"DIABETES BEGETS DIABETES"

or

THE VICIOUS CYCLE OF DIABETES

When your pregnancy is 'sweeter' than usual ...

Some 18% of pregnant women suffer gestational diabetes, says study

ALICIA WONG
alicia@mediacorp.com.sg

SINGAPORE — The proportion of women suffering from gestational diabetes has turned out to be higher than expected, preliminary findings have shown. But a wider and more

how to prevent or treat metabolic diseases such as obesity and Type 2 diabetes.

Doctors could then, for example, tell mothers if their child has a higher risk of say, obesity, and what preventive measures should be taken, said

Paul Zimmet AO MD PhD Doctor of Laws (Monash)

Monash University, Melbourne

GESTATIONAL DIABETES

Gestational diabetes (GDM) is glucose intolerance with onset or first recognition during pregnancy

- Affects 3- >16% of pregnancies*
- Identifies women who are at risk of future diabetes
- Increased risk of obesity and diabetes in the child and in adult life
- Presents an opportunity for lifestyle intervention

* Depends on ethnicity

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COMMENTARY

Gestational diabetes: what's up?

Kerstin E. Berntorp[1,2]

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Keywords Fetal over-nutrition · Gestational diabetes · Macrosomia · Maternal obesity · Metabolic syndrome · Prevention · Treatment · Type 2 diabetes

Abbreviation
GDM Gestational diabetes mellitus

Gestational diabetes mellitus (GDM), until recently defined as any degree of hyperglycaemia first detected in pregnancy [1], is a growing public health concern [2]. The prevalence of GDM shows an increasing trend in most racial/ethnic groups and parallels the global epidemic of obesity and type 2 diabetes [3]. GDM and type 2 diabetes have many risk factors in common and they share the same genetic susceptibility [4, 5]. Both are characterised by insulin resistance and an inability of the beta cells to compensate with a sufficient increase in insulin secretion [4]. Although glucose tolerance usually reverts to normal after delivery, affected women remain at high risk of developing type 2 diabetes during their lifetime, with an estimated lifetime risk of about 50–70% [6]. In addition to hypertensive pregnancy disorders [4], GDM is associated with dyslipidaemia and other components of the metabolic syndrome [7], and if present, an increased risk of cardiovascular disease [8].

✉ Kerstin E. Berntorp
kerstin.berntorp@med.lu.se

[1] Department of Clinical Sciences Malmö, Lund University, Malmö, Sweden

[2] Department of Endocrinology, Skåne University Hospital, SE-205 02 Malmö, Sweden

GDM and maternal obesity are independently associated with adverse pregnancy outcomes, and children born to mothers with GDM and overweight/obesity are more likely to be macrosomic and large for their gestational age [9–11]. In addition to short-term complications, they also have an increased risk of long-term complications similar to those in their mothers [12, 13]. Studies indicate that offspring exposed to maternal diabetes or GDM in utero are at a higher risk of developing childhood obesity and glucose intolerance in early adulthood than offspring not exposed to maternal diabetes [12, 14]. Moreover, if the offspring is female, she is more likely to develop GDM herself and thereby create a vicious circle. Prevention of GDM and fetal over-nutrition in pregnancy could therefore be important strategies to interrupt this trans-generational cycle of obesity and diabetes (Fig. 1).

To date, several studies have demonstrated the effectiveness of lifestyle interventions in the prevention of type 2 diabetes [15]. A beneficial effect on the risk of diabetes was also found in the Diabetes Prevention Program in women with a history of GDM, which was sustained during a 10-year follow-up period [16]. Since obesity is one of the most powerful modifiable risk factors for GDM in pregnant women [12, 17], many intervention studies have focused on reducing weight or on reducing gestational weight gain in pregnancy, most often by changes in diet and physical activity. The effects of combined diet and exercise interventions during pregnancy were recently reviewed by Cochrane [18]. No clear evidence for the prevention of GDM was found. In contrast, a newly published meta-analysis concluded that moderate exercise programmes initiated early during pregnancy reduce the risk of GDM and excessive gestational weight gain [19]. Ideally, interventions aimed at improving metabolic conditions and placental function in obese women should take place before pregnancy, prior to conception [20]. Interestingly, Zhang et al recently reported that adherence to a healthy lifestyle in the middle of last year and plans to recruit 600 women, aims to use balanced nutrition to prevent these women from getting this disease.

Sir Peter, also a principal investigator in Gusto, a longitudinal baby study at NUH and the KK Women's and Children's Hospital (KKH) that started in 2009, said the rate of GDM in Singapore is very high.

Based on Gusto, one in five of 1,136 pregnant women here tested had GDM, more than double the 9.2 per cent in the United States. This was even though half of the Singapore women were thought to be at low risk and would normally not have been checked for it.

Prof Chong, also SICS executive director, said doctors here were surprised at the high rate of GDM in Singapore.

The finding has led KKH and the Singapore General Hospital (SGH) to test all pregnant women for GDM from last month. NUH plans to start testing later this year.

Diabetes fight focuses on pregnant women

Authorities aim to cut risk for next generation by preventing gestational diabetes mellitus

Salma Khalik
Senior Health Correspondent

Many people who are obese or diabetic are afflicted by these conditions because their mothers had gestational diabetes mellitus (GDM) while carrying them.

Three out of four babies born to such mothers will be severely obese or diabetic some time in their lives, said Sir Peter Gluckman, chief scientific officer of the Singapore Institute for Clinical Sciences (SICS), which is part of the Agency for Science, Technology and Research.

The National University Hospital (NUH) hopes to reduce the rate of obesity and diabetes in the next generation of Singaporeans by preventing GDM, or diabetes caused by the stress of pregnancy.

Associate Professor Chong Yap Seng of the National University Health System said a trial called Nipper, which started at NUH in the middle of last year and plans to recruit 600 women, aims to use balanced nutrition to prevent these women from getting this disease.

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If left uncontrolled, GDM can cause a host of problems including premature birth. Women who get this disease tend to already be somewhat insulin-resistant.

GDM can disappear after the baby is born. But Sir Peter, who is the co-chair of the World Health Organisation's Commission on Ending Childhood Obesity, said women with GDM will need to be careful after they give birth, as many of them will become diabetic unless they exercise and watch their diet.

Prof Chong added that women with GDM are more than seven times as likely as other women to get diabetes. The Gusto study found 10 per cent of these women developed full-blown diabetes within five years of childbirth, when they were only in their 30s.

This has alerted all hospitals here to monitor women with GDM for diabetes in the years after childbirth.

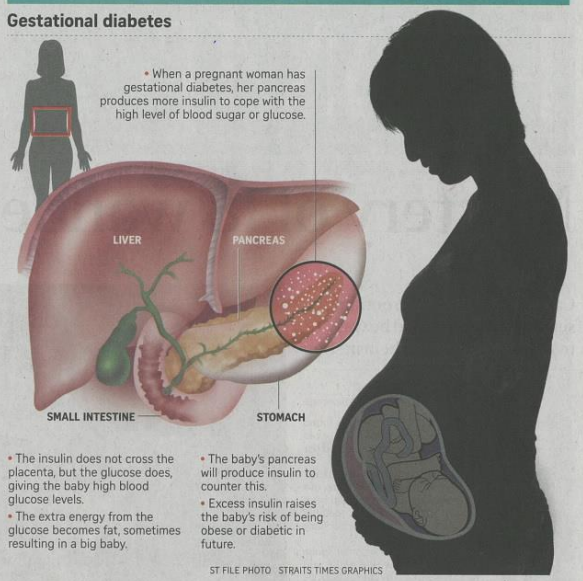
The study showed that the rate of GDM here is far higher in Indian and Chinese mothers than in Malay mums. Sir Peter said Indians are of particular concern, as some Indian babies are born with more "bad fat" than others.

He said: "By the age of 4½ years, Indian children have shown signs that they are well on the pathway to insulin resistance and diabetes."

Sir Peter, who is chief science adviser to New Zealand Prime Minister John Key, is confident that Singapore is in a good position to correct the situation.

He said: "It's being taken seriously in Singapore, which knows diabetes is a top public health problem. And Singapore has always been willing to invest heavily in children."

salma@sph.com.sg
facebook.com/ST.Salma



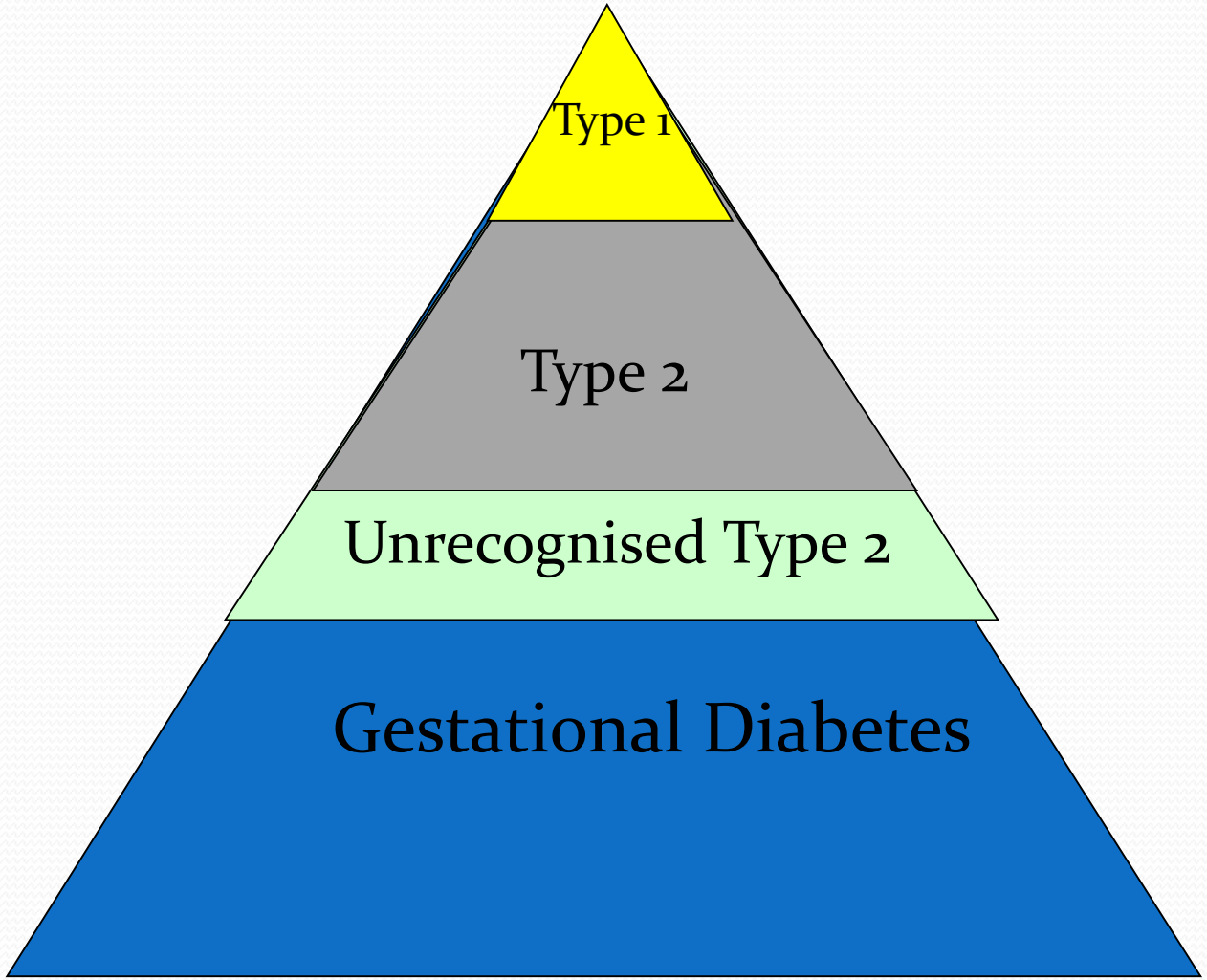
Gestational Diabetes defined

- Gestational Diabetes (GDM) is glucose intolerance with onset or first recognition during pregnancy[1]
- GDM is a heterogeneous condition:
  - Glucose intolerance arising in the third trimester due to increased maternal insulin resistance
  - Un-diagnosed pre-GDM is usually Type 2 diabetes[2]
  - Pre-clinical phase of Type 1 diabetes[2]

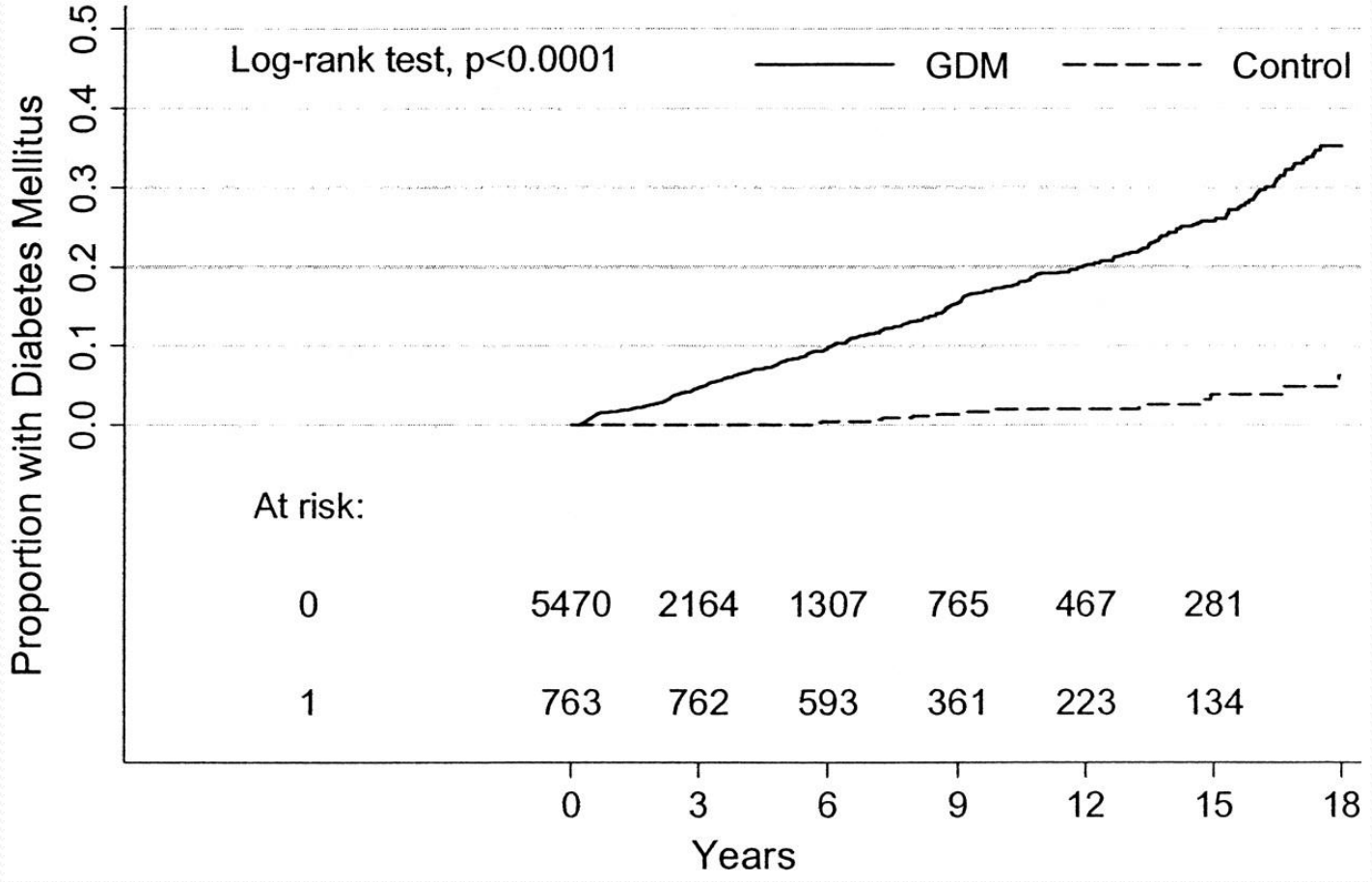
1. Metzger BE,Coustan DR, Diabetes Care.21(suppl 2):B161-B167, 1998.

2 Kim C et al. Diabetes Care 30:1314-9, 2007

TYPES OF DIABETES SEEN IN PREGNANCY



Long-term consequences of Gestational Diabetes pregnancy for the Mother

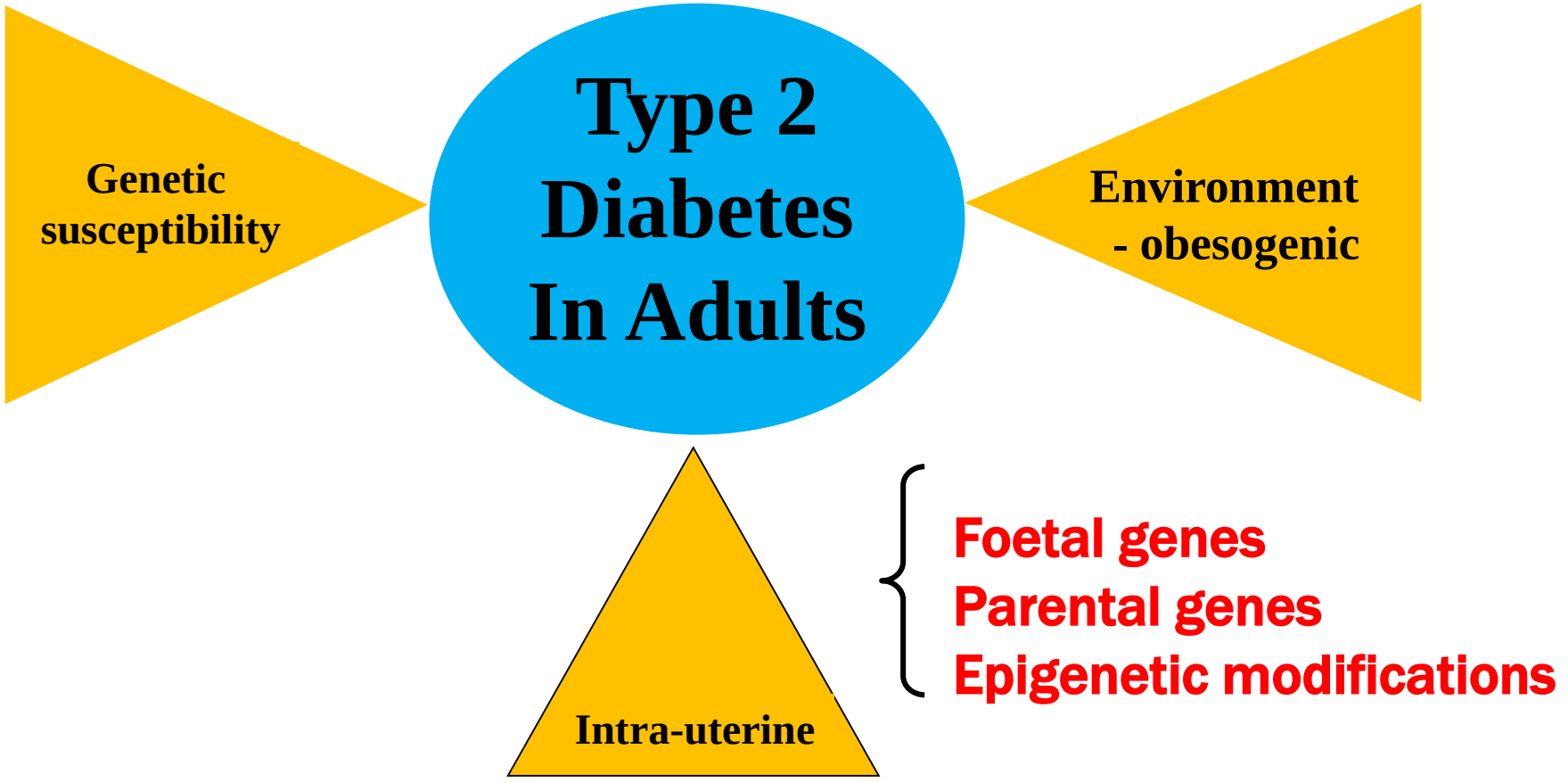


A retrospective Australian cohort study on 5470 women diagnosed with GDM and 783 controls followed up between 1971 and 2003[1]

Lee, AJ et al, Diabetes Care 30:878-883, 2007

CONTRIBUTING FACTORS TO THE EPIDEMIC OF TYPE 2 DIABETES

Gestational diabetes: potential long-term consequences to child



EXCESSIVE OBESITY IN OFFSPRING OF PIMA INDIAN WOMEN WITH DIABETES DURING PREGNANCY

DAVID J. PETTITT, M.D., H. ROBERT BAIRD, M.S., KIRK A. ALECK, M.D., PETER H. BENNETT, M.B., AND WILLIAM C. KNOWLER, M.D., DR.P.H.

Abstract We studied the relation in Pima Indians between obesity in children and diabetes during pregnancy in their mothers. Sixty-eight children of 49 women who had had diabetes during pregnancy had a higher prevalence of obesity than 541 children of 134 women who subsequently had diabetes (prediabetics) or than 1326 children of 446 women who remained nondiabetic. At 15 to 19 years of age, 58 per cent of the offspring of diabetics weighed 140 per cent or more of their desirable weight, as compared with 17 per cent of the offspring of nondiabetics and 25 per cent of those of prediabetics ($P<0.001$). Obesity in the offspring was directly related to maternal diabetes, since the association was not substantially confounded by maternal obesity. The findings strongly suggest that the prenatal environment of the offspring of diabetic women results in the development of obesity in childhood and early adulthood. (N Engl J Med. 1983; 308: 242-5.)

THE third trimester of pregnancy is a critical period for adipose-cell hyperplasia.[1,2] During this period maternal–fetal undernutrition has been shown to be associated with less frequent obesity in early adult life.[3] Because diabetes occurring during gestation results in a state of maternal hyperglycemia and fetal overnutrition,[4,5] the offspring of diabetic women might be expected to be more obese than the offspring of nondiabetic or prediabetic women. Hyperglycemia during the third trimester is associated with giving birth to large infants,[6-9] but the long-range outlook for obesity in these infants is unclear.[2,9-12]

We report the effects of non-insulin-dependent diabetes mellitus in the mother during pregnancy on the prevalence of obesity in offspring 5 to 19 years old.

METHODS

Offspring were stratified into five-year age groups; because of repeated examinations, they could appear in more than one age group at different times. When anyone was examined more than once in a given age range, the data from the examination closest to the midpoint of that range were used. In all, 1935 offspring of 625 mothers were studied. One thousand sixty-eight offspring were examined in at least two age groups, and 375 were examined in all three. Records of birth weight were available for 303 of these 375.

Offspring were defined as obese if they weighed at least 140 per cent of their desirable weight. The percentage of desirable weight was derived by dividing actual weight by desirable weight and expressing the result as a percentage. Desirable weight was defined as follows: at birth, as the 50th percentile weight for gestational age, according to Lubchenco et al.[15]; at ages 5 to 14 years, as the 50th percentile of weight for height, according to standards derived from Falkner[16]; and after 15 years of age, as the midpoint of the range of desirable weight for height, according to the National Research Council standards.[17] Exact 95 per cent confidence limits[18] were calculated for the prevalence of obesity among the offspring. The method of Mantel and Haenszel was used to control for confounding by maternal obesity.[18,19]

Consequences of GDM for the child - obesity

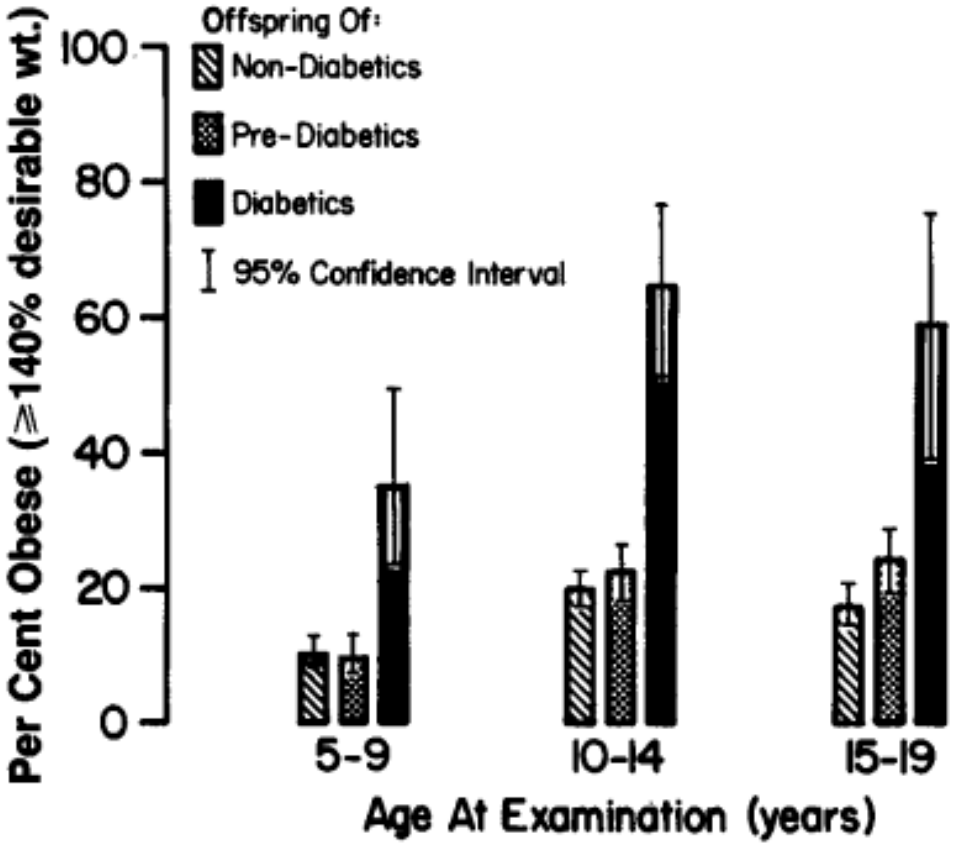
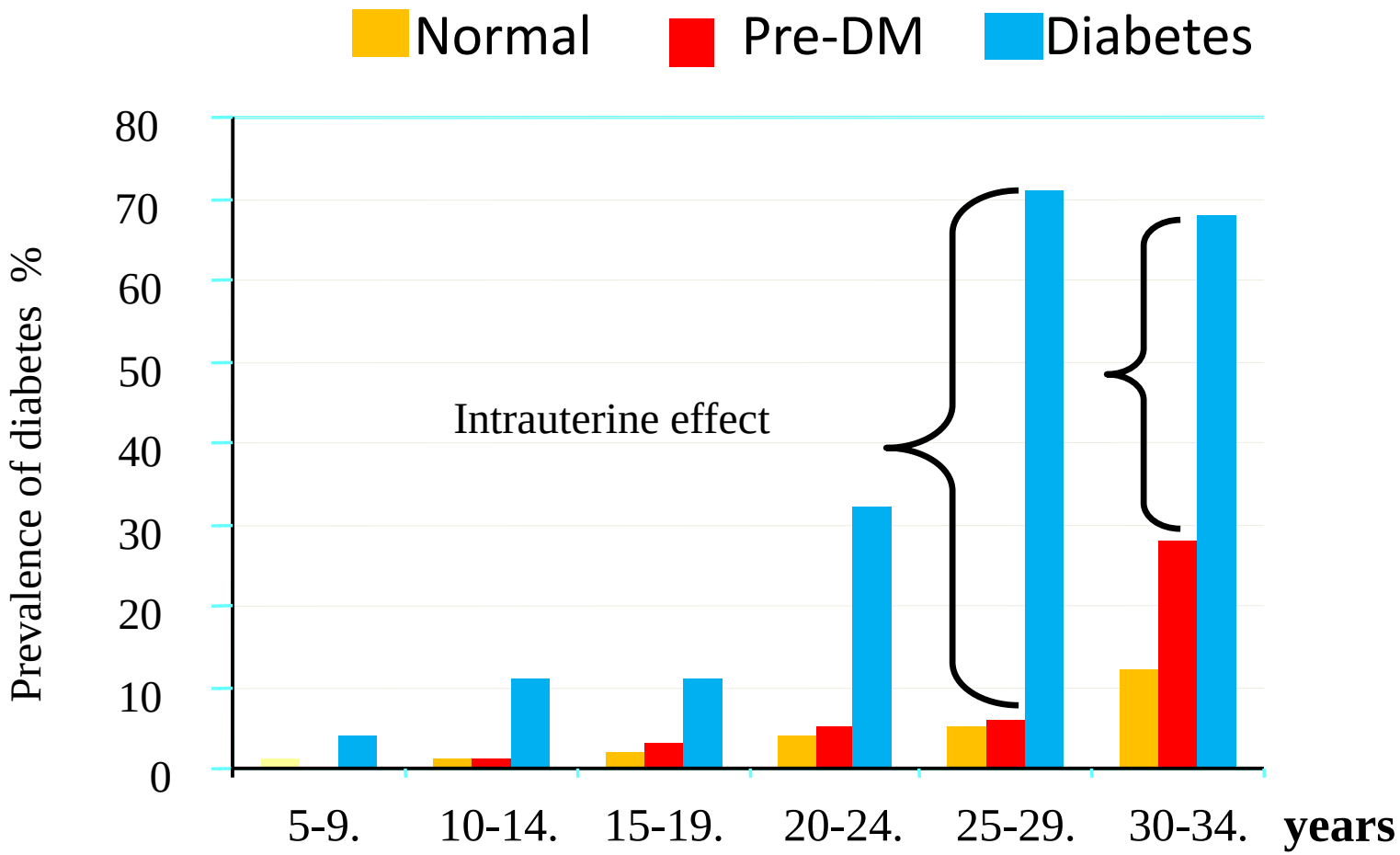


Figure 1. Prevalence of Obesity among Offspring of Pima Indians, According to Age at Examination and Maternal Status with Respect to Diabetes during Gestation.

GESTATIONAL DIABETES: POTENTIAL LONG-TERM CONSEQUENCES TO THE CHILD

Type 2 DM in a Pima cohort of 5,274 children
according to diabetic status of mother



Dabelea D. J Matern-Fetal Med 2000

Drivers of Type 2 diabetes

Lifestyle

Inactivity

Caloric excess

Obesity

Ageing

Modernisation

Foetal

Programming

In *Utero* Conditions and Chronic Disease

MECHANISMS OF DISEASE

Effect of In Utero and Early-Life Conditions on Adult Health and Disease

Peter D. Gluckman, M.D., D.Sc., Mark A. Hanson, D.Phil., Cyrus Cooper, M.D., and Kent L. Thornburg, Ph.D.

A LONG LATENCY PERIOD BETWEEN AN ENVIRONMENTAL TRIGGER AND the onset of subsequent disease is widely recognized in the etiology of certain cancers, yet this phenomenon is not generally considered in the etiology of other conditions such as cardiovascular disease, metabolic disease, or osteoporosis. However, many lines of evidence, including epidemiologic data and data from extensive clinical and experimental studies, indicate that early life events play a powerful role in influencing later susceptibility to certain chronic diseases. An increased understanding of developmental plasticity (defined as the ability of an organism to develop in various ways, depending on the particular environment or setting) provides a conceptual basis for these observations.[1]

Developmental plasticity requires stable modulation of gene expression, and this appears to be mediated, at least in part, by epigenetic processes such as DNA methylation and histone modification. Thus, both the genome and the epigenome interactively influence the mature phenotype and determine sensitivity to later environmental factors and the subsequent risk of disease. In this review, we synthesize evidence from several disciplines to support the contention that environmental factors acting during development should be accorded greater weight in models of disease causation.

From the Liggins Institute, University of Auckland, and National Research Centre for Growth and Development, Auckland, New Zealand (P.D.G.); Institute of Developmental Sciences, University of Southampton (M.A.H.), and Medical Research Council Epidemiology Resource Centre, University of Southampton (C.C.) — both in Southampton, United Kingdom; and Heart Research Center, Oregon Health & Science University, Portland (K.L.T.). Address reprint requests to Dr. Gluckman at the Liggins Institute, University of Auckland, Private Bag 92019, Auckland, New Zealand, or at pd.gluckman@auckland.ac.nz.

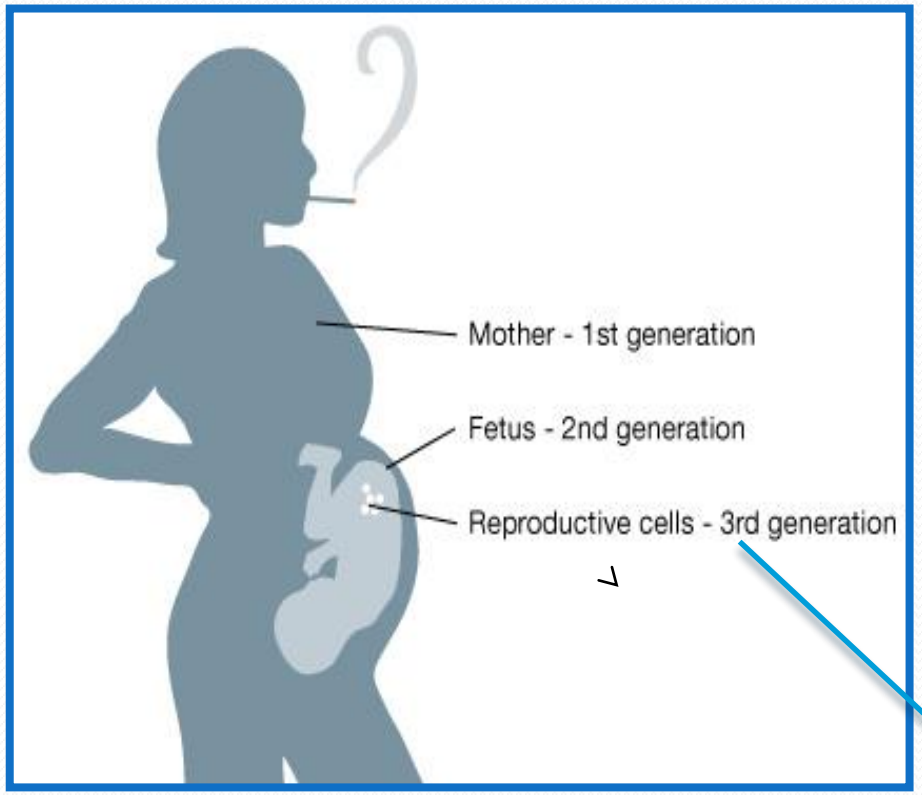
N Engl J Med 2008;359:61-73.

EPIDEMIOLOGIC AND CLINICAL OBSERVATIONS

The epidemiologic observations that smaller size or relative thinness at birth and during infancy is associated with increased rates of coronary heart disease, stroke, type 2 diabetes mellitus, adiposity, the metabolic syndrome, and osteoporosis in adult life[2-6] have been extensively replicated. Perinatal events appear to exert effects that are independent of environmental risk factors in adults[7,8] or may be amplified by other risk factors.[9] Slow growth in utero may be associated with increased allocation of nutrients to adipose tissue during development and may then result in accelerated weight gain during childhood,[10,11] which may contribute to a relatively greater risk of coronary heart disease, hypertension, and type 2 diabetes mellitus. There is a continuous relation between birth weight and future risk — not just for extreme weights but also for normal weights.[12] Prematurity itself, independent of size for gestational age, has been associated with insulin resistance and glucose intolerance in prepubertal children[13] that may track into young adulthood and may be accompanied by elevated blood pressure.[14]

In mammalian development, the mother transduces environmental information such as nutritional status to her embryo or fetus through the placenta or to her

FOETAL PROGRAMMING & INTERGENERATIONAL RISK



- Smoking
- Alcohol
- Malnutrition
- Under-nutrition
- Stress
- Hypertension

Gestational Diabetes

Experimental animal studies… these effects persist through many generations –risk is **Intergenerational**

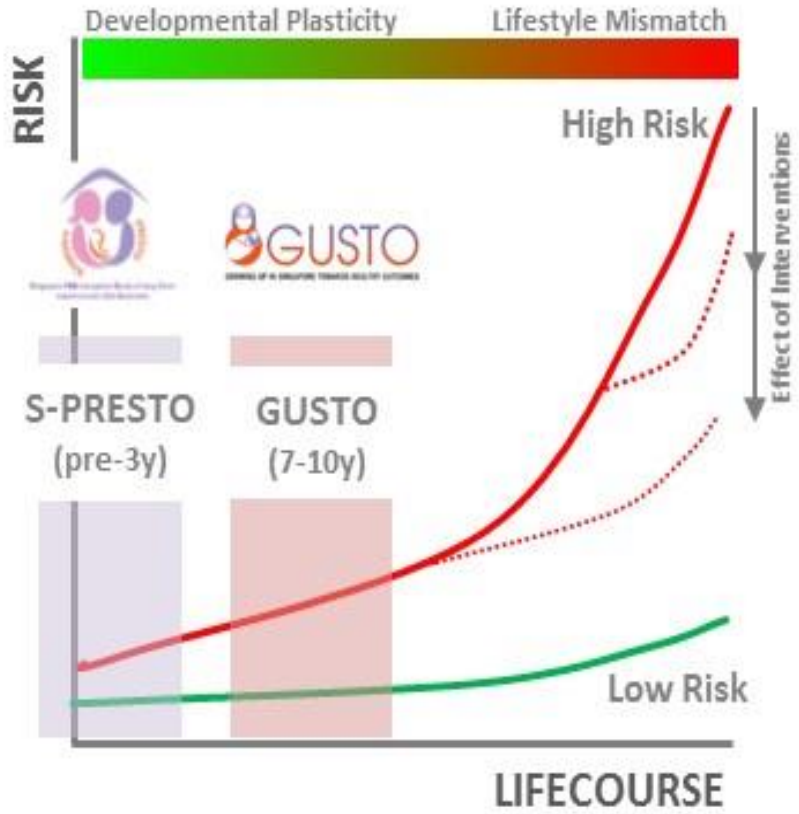
GUSTO Birth Cohort Study

Agency for Science, Technology and Research
SINGAPORE

Singapore Institute for Clinical Sciences
A*STAR

Singapore PREconception Study of long-Term maternal and child Outcomes

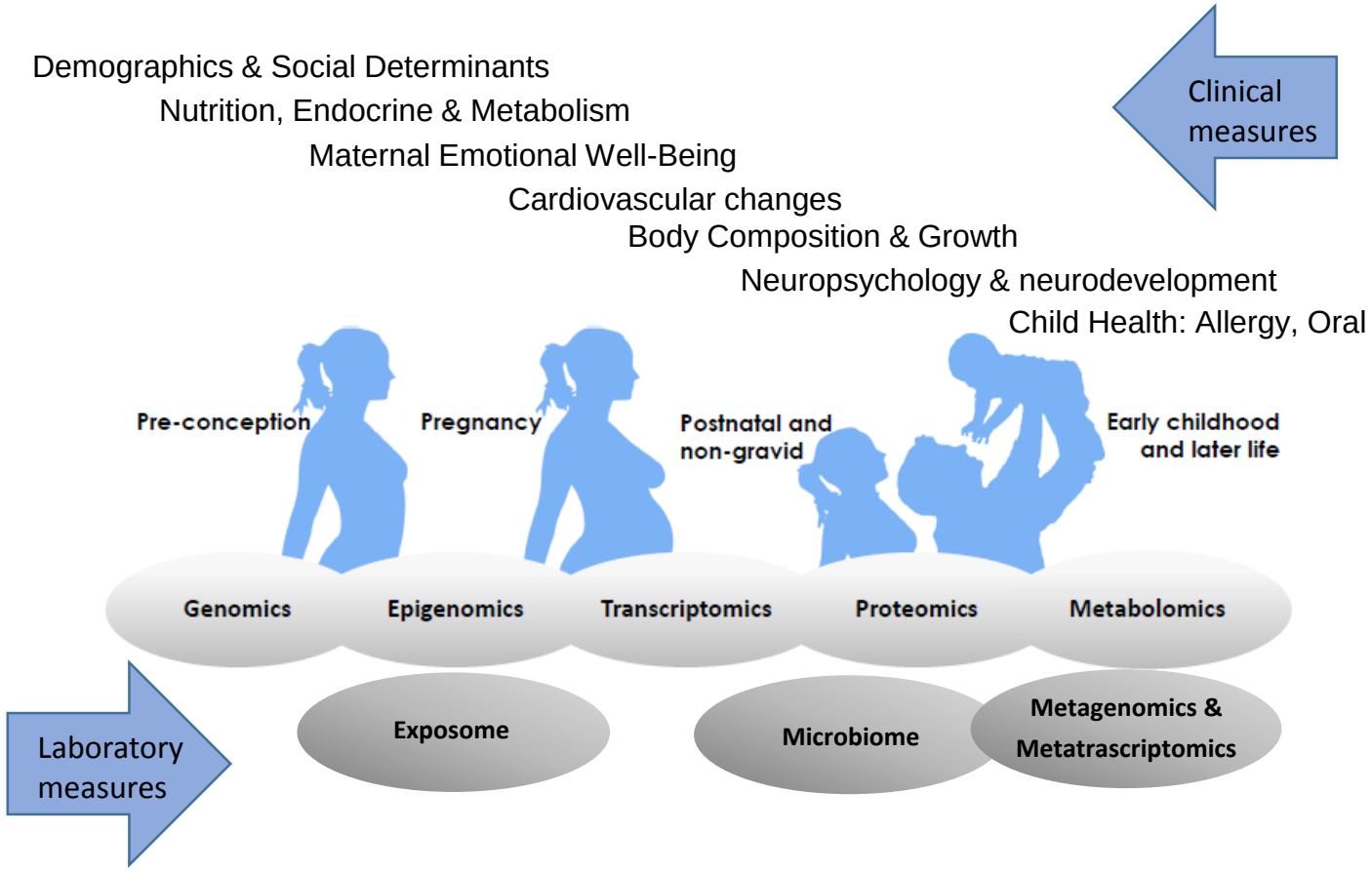
GUSTO
GROWING UP IN SINGAPORE TOWARDS HEALTHY OUTCOMES



Health Trajectory from Conception - A Life Course Approach

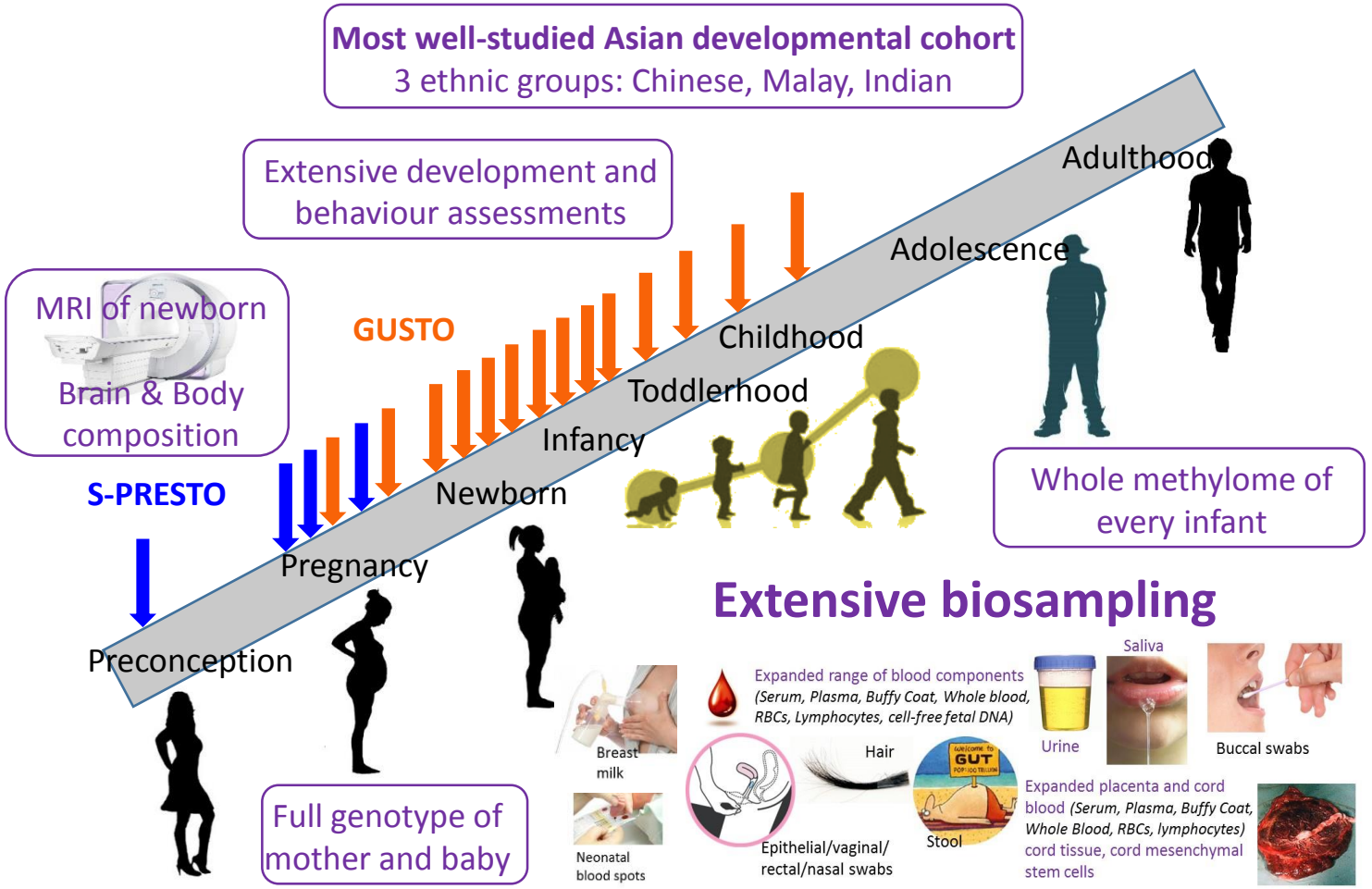
Courtesy of Professor Chan Shiao-yng

Longitudinal Deep Phenotyping Throughout Development



Courtesy of Professor Chan Shiao-yng

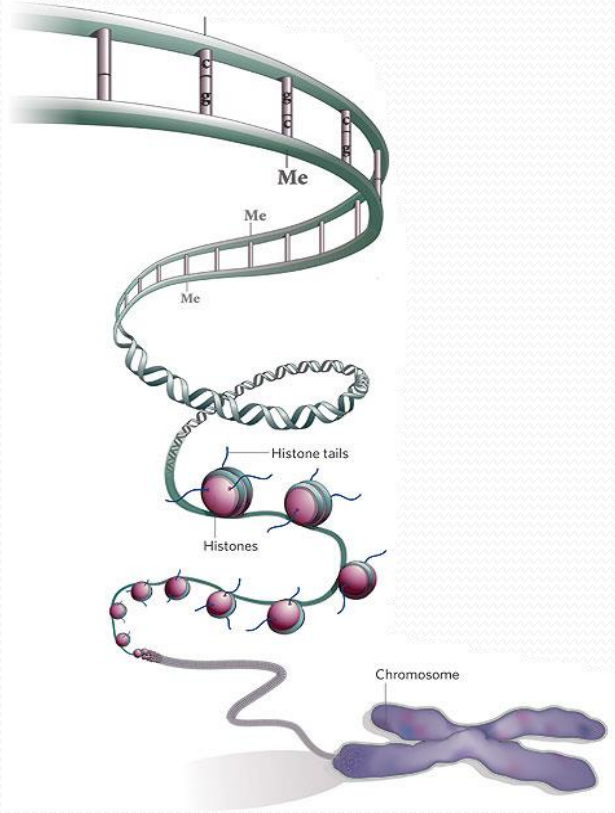
Intensive, deep, repeated phenotyping



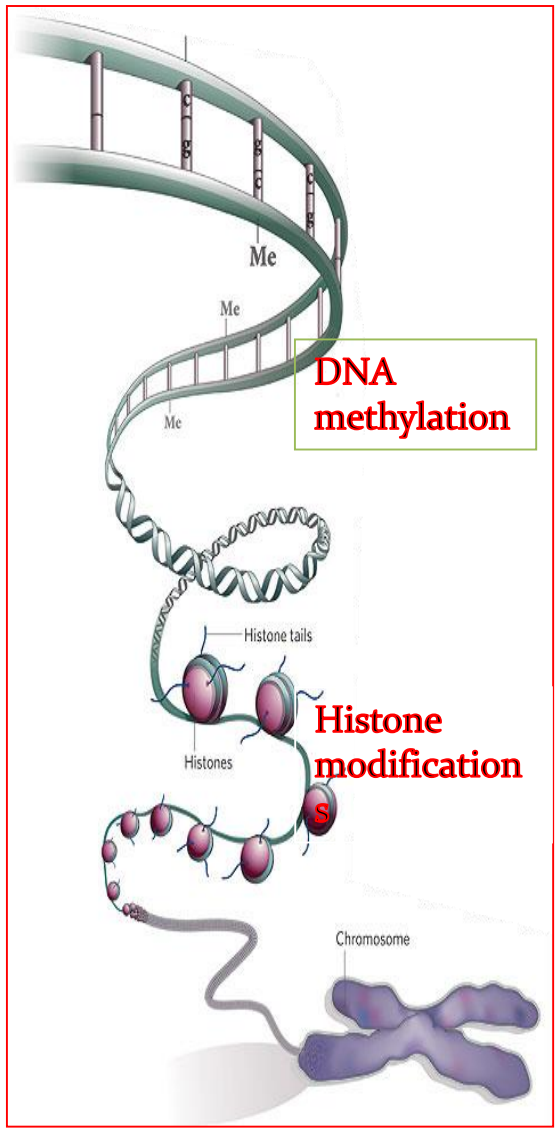
Courtesy of Professor Chan Shiao-yng

GENES OR EPIGENES?

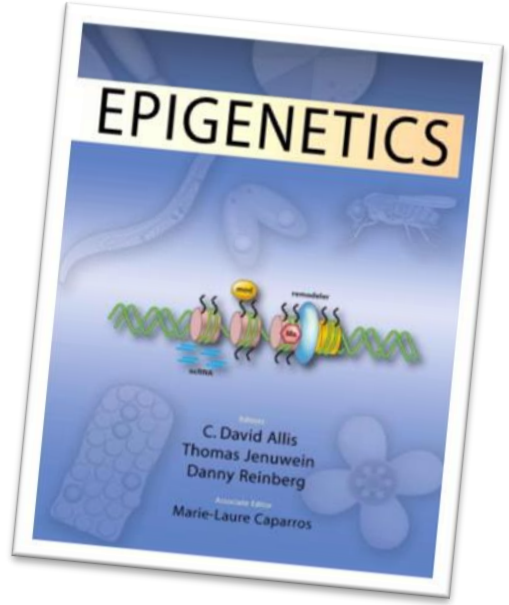
PRE-PROGRAMMING FOR DIABETES *IN UTERO*



Epigenetics: A New Paradigm for Type 2 DiabetesPrevention



- The study of heritable changes in gene function that occur without a change in the sequence of the DNA
- Epigenetics - how we eat and live can change the way our genes behave
- The maternal environment may be the key to stemming the epidemic



ORIGINAL ARTICLE

Famine Exposure in the Young and the Risk of Type 2 Diabetes in Adulthood

Annet F.M. van Abeelen,[1,2] Sjoerd G. Elias,[1] Patrick M.M. Bossuyt,[2] Diederick E. Grobbee,[1] Yvonne T. van der Schouw,[1] Tessa J. Roseboom,[2,3] and Cuno S.P.M. Uiterwaal[1]

The developmental origins hypothesis proposes that undernutrition during early development is associated with an increased type 2 diabetes risk in adulthood. We investigated the association between undernutrition during childhood and young adulthood and type 2 diabetes in adulthood. We studied 7,837 women from Prospect-EPIC (European Prospective Investigation Into Cancer and Nutrition) who were exposed to the 1944–1945 Dutch famine when they were between age 0 and 21 years. We used Cox proportional hazards regression models to explore the effect of famine on the risk of subsequent type 2 diabetes in adulthood. We adjusted for potential confounders, including age at famine exposure, smoking, and level of education. Self-reported famine exposure during childhood and young adulthood was associated with an increased type 2 diabetes risk in a dose-dependent manner. In those who reported moderate famine exposure, the age-adjusted type 2 diabetes hazard ratio (HR) was 1.36 (95% CI [1.09–1.70]); in those who reported severe famine exposure, the age-adjusted HR was 1.64 (1.26–2.14) relative to unexposed women. These effects did not change after adjustment for confounders. This study provides the first direct evidence, using individual famine exposure data, that a short period of moderate or severe undernutrition during postnatal development increases type 2 diabetes risk in adulthood. ***Diabetes* 61:2255–2260, 2012**

and the risk of type 2 diabetes (5). Furthermore, there is ample evidence of an association between small body size at birth and the development of impaired glucose tolerance and insulin resistance in adult life (6,7). The Dutch Famine Birth Cohort Study shows that people born around the time of the Dutch famine, who had been undernourished during gestation, had impaired glucose tolerance in later life (8).

The long-term effects on adult health of disturbances during postnatal development, including undernutrition, are less well studied. The combination of low birth weight and rapid childhood growth has been associated with an increased central fat deposition and insulin resistance (9). A study among girls from Barcelona shows that those who had relatively lower birth weights and showed rapid childhood growth had increased central fat mass and became insulin resistant (10). The Helsinki Birth Cohort Study shows that the combination of low weight at birth, low weight gain during infancy, and rapid childhood growth was associated with an increased risk of type 2 diabetes in adult life (11–13). An ecological study among people who were exposed to the Chinese famine finds an association between severe famine exposure during early childhood and an in-

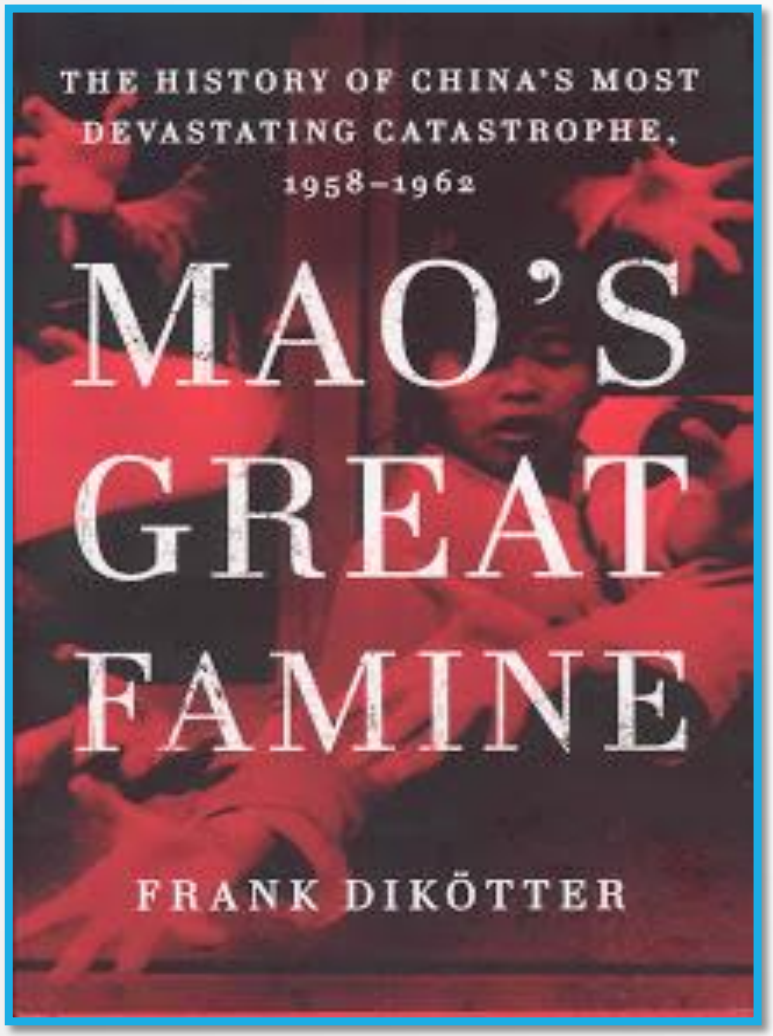
GESTATIONAL EXPOSURE TO FAMINE: INCREASED RISK OF ADULT HEALTH

- The tragic circumstances of the Dutch Hunger Winter of 1944-1945 created a unique opportunity to demonstrate that exposure to famine during gestation and childhood has life-long effects on health risk in adults.

- Exposure to famine resulted in adult life increased risk of:

1. Type 2 diabetes
2. Obesity
3. Coronary heart disease
4. Atherogenic lipid profile
5. Hypertension
6. Microalbuminuria
7. Schizophrenia & affective disorders

The Chinese Famine: 1958 -1962



- Exposure to the Chinese famine during foetal life or infancy was associated with an increased risk of diabetes in adulthood.
- This associations was stronger among subjects with a Western dietary pattern or who were overweight in adulthood.

Li Y et al Diabetes Care 34(4): 1014-8,2011

THE WINDSOR CASTLE CONSULTATION

ANALYSIS

Time for the UK to commit to tackling child obesity

The UK government missed an opportunity for global leadership on child obesity. Now it's time to commit, say **Mark Hanson and colleagues**

Mark Hanson *British Heart Foundation professor*[1], Edward Mullins *specialty trainee year 6 in obstetrics and gynaecology*[2], Neena Modi *professor of neonatal medicine*[3]

[1]Institute of Developmental Sciences, University of Southampton, Tremona Road, Southampton SO16 6YD, UK; [2]Queen Charlotte's and Chelsea Hospital, Imperial College Healthcare NHS Trust, Du Cane Road, London W12 0HS, UK; [3]Department of Medicine, Imperial College London, Chelsea and Westminster Campus, 369 Fulham Road, London SW10, UK,

The UK government published its report *Childhood Obesity: a Plan for Action*, after a protracted delay, on 18 August 2016, when parliament was in recess and the nation was focused on the success of Team GB at the Rio Olympics.[1] The plan received very little media coverage or public response. There was, however, an immediate outcry from the medical and public health communities, who had hoped for much more.[2-6] The draft version had been 50 pages in length, but the published plan ran to just 10 pages; strong actions were conspicuous by their absence, and the desired discussion of anti-obesogenic medicine had been watered down to an emphasis on voluntary actions by industry, consumers, and schools.

One of the most important omissions was reference to the recommendations of the World Health Organization Commission on Ending Childhood Obesity (ECHO).[7] The final ECHO report, published in January 2016, was the culmination of about 18 months of evidence review and wide consultation. It was presented at the World Health Assembly in May 2016,[8] where a decision was made to request the director general to develop an implementation plan to guide further action on the recommendations, in consultation with member states. The implementation report is now available.[9]

A missed opportunity for global leadership

The ECHO report directs specific actions and responsibilities to governments of member states (box 1). By not referring to it in the obesity report, the UK government missed an opportunity to show global leadership in child health by announcing advance commitment to implementing some of the ECHO commission's recommendations—for example, an industry levy on sugar sweetened beverages, nutrient profiling to identify healthy and unhealthy foods, clearer food labelling, and promotion of physical activity in schools. Other recommendations, such as stronger controls on advertising, mandatory food reformulation, and nutrition education were absent from the report.

In June 2016, while waiting for the UK government to publish its report on child obesity, an international group of researchers, policy makers, and representatives of research funders, professional organisations, and WHO met at St George's House, Windsor Castle, under the aegis of the Royal College of Paediatrics and Child Health and the University of Southampton. The group discussed effective action to combat childhood obesity, nationally and globally. This paper arose from that discussion.

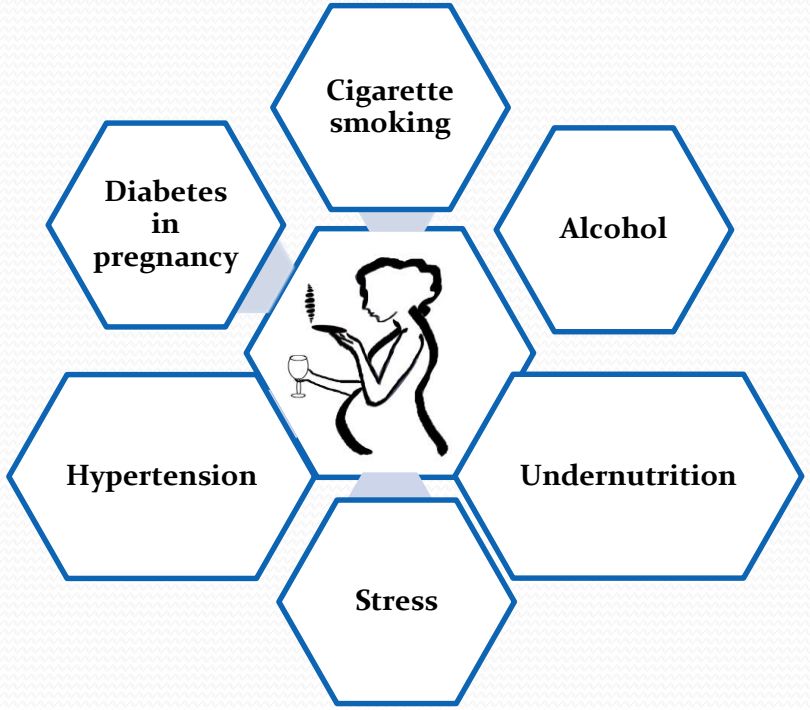
What's missing from the government's plan?

Overweight and obese children are likely to remain so as adults,[10] when they will be at greater risk of non-communicable diseases such as type 2 diabetes, cardiovascular disease, some cancers, asthma, and other atopic conditions.[11 12] The economic consequences of child overweight and obesity relate not only to direct healthcare costs[13] but to a range of indirect healthcare costs extending across the life course and reducing longevity. The government's plan notes the short and long term damage to the health of individuals from obesity, but it fails to recognise that overweight and obesity in children and young people are driven by multiple modifiable biological, behavioural, environmental, and commercial factors, some of which operate before conception and birth.[14] Nor does it recognise that the harm extends across generations. This failure represents a major lost opportunity for effective prevention.

Many communities typically affected by undernutrition are now experiencing overnutrition through changes in diet, sedentary lifestyles, and a lack of focus on promoting broader health. In these settings, the adverse health effects of poor maternal health and childhood stunting are amplified by the increased risk of later overweight and obesity.[15] Furthermore, the rising

Correspondence to: M Hanson m.hanson@soton.ac.uk

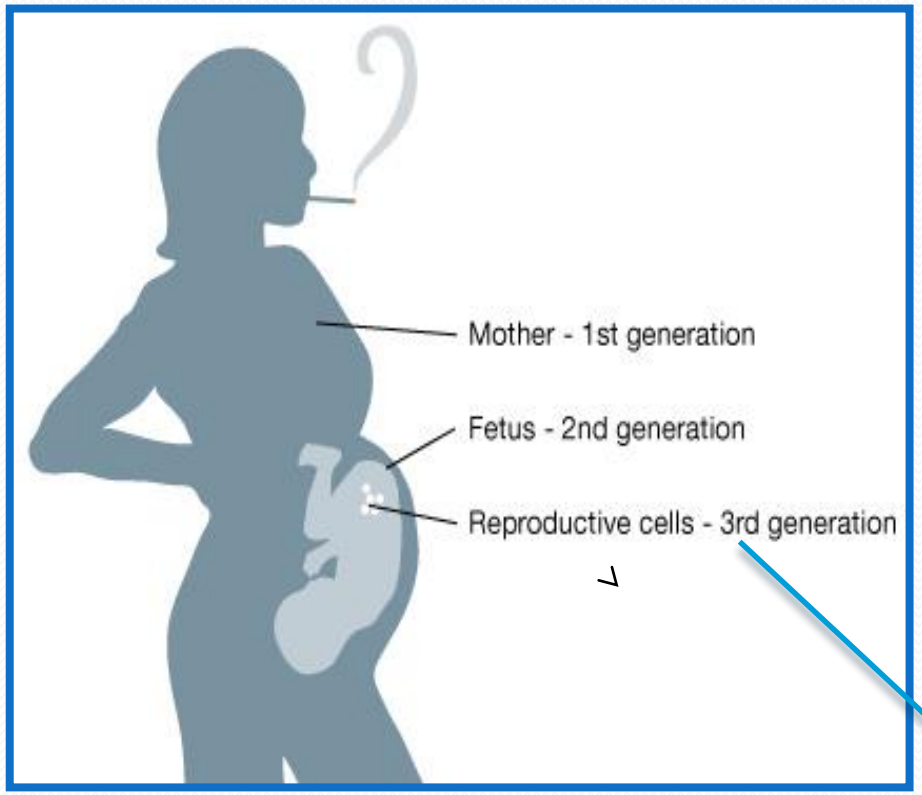
A Healthy Pregnancy Provides Unique Opportunities for Type 2 Diabetes Prevention



Experimental rodent studies show that these effects persist through many generations – intergenerational

THE END

FOETAL PROGRAMMING & INTERGENERATIONAL RISK



Smoking

Alcohol

Malnutrition

Under-nutrition

Stress

Hypertension

Type 2 & Gestational Diabetes

Experimental animal studies… these effects persist through many generations –risk is **Intergenerational**