is a major pregnancy pathology, which may cause medium- and long-term problems in mother and child. Given the increasing prevalence of GDM in the Western world, which is in part driven by the sendentary lifestyle and obesity, an economic analysis of GDM for health care systems is of paramount importance. In addition it is also known that T2D, one of the potential consequences of GDM, has an effect on the labor market (81).
Little is known regarding prevention strategies for minimizing GDM impact and no studies have compared the efficiency of the available prevention strategies. Thus, taking into account that decision-makers must choose between various types of interventions for preventing GDM, economic evaluation of these different prevention strategies serves as a capital tool for helping them to set priorities and allocate resources efficiently. In consequence it is important to evaluate the strategies most likely to be used for preventing GDM. Recommended best practice is for economic evaluation to be integral with randomized clinical trials (82). This has the advantage of generating patient-level data for relatively modest research protocol added costs. The present study aims to assess the cost and the effectiveness of different approaches for preventing GDM.
The health economic analyses applied in this study will be based on the general principles of economic evaluation (82, 83) and this will allow investigators recommending one strategy among the others in terms of cost-effectiveness.

The impact of foetal sex
It is well-recognized that newborn sex influences prevalence, severity, evolution and mortality of many neonatal conditions, with male foetuses generally having a worse prognosis. This is also true for the growth response to the diabetic intrauterine milieu (84). Thus, DALI also aims at analyzing all outcome parameters of the foetus und neonate according to sex, which may further contribute to a better understanding of the interplay between sex of the offspring, maternal intrauterine environment and foetal programming.

Generation of a biobank linked with a comprehensive database
DALI will generate study cohorts of pregnant women with and without GDM and of their offspring. One objective is to establish a DALI biobank as repository of biological material from subjects which are clinically well-characterised in a standardised, high quality process will be closely linked to a state-of-the art database. All demographic, clinical, biochemical, genomic and diagnostic imaging data, the latter comprising images from ultrasound and MRI, will be stored in a secure manner within a remote accessible electronic database. The core design of the research informatics storage infrastructure already exists within the consortium and will be adapted to the architectural needs of the project. Data systems have been built to the same security and confidentiality standards as those of hospital electronic patient records. Innovative features of the informatics platform are that demographic, clinical, biochemical, genomic and diagnostic imaging data, the latter comprising images from ultrasound and MRI, can all be stored within the same architecture, and can be co-visualized for comparisons. Data will be entered at each participating centre onto a common web based interface with drop-down menus to ensure high quality of data capture. The unique subject identifier will also be linked within the database to sample identifiers within the Biobank to allow rapid selection of proteomic or genomic analyses that will be required to

support secondary studies and phenotypically dissect the study population. The database is readily expandable such that the framework established for this project could form the basis of wider, pan-European studies or follow-up cohorts of both mother and child from the present studies.

B1.1.5 Addressing EC objectives

Relevance to the Call Topic

DALI will focus on assessing suitable prevention measures for GDM in preparation for a pan-European trial, but also support research into novel treatments by initiating general measures for GDM, new diagnostic methods and a large data and bio-bank of mother-foetus couples. Considering the heavy toll taken on life expectancy by diabetes, particular attention will be given to paediatric aspects, by assessing foetal measures and preventing GDM, which is the only way to protect our next generation from the deleterious effects of GDM.

The most effective and cost efficient measures to prevent GDM appear to be implementing healthy life styles, which is a pre-requisite to any stabilisation of escalating costs of diabetes. As life style changes are notoriously difficult to initiate, we will asses innovative approaches to reach pregnant women at risk with the goal to achieve healthier diets and increased physical exercises. As the mounting costs of diabetes threaten the European health systems we will carefully assess the cost effectiveness of all measures in order to provide policy makers and our society at large with a clear view of the societal implications we are facing with regard to the mounting threat of T2D.

Policy objectives of the 7th Framework Programme

As detailed below, we fully address all the objectives of the call topic "Novel therapeutical approach to pregnancy-induced diabetes" (HEALTH-2009-2.4.3-1) and respond to the 2009 Work Programme strategy, funding translational research on diabetes (HEALTH-2009-2.4.3) as a major disease:

DALI will collect and analyse **epidemiologic data** on GDM prevalence across 10 European sites. It will then be centered on the prevention of GDM by **lifestyle-interventions and by using a novel form of prevention** (vitamin D) in a pan-European setting. The project will compare by testing the currently **best available prevention measures** and calculate the cost-benefit of the intervention thus examining how DALI's results will contribute to the **societal issues** linked to GDM. Several substudies will carry out research contributing to a better understanding of GDM **aetiology**, its effect on the mother and offspring **(paediatric aspects**). DALI will facilitate further studies about aetiology and in particular on **genetic** aspects by establishing and maintaining a biobank of the well-characterised mother-offspring pairs.

DALI addresses:

- **the aetiology** of GDM with the first pan-European epidemiological study of T2D. A pre-requisite for this landmark achievement will be unified measurements and definitions on the basis of recommendations of the WHO, which DALI will evaluate. In addition DALI will provide defined cohorts, a comprehensive database and biobank of mother-foetus couples, which will promote further studies in the aetiology of T2D and GDM in Europe.
- **preventing GDM**, as relevant studies are currently missing, it is reasonable to assume that similar prevention measures are effective as for T2D, namely diet and physical exercise. We will therefore focus on innovative activities to reach women at risk of developing GDM to promote the uptake of relevant life style changes. Treatment of principally healthy pregnant women is ethically not acceptable due to the potential risk to the foetus. The only preventive treatment we will therefore evaluate for GDM is thus Vitamin D treatment.
- **research** into GDM, as there is little research conducted in this area, despite the fact that GDM might underlie the deleterious amplification of T2D prevalence. It is particularly complicated through the fragmentation of the European Research area, which results in a variety of measurements and guidelines, which inhibit comparison and cooperative evaluation of national data. DALI will therefore initiate the adoption of pan-European measurements and definitions in order to promote European research into GDM. It is expected that several participants will use the integration of resources to initiate their individual research programmes on the basis of national funding to study GDM.
- **global health issues,** as increasing prevalence of diabetes constitutes a global problem of immense proportions. While sedentary life style and diet are at the heart of the problem, the steep increase can only be explained with additional factors acting across generations. GDM might therefore be a lynchpin of the T2D epidemic. DALI will attempt to find the best ways of convincing pregnant women at risk to initiate life style changes, which holds the potential to break the current positive feed-back loop.

- **child health**, as GDM poses a major health threat, ranging from serious acute effects including perinatal death to long term effects like juvenile T2D. DALI addresses the link between GDM and T2D in juveniles, considering life style, GDM induced effects on the foetus and genetic factors. Treating GDM is considered insufficient to reduce these threats, therefore DALI will focus its efforts on bringing effective preventive measures to the clinic. This concept holds the potential to reduce the burden of juvenile T2D not only on many individuals.
- **translating research into GDM for human health**. The focus on translational research is very strong across all activities of the work programme. DALI therefore combines the expertise of some of the best treatment centres of GDM and T2D in Europe to create a critical mass necessary to promote GDM research in Europe. While GDM appears central to the T2D epidemic, which medical tools and technologies are suitable to prevent GDM remains to be established. Therefore DALI will initiate a comprehensive pan-European research programme with the goal to create a sustainable platform for GDM research in Europe which can promote the clinical application of research results in the wider area of T2D.

B1.1.6 SME participation

T2D is one of the major markets for the pharmaceutical industry, which focuses on treatments once the disease has developed. The preventive measures DALI will focus on are intrinsically not the focus of these companies However, DALI will partner with the SMEs BAP and Lawson, which have expansive expertise in their respective fields. Both SMEs will provide relevant expertise to promote the implementation of any measures DALI will establish as a useful way forward to prevent GDM. The participation of the two SMEs in this FP7 project is evidence that we are committed to fulfil the aims of this framework programme with regards to SME participation and stimulating the European economy.

B1.1.7 Gender objectives

Gender objectives are relevant for DALI at the level of participant ratios and for gender considerations of its research. Positive action towards redressing the balance of equal gender participation is being promoted by having five female principal imvestigators in the consortium. The current ratio of female participation in responsible positions currently stands at about 65%, this exceeds the proportion of women in leading positions in science. This can serve as role models for other women in this project. It is well known that role models are one of the most effective ways to support female participation in science and technology. Their participation will ensure an atmosphere within the project, which ensures that participating junior scientists independent of their sex will gain confidence and independence in taking credit for their achievements.
Moreover, the full number of participating women will not be determined until the start of the project, but the involvement of higher numbers of women will be taken into consideration.
Gender aspects in research:
DALI uses an European exploratory trial approach to develop the best intervention for preventing GDM. This type of diabetes can develop during pregnancy in a woman who hasn't previously had the condition. It affects a significant proportion of pregnant women. It can lead to problems for the mother and the baby if it is not properly managed. Therefore women are bound to benefit from this research. Associated training and education of health practitioners will include this issue.

B1.1.8 Societal implications

The impact diabetes has on European society is significant and manifold. DALI sees itself as an essential part in a necessary bundle of activities to meet the threat T2D poses to Europe and the world at large, which include loss of productivity, loss of quality of life and premature death as well as costs to the society including health care systems.
The T2D epidemic incurs costs up to 15 % of the total expenditure of national health care systems in Europe. While prevalence of T2D is mounting, the causes of T2D have been known for 2600 years, but preventive measures are still not established to tackle sedentary life style and unhealthy diets. DALI holds the potential to contribute to sustainable and efficient health care systems by evaluating best practice models suitable to reduce T2D prevalence and thus the mounting costs of this disease to our economies.

B1.2 Progress beyond the state-of-the-art

Research into GDM is currently hampered by European fragmentation, resulting in variable measures, definitions and assays, which complicates not only the unequivocal assessment of prevalence throughout Europe, but also

studies into the causes and effects of GDM. Therefore to date there is little known about effective strategies to specifically prevent GDM. DALI will tackle this fragmentation and provide a unique opportunity for a European group of investigators to move ahead in designing a cross cultural approach to preventing GDM, while advancing our understanding of its epidemiology, pathogenesis and impact in Europe. It will create data and cohorts available for future studies, and in particular will provide an assessment of state-of-the-art interventions in preparation for a full trial to demonstrate effective measures for prevention of GDM. It will also provide an insight into the effectiveness of the intervention within genetically and demographically different groups and potentially allow the identification of phenotypes which are more or less susceptible to different interventions.

Each component of DALI has been designed to make best use of available knowledge and technology to allow progress beyond the current state of the art in GDM research and provide a maximum of novel insights:

Epidemiology of GDM in Europe
The DPSG knows of a plethora of different approaches to screening for and diagnosing of GDM across Europe. Due to the use of different standards and criteria these data provide little information about the prevalence of GDM in Europe. Moreover the transfer of successful approaches is inhibited by the existing fragmentation. The impact of moving to a single set of global criteria as proposed following the HAPO study might be considerable as it will free substantial resources for international research. There is currently a global group (under the auspices of the International Association of DPSG) using the HAPO data to define a set of glycaemic criteria balancing the obstetric and future needs of the offspring with minimising the proportion of normal pregnancies which would receive unnecessary but costly intervention. However, if such a set of criteria were agreed upon and the current fragmentation overcome, the translation of scientific criteria into uniform guidelines and standard operating procedures (SOPs) for use in public health and clinical systems requires a considerable investment of resources. DALI with its 10 international centers could provide an important platform to aid the international implementation of new criteria for GDM diagnosis and monitoring and thus overcome many obstacles of such an implementation process. This will provide the basis for the first and future epidemiological studies of GDM in Europe which will provide an assessment of the impact of obesity on the prevalence of GDM across Europe.

HAPO did not consider whether those women who would progress to GDM by 24-28 weeks are identifiable earlier in pregnancy. DALI will provide an estimate of this among obese women across 10 European centres at 12-14 weeks - this data itself may change the current approach to screening, especially with the current concern over pre-existing undiagnosed Type 2 diabetes in pregnancy and the increasing prevalence of impaired glucose tolerance (IGT) in women of childbearing age.

B1.2.1 Maternal obesity: Effect on the growing foetus
Until relatively recently, the effect of maternal obesity on the foetus was both under-studied and little understood. There is growing evidence that GDM and obesity have additive impacts on the baby in terms of both the antenatal milieu (eg vis a vis fuel mediated teratogenesis), but also potentially other mal-adaptations relating to altered cell signalling by adipokines and other secreted factors. DALI provides a unique cohort of mother-baby pairs, including serum, DNA and placenta with extensive relevant documentation, including gain of weight, blood sugar levels and medical complications. Combined with comprehensive epidemiology, the ability to relate differences in relevant parameters as a result of the intervention to differences in the development of foetal adiposity, placental inflammation and foetal metabolism will provide a powerful resource. This will be a major advance beyond the current situation and allow far–reaching analyses revealing the interplay between several parameters. Of additional benefit is the ability to differentiate between interventions relating to physical activity (ergo insulin sensitivity and fitness with some fat loss) and/or eating habits-something not tried previously.

B1.2.2 How to prevent GDM
DALI will not have adequate resources to assess interventions for their potential to prevent GDM, which would require a multicentric trial of enormous proportions, including at least 4000 patients. Instead we have chosen to advance the current state of knowledge to identify interventions with the potential to prevent GDM and thus should enter such a full trial. To achieve this, we have identified 3 potential population surrogates for GDM, amenable to change: fasting glucose, weight gain and insulin sensitivity. DALI is expected to yield better surrogates across the

trial cohort and therefore advance trial design as well as diagnosis and research. This is expected to provide for a significant boost of GDM research and promote discovery in this area.

We have structured an innovative trial with a minimal number of subjects to test the impact of life style and Vitamin D in the prevention of GDM. The systematic assessment of Vitamin D is overdue, as there exists genuine uncertainty as to whether Vitamin D deficiency is important in the pathogenesis of GDM in some individuals or simply a confounding bystander. DALI will determine the optimal dose of Vitamin D for supplementation to achieve an adequate increase in Vitamin D serum concentrations.

The innovative design of the DALI study will test whether physical activity and changes in diet individually or in combination have the greater impact. Such a comparison has not been undertaken for preventing GDM and indeed not even T2D since the Da Qing study (85).

DALI will also be the first study to assess whether Vitamin D supplementation will provide additional benefits on the capability to reduce the risk of GDM beyond lifestyle alone. If Vitamin D does have an effect, lifestyle interventions could be a prerequisite, an alternative or an amplifier of effect. The factorial design of the DALI trial is powered to allow this to be investigated.

We believe that our lifestyle trial is cutting edge combining the latest in behavioural theories (themselves combining individual theories such as the transtheoretical and social cognitive theories), with the latest in lifestyle trial activities. The offering of a smorgasborg of interventions emphasises choice and self efficacy and the creation of a toolbox with items to support goal setting and knowledge acquisition maximises the chance of success with achievement of small steps through the pregnancy. We have placed substantial emphasis on maintaining fidelity of the trial, something of particular importance when intervening across 10 countries with their own languages, cultures and health systems. This includes objective measures of both physical activity (accelerometer) and nutrition (blood vitamin concentrations). The issues that arise with this and the ability to monitor the intervention real time will allow new knowledge to be gained not only on how to undertake the final definitive trial, but how to translate findings into every day practice across Europe.

B1.2.3 Mechanisms behind the intervention

Just as we are able to investigate the relationship between maternal obesity, fat loss and foetal development, DALI provides a unique opportunity to assess the physiological impact of slow fat loss on insulin sensitivity and insulin secretion through pregnancy. It is for this reason that we not only include measures of adiposity through the use of callipers, but include consecutive leptin measurements as a measure of fat mass (albeit mitigated by pregnancy and leptin resistance). The ability to model these relationships using measures combining maternal insulin and glucose concentrations during pregnancy is itself novel with few past studies able to assure themselves of steady lifestyle change that can occur with the type of intervention we have chosen here. We expect to use serum samples for measurement of eg adiponectin as a measure correlated with insulin resistance.

DALI will provide opportunities to investigate other putative risk factors for developing GDM including new biochemical markers, but goes beyond this in the areas available for testing ie lifestyle and Vitamin D supplementation.

B1.2.4 Pediatric aspects: Innovation in measuring impact on foetus

To date, studies on the impact of maternal glycaemia and obesity on the foetus have been cross sectional or following the natural history of the development of foetus (including metabolic development and growth) after exposure (sometimes for many years). DALI will allow the impact of maternal dynamic metabolic changes on the foetus in a randomised controlled format. Our trial has been designed to allow both cross sectional and prospective obsveration of the offspring.

As the maternal milieu and foetal anthropometry and metabolic state will be carefully assessed during DALI, the trial also creates an opportunity to compare these traditional methods with new foetal measures. Thus, the current standard approach to assess the impact of maternal glycaemia on the foetus is to include anthropometric, umbilical cord and clinical outcome measures. With the exception of ultrasound assessment of foetal growth, these can only

be done after delivery. Additionally, standard sonographic assessement of foetal growth is disappointing, especially in the overgrown foetus. Currently, early non-invasive markers during pregnancy to predict adverse short and long-term outcome in these pregnancies are lacking. In the DALI project, we have included substudies on three new measures of foetal growth and wellbeing: (i) a comparison of the use of MRI and ultrasound for monitoring foetal growth, organomegaly and bodymass composition, (ii) the use of the ESAOTE arterial analyser (ART-LAB®) for the assessment of uterine and foetal vessel-wall properties, (iii) the use of umbilical cord EPO for assessing exposure to past intrauterine hypoxia. These techniques are already cutting edge and the information gained from these studies will provide major new information on their application in the foetal situation. Additionally, we hypothesise that these non-invasive measures will add significantly to identifying the impact of GDM on the foetus in utero, to determine potential changes as the result of the intervention and to managing women at risk of GDM. Although not part of DALI, the greatest potential benefit would be the future early identification of foetuses at risk for developing childhood obesity and related morbidities they could benefit from early and monitorable intervention.

B1.2.5 Safety of the intervention

Pregnancy poses a specific problem, as any treatment might have an adverse effect on the foetus. Therefore pharmacological or surgical intervention at a stage before GDM has developed is ethically and medically not feasible. Furthermore, we have to make sure the interventions studied in DALI are safe and do not jeopardise the health of mother or child. Pharmaceutical agents, such as incretins, acarbose, thiazolidinediones, and orlistat are contra-indicated in pregnancy. Bariatric surgery, while effective when used before pregnancy, will not lightly be performed during pregnancy and the related intraluminal devices are not yet ready for such trials. Metformin is a drug which is considered safe for treating GDM once developed (86) and for treating women with diabetes or polycystic ovarian syndrome (PCOS) prior to and during pregnancy (87). Metformin may even prevent progression to GDM in some women with PCOS (88). However, metformin does cross the placenta and there remains concern about its use by many clinicians. As a result, metformin is also not widely considered appropriate for an antenatal study for the prevention of GDM.

Safety of the mother

The monitoring of the interventions will allow the quantification of any adverse events as with any trial. This would include pre-eclampsia and intra-uterine growth retardation, two adverse events in other trials. A key advance in DALI will be the measurement of ketones (3 beta hydroxy butyrate; 3BHB) at different points in pregnancy to compare the extent of ketogenesis during weight loss and lifestyle change. This has been considered a concern in the past, but we expect our weight loss to be slow, to allow enhancement of insulin sensitivity through minimisation of visceral fat overflow, and maximal likelihood of maintenance of behavioural change (at least through the remaining 6-7 months of pregnancy). We will compare the differences between groups of the fasting 3BHB at our 3 time points and assess if any real difference in 3BHB has occurred. Follow up of the cohort will be crucial to be able to measure cognitive function prospectivelyI n the offspring to see whether there has been any negative impact (or indeed positive impact with the improved maternal nutrition, potentially reduced placental inflammation and fuel supply) of the different interventions. This, however, is outside the scope of DALI.

B1.2.6 Societal aspect of GDM: Health economics of the intervention

The current health systems and services provided throughout Europe are in many ways more concerned with cure rather than prevention. While in many cases this is not cost effective, introduction of prevention measures may not be funded, even where major financial burdens are imminent. This might be due to several factors including the complexity of health systems and the influence of strong lobby groups. While these will not change in the near future, there is clearly a requirement to provide policy makers, patient organisations and other stakeholders with a comprehensive assessment of the cost effectiveness of prevention, in this instance, interventions to prevent GDM. Although methodologically not an innovation per se, the details of health economics applied to a continuously changing system will be a major step forward. These costs for GDM prevention will be compared with the costs of GDM treatment at each site. DALI will provide the latest in costs of the intervention, benefits and adverse outcomes across the trial centres beyond costs for GDM. This will allow greater ability to assist with the translation of the intervention research into services following completion of this exploratory trial and as we move to the definitive trial.

B1.2.7 Sustainability of the project

The required sample size of cohorts designed to address key questions on individual's susceptibility to GDM and on its response to prevention measures cannot be achieved by single institutions. Furthermore, the detailed disease phenotype characterization and highly specified sample collection procedures are very expensive and can only be afforded in a collaborative multinational effort. Several children biobanks have been set up world wide such as the Norwegian Mother and Child Cohort (MoBa), the Danish National Birth Cohort, the Avon Study of Parents and Children (ALSPAC) etc. These have all been designed as population-based biobanks. So far no collection disease-based biobank with biological material from pregnancies complicated by GDM is registered in pan-European Biobanking and Biological Resources Research Infrastructure (BBMRI). One key element for a multinational, multisite disease-based databank for GDM is that GDM detection criteria and clinical measurements are harmonised across participating centers.

DALI will fill this gap by generating a pan-European cohort of mothers and offspring in pregnancies with and without GDM, using the same set of criteria and clinical characterisation parameters. The cohort will comprise a full data set of each individual mother-offspring pair as well as a collection of biological material from mother and offspring (Biobank). The Biobank will be set up, maintained and administrated according to the accepted standards for BBMRI. This collection of data and biological material represents a unique tool and opportunity for addressing questions such as about unknown risk factors for GDM, its underlying pathophysiology, predicting the response to intervention and will allow follow-up studies. Thus the cohort and biobank may also contribute to future research on intrauterine programming of adult disease.

B1.2.7.1 Biobank

Biobanking on a European level has been recognised as one of the major resources promoting biomedical research. Provided data are curated effectively, tissue is collected reproducibly and samples are made available to the research community biobanks are deemed crucial to open a medical indication to molecular scrutiny and allow the translation of research results into therapeutic intervention. However currently such a resource for GDM is lacking in Europe. The epidemiology of T2D suggests however that the variability of life style and diets throughout Europe could provide rich data for epidemiological analysis. Therefore DALI will invest substantially into the central storage of DNA, tissue and serum, which will allow future comparison of the metabolic phenotype and genotype of responders and non responders after consideration of the psychological and situational characteristics of participating women. The robust trial monitoring and methods to maintain fidelity of the trial will maximise the confidence that any differences in response are due to differences between participants rather than differences in the way the trial was delivered. The collection of detailed maternal and foetal data will allow an understanding of the impact of the interventions on the offspring, including their safety, of the maternal metabolic determinants taking into account the other identifiable factors measured in the study. This study has the potential to become a worldwide milestone in GDM research and set new standards in Europe.

B1.2.7.2 Database and Health Informatics

Our vision for health Informatics is to extend data storage and integration to innovative data mining and predictive modeling within the expanded cohorts. Current tools employed include data visualization graphics, genetic algorithms, neural networks and decision trees. Innovative data mining techniques will be increasingly important in the analysis of relatively uncontrolled data sets collected at the point of care as opposed to the controlled environment of the academic hospital. These analysis tools applied in DALI will be valuable in identifying which combinations of variables, such as socio-economic, behavioral, genomic or ethnic are indicative of the probability of either a successful or unsuccessful intervention to prevent diabetes in pregnancy. It is anticipated that new mathematical algorithms and intellectual property will result from these multi-disciplinary studies that will include computer scientists, biostatisticians, clinicians and basic scientists.

B1.3 Scientific and/or technological methodology and associated work plan

B1.3.1 Overall strategy of the work plan

The overall objective of DALI is the identification of the best available prevention measure for GDM in a cohort representative for the European population.

The DALI objectives are perfectly mirrored in the DALI work packages (WPs). Work packages will be grouped according to 2 types of activity:

A) General provisions (WP8-WP9)

WP8 Management

WP9 Dissemination

The Medical University of Graz (MUG, P1) which covers a broad spectrum of pre-clinical and clinical fields will coordinate and manage the project. Her staff has considerable experience in project management, in particular of FP6- and FP7-funded EU projects. The coordinator and his team will ensure the effective implementation of the ambitious work plan to ensure coordinated progress towards the projects aims and the optimal dissemination of its expected results to obtain optimal visibility. Moreover, the IPR produced by will be efficiently managed by their combined expertise. In addition, dissemination will include a workshop with external experts and lead users in which DALI's results will be translated into recommendations for care givers, pregnant women and policy makers.

B) Translational and clinical research (WP1-WP7)

The core of DALI includes a trial overseen by a trial manager (MRC, P3). It adopts a range of innovations to identify the "best" approach to prevent GDM as a pilot for a larger, definitive trial. Its implementation comprises three phases:

Preparatory phase: WP1 provides information on the final criteria for entry into the exploratory trial (the feasibility of selecting a BMI of 30kg/m2 to enter the trial) from a comprehensive collection of epidemiological data from countries involved in the study and nations linked with the research team across Europe through the Diabetes in Pregnancy Study Group. Further epidemiological insights will come from the data collected during the initial screening period for entry into the trial and through the pregnancy. WP2 provides intervention protocols developed for testing before the exploratory trial is undertaken. WP's 3 and 4 will provide measures and collection methodology for the exploratory trial.

Execution phase: WP5 is for the exploratory trial itself, to select the intervention that is best for entering into a full GDM prevention trial. It includes:

- The use of 3 surrogates for GDM (fasting glucose, weight gain, insulin sensitivity)
- A randomized study design that allows comparison of the impact of Vitamin D alone and with dietary/physical activity changes and comparison of physical activity and dietary changes alone and in combination
- A focus on obese women with stratification of randomization by past GDM to avoid unbalanced randomisation
- A lifestyle intervention, grounded in the trans-theoretical, social cognitive and Health Action Process Theories, able to be used across 10 European countries, through the use of high level messages, a structured personal goal orientated programme maximizing participant choice/ prioritization and culturally tailored toolkits
- A real time intervention monitoring programme to address trial fidelity
- Innovative assessment of impact on foetal patho-physiology and overall safety.

After an initial preparatory/development phase with GDM screening at 12-14 weeks, the trial involves delivery of the lifestyle intervention by trained coaches and/or Vitamin D supplementation. Surrogate markers for GDM development will also be assessed at 26-28 and 36 weeks among 880 women.

Analysis phase: WP6 comprises laboratory analyses of all samples collected, analysis of trail results and a health economic assessment of the intervention to highlight the most efficient strategy in terms of cost-effectiveness analysis for the prevention of GDM.

In order to make the project sustainable and to facilitate further and future European research into GDM, we will establish an internet-based database and repository of biological material from the study subjects and their offspring (mother-offspring paired Biobank; WP7). This material will comprise maternal serum from the 3 time periods in gestation, DNA, as well as foetal i.e. cord blood, DNA and placental tissue.

B1.3.2 Risks and Contingency plans

Technical contingency plans for each work package are given in the work package forms (Tables B1.3c).

Management contingencies

In general, in Group A work packages WP8 and WP9, the coordinator and project manager will initiate a continuous reporting system to monitor project progress, which will allow early detection of deviation from the overall work plan.

WP8 and WP 9 cover project management and dissemination, respectively; they will be lead by MUG (P1). If project management should fail however for any reason, the CA will stipulate clear guidelines how failures of individual partners have to be remedied or even compensated by the consortium, if partners need to be excluded from the consortium. Close monitoring of deliverables and financial allocation to partners will allow the coordinator to minimize potential risks and initiate appropriate measures at earliest possible time.

In Group B WP1-7 are led by different work package leaders. They represent a second layer of trouble shooters beyond responsible PIs at each site. Major contingencies that may jeopardize one partner or even the whole project are difficult to foresee. Three possibilities can be envisaged and mechanisms will be described in the CA how each of these will be dealt with:

1) The PI at one site is not capable of fulfilling her/his function; a deputy PI will have to be nominated in the CA

2) A contract partner is not able to continue contributing to the project. Depending on the project stage at which this happens the data collected until that stage will be used. The unfulfilled tasks will be taken over from other sites and the remaining resources will be reallocated accordingly.

3) The EC discontinues the project. Then EC regulations will come into effect.

B1.3.3 Collaborative actions within DALI

Collaborative actions are a particular strength of the DALI consortium. Numerous individual collaborations will take place between partners on WP-specific issues as illustrated in the Interaction chart (Fig.3).

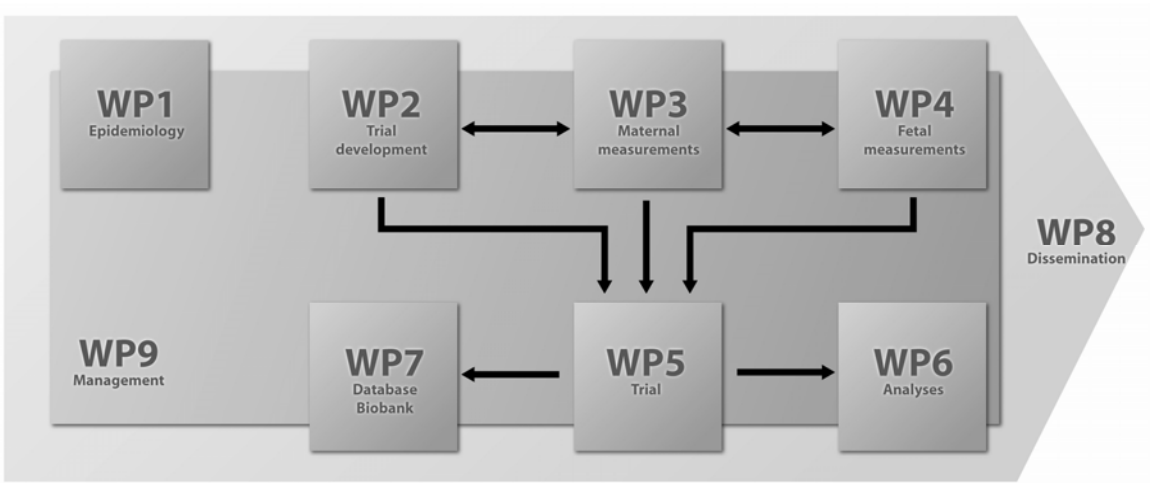

Figure 3: DALI interactions

B1.3.4 Timing of different WPs and their components (Gantt chart)

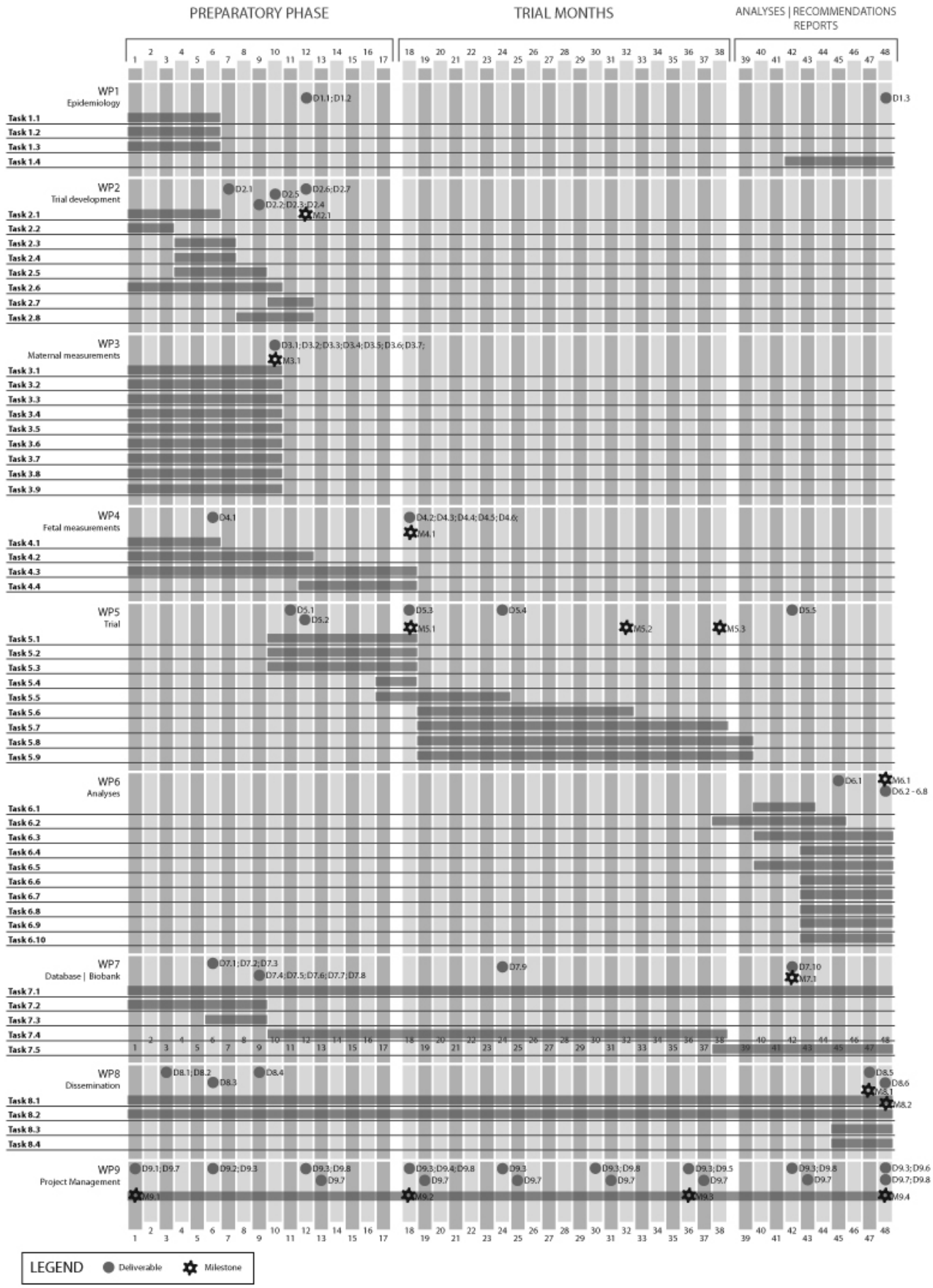

Figure 4: Timing of the work packages

B1.3.5 References

1. Cheung NW, Blyth K (2003). Population health significance of gestational diabetes. Diab Care 26: 2005-2009.
2. Metzger BE (1991). Biphasic effects of maternal metabolism on foetal growth. Quintessential expression of fuel-mediated teratogenesis. Diabetes 40 Suppl 2: 99-105.
3. Massi-Benedetti M, CODE-2 Advisory Board (2002). The cost of diabetes Type II in Europe: the CODE-2 Study. Diabetologia 45: S1-4.
4. EU document A6-0450/2006
5. World Health Organisation and Department of Non-communicable Disease Surveillance. (1999). Definition, Diagnosis and Classification of Diabetes Mellitus and its complications.. Part 1 Geneva: WHO 1999.
6. HAPO Study Cooperative Research Group (2008). Hyperglycemia and Adverse Pregnancy Outcomes. N Eng J Med; 358: 1999-2002.
7. Lauenborg J, Mathiesen E, et al (2005). Prevalence of the metabolic syndrome in a Danish population of women with previous GDM is three fold higher than in general population. J Clin Endo Metab; 90: 4004-4010.
8. Silverman BL, Metzger BE, et al (1995). Impaired glucose tolerance in adolescent offspring of diabetic mothers. Diabetes Care; 18: 611-617.
9. Van Assche FA, Holemans K, et al (2001). Long-term consequences for offspring of diabetes during pregnancy. Br Med Bull. 60: 173-82.
10. Rizzo TA, Metzger BE, et al (1997). Early malnutrition and child neurobehavioural development: insights from the study of children of diabetic mothers. Child Dev; 68: 26-28.
11. Tieu J, Crowther CA, et al. Dietary advice in pregnancy for preventing gestational diabetes mellitus. Cochrane Database Syst Rev. 2008: CD006674.
12. Dempsey JC, Sorensen TK, et al (2004). Prospective study of gestational diabetes mellitus risk in relation to maternal recreational physical activity before and during pregnancy. Am J Epidemiol; 159: 663-670.
13. Behavioral Risk Factor Surveillance System: http: //apps.nccd.cdc.gov/brfss/trends.
14. Centres for Disease Control (2003). Births: Final Data 2002. Atlanta, GA. (DHHS publ. no. PHS 2004-1120.
15. Prochaska JO, Velicer WF (1997). Transtheoretical model of health behavior change.Am J Health Promot; 12: 38-48.
16. Bandura A (2001). Social cognitive theory: an agentic perspective. Annu Rev Psychol; 52: 1-26.
17. Renner B, Kwon S,et al (2008). Social-cognitive predictors of dietary behaviors in South Korean men and women. Int J Behav Med; 15: 4-13.
18. Meyer D, Leventhal H, et al (1985). Common-sense models of illness: the example of hypertension. Health Psychol; 4: 115-35.
19. Simmons D, Rush E, et al. Development and piloting of a community health worker based intervention for the prevention of diabetes among New Zealand Maori in Te Wai o Rona: Diabetes Prevention Strategy. Public Health Nutrition 2008; 11: 1318-1325
20. Tuomilehto J, Lindstrom J, et al (2001). Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med. 344: 1343-50.
21. Knowler WC, Barrett-Connor E, Fowler SE et al (2002). Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 346: 393-403.
22. Clapp JF, III, Capeless EL (1991). The changing glycemic response to exercise during pregnancy. Am J Obstet Gynecol; 165: 1678-1683.
23. Clapp JF, III, Rokey R, et al (1992). Exercise in pregnancy. Med Sci Sports Exerc, 24: S294-S300.
24. Jovanovic-Peterson L, Durak EP, et al (1989). Randomized trial of diet versus diet plus cardiovascular conditioning on glucose levels in gestational diabetes. Am J Obstet Gynecol; 161: 415-419.
25. Avery MD, Walker AJ (2001). Acute effect of exercise on blood glucose and insulin levels in women with gestational diabetes. J Matern Foetal Med; 10: 52-58.
26. Garcia-Patterson A, Martin E, et al (2001). Evaluation of light exercise in the treatment of gestational diabetes. Diabetes Care; 24: 2006-2007
27. Brankston GN, Mitchell BF, et al (2004). Resistance exercise decreases the need for insulin in overweight women with gestational diabetes mellitus. Am J Obstet Gynecol; 190: 188-193.
28. Aittasalo M, Pasanen M, et al (2008). Physical activity counseling in maternity and child health care - a controlled trial. BMC Women's Health; 8: 14 [Epub]
29. Bantle JP, Wylie-Rosett J, et al (2008). Nutrition recommendations and interventions for diabetes: a position statement of the American Diabetes Association. Diabetes Care. 31 Suppl 1: S61-78.

30. Rizzo T, Metzger BE, et al (1991). Correlations between antepartum maternal metabolism and child intelligence. N Engl J Med; 325: 911-6.
31. Barclay AW, Petocz P, et al (2008). Glycemic index, glycemic load, and chronic disease risk--a meta-analysis of observational studies. Am J Clin Nutr. 87: 627-37.
32. Brand-Miller JC, Petocz P, et al (2003). Meta-analysis of low-glycemic index diets in the management of diabetes: response to Franz. Diabetes Care. 26: 3363-4.
33. Opperman AM, Venter CS, Oosthuizen et al (2004). Meta-analysis of the health effects of using the glycaemic index in meal-planning. Br J Nutr. 92: 367-81.
34. Moses RG, Luebcke M, et al (2006). Effect of a low-glycemic-index diet during pregnancy on obstetric outcomes. Am J Clin Nutr. 84: 807-12.
35. Kaline K, Bornstein SR, et al (2007). The importance and effect of dietary fiber in diabetes prevention with particular consideration of whole grain products. Horm Metab Res. 2007; 39: 687-93.
36. Snijder MB, van Dam RM, et al (2005). Adiposity in relation to vitamin D status and parathyroid hormone levels: a population-based study in older men and women. J Clin Endocrinol Metab; 90: 4119-23.
37. Ford ES, Ajani UA, et al (2005). Concentrations of serum vitamin D and the metabolic syndrome among U.S. adults. Diabetes Care: 28: 1228-1230.
38. Norman A, Frankel J (1980). Vitamin D deficiency inhibits pancreatic insulin secretion. Science 109: 823- 825.
39. Forouhi NG, Luan J, et al (2008). Baseline serum 25-hydroxy vitamin d is predictive of future glycemic status and insulin resistance: the Medical Research Council Ely Prospective Study 1990-2000. Diabetes; 57: 2619-25.
40. Wallis DE, Penckofer S et al (2008). The "sunshine deficit" and cardiovascular disease. Circul; 118: 1476-85.
41. Bodnar LM, Catov JM, et al (2007). Prepregnancy obesity predicts poor vitamin D status in mothers and their neonates. J Nutr; 137: 2437-42.
42. Clifton-Bligh RJ, McElduff P, et al. (2008) Maternal vitamin D deficiency, ethnicity and gestational diabetes. Diabet Med; 25: 678-84.
43. Maghbooli Z, Hossein-Nezhad A, et al (2008). Correlation between vitamin D3 deficiency and insulin resistance in pregnancy. Diabetes Metab Res Rev; 24: 27-32.
44. Farrant HJ, Krishnaveni GV et al (2008). Vitamin D insufficiency is common in Indian mothers but is not associated with gestational diabetes or variation in newborn size. Eur J Clin Nutr; [epub]
45. Zhang C, Qiu C, Hu FB, et al (2008). Maternal plasma 25-hydroxyvitamin d concentrations and the risk for gestational diabetes mellitus. PLoS ONE 3: e3753.
46. Nilas L, Christiansen C (1984). Treatment with vitamin D or its analogues does not change body weight or blood glucose level in postmenopausal women. Int J Obes 8: 407- 411.
47. Heaney RP, Davies KM, et al (2003). Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol .Am J Clin Nutr; 77: 204-10.
48. Pittas AG, Harris SS, et al (2007). The effects of calcium and vitamin D supplementation on blood glucose and markers of inflammation in nondiabetic adults. Diabetes Care 30: 980 -986.
49. Rudnicki PM, Mølsted-Pedersen L (1997). Effect of 1,25-dihydroxycholecalciferol on glucose metabolism in gestational diabetes mellitus. Diabetologia; 40: 40-44.
50. Norman AW, Frankel JB, et al (1980). Vitamin D deficiency inhibits pancreatic secretion of insulin. Science 209: 823- 825.
51. Vieth R, Bischoff H, et al (2007) Urgent need to recommend intake of vitamin D. Am J Clin Nutr 85: 649-650.
52. NICE (2008) Antenatal care routine care for the healthy pregnant woman. National Collaborating Centre for Women's and Children's Health Commissioned by the National Institute for Health and Clinical Excellence. March 2008
53. http: //clinicaltrials.gov#R01 HD 043921
54. Carson BS, Philips AF, et al. (1980). The effect of sustained insulin infusion upon glucose uptake and oxygenation in ovine foetus. Pediatr Res; 14: 147-152
55. Widness JA, Teramo K,et al (1990). Direct relationship of antepartum glucose control and foetal erythropoietin in human type 1 diabetic pregnancy. Diabetologia; 9: 75-79
56. Teramo K, Kari MA, et al (2004). High amniotic fluid erythropoietin levels are associated with an increased frequency of foetal and neonatal morbidity in type 1 diabetic pregnancy. Diabetologia, 47: 1695-1703.
57. Widness JA, Susa JB, et al (1981). Increased erythropoiesis and elevated erythropoietin in infants born to diabetic mothers and in hyperinsulinemic foetuses. J Clin Invest; 67: 637-642.

58. Teramo K, Widness JA (2008). Increased foetal plasma and amniotic fluid erythropoietin concentrations: markers of intrauterine hypoxia. Neonatology: 95: 105-116.
59. Casson IF, Clarke CA, et al (1997). Outcomes of pregnancy in insulin dependent diabetic women: results of a five year population cohort study. BMJ; 15: 275-278
60. Lauenborg J, Mathiesen E, et al (2003). Audit on stillbirths in women with pregestational type 1 diabetes.Diabetes Care. 2003; 6: 1385-9.
61. Cetin I, Morpurgo PS, et al (2000). Foetal plasma leptin concentrations: relationship with different intrauterine growth patterns from 19 weeks to term. Pediatr Res. 48: 646-51.
62. Wolf HJ, Ebenbichler CF, et al (2000). Foetal leptin and insulin levels only correlate in large-for-gestational age infants. Eur J Endocrinol. 142: 623-9.
63. Hoeks AP, Brands PJ, et al (1999). Non-invasive measurement of mechanical properties of arteries in health and disease Proc Inst Mech Eng. 213: 195-202.
64. Cetin I, Boito S, Radaelli T (2008) Evaluation of foetal growth and well-being. Semin Ultrasound 29: 136-46
65. Pietryga M, Brazert J, et al (2006). Placental Doppler velocimetry in GDM. J Perinat Med. 2006; 34: 108-10
66. Mongelli M, Benzie R (2005). Ultrasound diagnosis of foetal macrosomie: a comparison of weight prediction models using computer simulation. Ultrasound Obstet Gynecol; 26: 500-3.
67. Ben-Haroush A, Chen R, et al (2007).Accuracy of a single foetal weight estimation at 29-34 weeks in diabetic pregnancies: can it predict large-for-gestational-age infants at term? Am J Obstet Gynecol; 197: 497.e1-6.
68. Larciprete G, Valensise H, (2003). Foetal subcutaneous tissue thickness (SCTT) in healthy and gestational diabetic pregnancies. Ultrasound Obstet Gynecol; 22: 591-7.
69. Crane SS, Avallone DA, et al (1996). Sonographic estimation of foetal body composition with gestational diabetes mellitus at term. Obstet Gynecol; 88: 849-54.
70. Prayer D (2006). Foetal MR. Eur J Radiol; 57: 171.
71. Bulas D (2007). Foetal MRI as a complement to foetal ultrasonography. Ultrasound ; 23: 3-22.
72. Baker PN, Johnson I et al (1994). Foetal weight estimation by echo-planar MRI. Lancet; 343: 644-5.
73. Kulemann et al (2008) MRI center Vienna, unpublished 2008.
74. Campbell M, Fitzpatrick R, et al (2000). Framework for design and evaluation of complex interventions to improve health. BMJ; 321: 694-6.
75. Kearney MH, Simonelli MC (2006). Intervention fidelity: lessons learned from an unsuccessful pilot study. Applied Nursing Research 19: 163-166.
76. Saunders RP, Evans MH, et al (2005). Developing a Process-Evaluation Plan for assessing Health Promotion Program Implementation: A How-To Guide. Health Promotion Practice 6: 134-147
77. Henggeler SW, Melton GB, et al (1997). Multisystemic therapy with violent and chronic juvenile offenders and their families: the role of treatment fidelity in successful dissemination. J Consult Clin Psychol 65: 821-833.
78. Kalichman SC, Belcher L, et al (1997). Primary prevention of sexually transmitted HIV infections: transferring behavioral research technology to community programs. J Primary Prev 18: 149-172.
79. Sechrest L (1982). Program evaluation: independent and dependent variables. Counseling Psychol 10: 73-74
80. Dumas JA, Lynch AM, et al (2001). Promoting intervention fidelity. Conceptual issues, methods and preliminary results from the EARLY ALLIANCE prevention trial. Am J Prev Med 20: 38-47 supplement
81. Latif E (2008). The impact of diabetes on emplyoment in Canada. Health Econ DOI: 10.1002/hec.1390.
82. Ramsey S, Willke R et al (2005),. Good Research Practices for Cost-Effectiveness Analysis Alongside Clinical Trials: The ISPOR RCT-CEA Task Force Report. Value in Health 8: 521-533.
83. National Collaborating Centre for Women´s and Children´s Health. Diabetes in pregnancy: management of diabetes and its complications from preconception to the postnatal period. Clinical Guideline commissioned by the National Institute for Health and Clinical Excellence, 2008.
84. Ricart W, López J, et al (2008). Maternal glucose tolerance status influences the risk of macrosomia in male but not in female foetuses. J Epidemiol Community Health. Aug 21 (epub ahead of print).
85. Pan XR, Li GW, Hu YH et al (1997). Effects of diet and exercise in preventing NDDM in people with impaired glucose tolerance: the Da Qing IGT and diabetes study. Diabetes Care 20: 537-544.
86. Rowan JA, Hague WM et al (2008). Metformin vs Insulin for Treatment of GDM. N Engl J Med 358: 2003-15.
87. Simmons D, Walters B et al (2004). Metformin therapy and diabetes in pregnancy. Med J Aust; 180: 462-464.
88. Glueck C, Wang P, et al (2002). Metformin therapy throughout pregnancy reduces the development of gestational diabetes in women with polycystic ovary syndrome. Fertil Steril 77: 520-525.