

Long Term Effects on Offspring of Maternal Obesity and DM2

The Perfect Storm

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Long Term Effects of Maternal Obesity and DM2 on Offspring

- ◆ The effects of:
 - Low Birth weight on development of DM2 in adults
 - Maternal obesity on children, adolescents, and adult offspring
 - Maternal diabetes on children, adolescents and adult offspring

Abbreviations Used

- ◆ DM – diabetes
- ◆ GDM – gestational diabetes
- ◆ PGDM – diabetes before pregnancy
- ◆ IGT - impaired glucose tolerance
- ◆ BW – birth weight
- ◆ SGA – small for gestational age
- ◆ LGA – large for gestational age
- ◆ IDE – intrauterine diabetes exposure

Fetal Programming of Diabetes

- ◆ Fetal programming – the process influencing long term fetal outcomes
- ◆ New specialty – Developmental Origins of Health and Disease (DOHaD)
- ◆ The intrauterine environment dictates how genes function
- ◆ Epigenetic – the processes which govern evolution of an individual phenotype from the genome

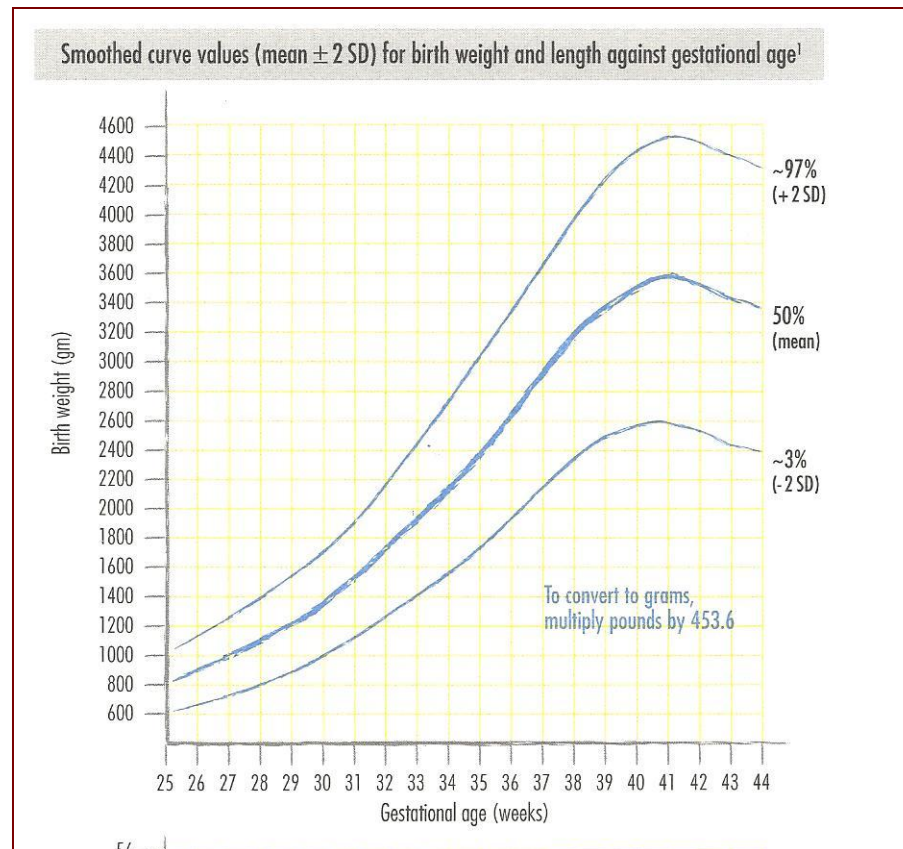
Yajnik, CS. Diabetes Care 33:1146, 2010

Fetal Programming

- ◆ “A stimulus or an insult at a critical and sensitive period of early life permanently alters the organisms physiology and metabolism.”
- ◆ “Programming may be induced by nutritional, metabolic, and hormonal events.”
- ◆ “The fetus exposed to maternal diabetes is “programmed” to display abnormal glucose tolerance later in life.”

Fetita L et al. JCEM:3721, 2006.

The Effect of Low Birth Weight



Intrauterine Undernutrition

- ◆ SGA - Small for gestational age
 - <2500 gm
 - Thrifty phenotype
 - Twin studies – lower BW twin has greater risk of DM2
 - SGA + catch-up growth in childhood causes high risk of DM2



<http://newborns.stanford.edu/images/sga1.jpg>

Low Birth Weight and DM2

- ◆ 1992 UK - 64 year old men who were smallest at birth were 6X more likely to have DM2
- ◆ Monozygotic twin discordant for diabetes – DM twin had significantly lower BW
- ◆ Dutch Hunger Winter 1944-1945 – poor maternal nutrition especially 3rd trimester caused decreased fetal growth. Then at 50 years old was associated with poor glucose tolerance and insulin resistance.

Reusens B et al. Current Drug Targets. 8:935, 2007.

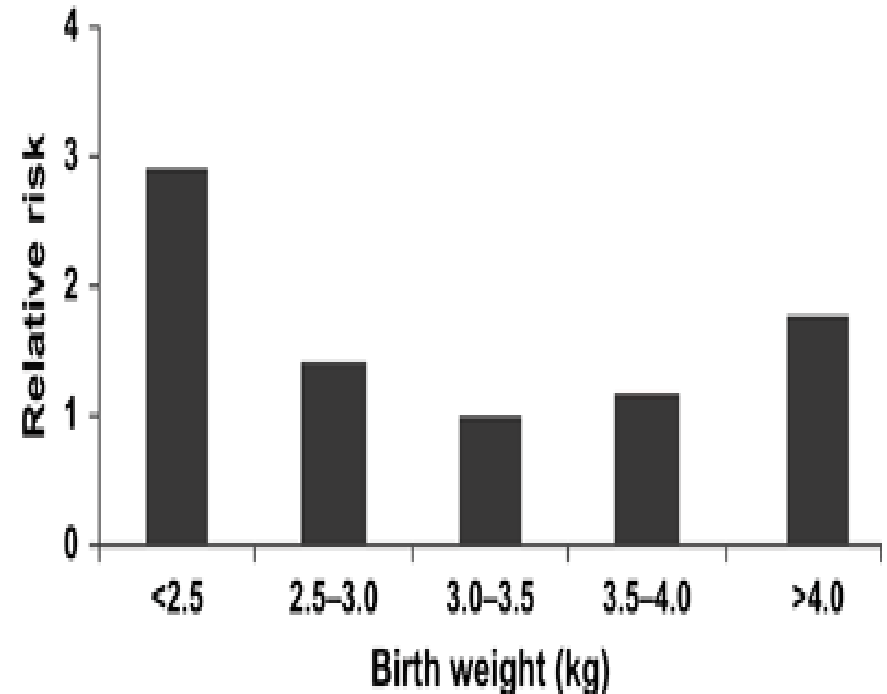
Low Birth Weight and DM2

- ◆ Catch up growth
 - South Africa – LBW with rapid childhood weight gain had worst glucose tolerance
 - India – LBW but were the heaviest at age 8 were most insulin resistant
 - Finland – LBW but accelerated growth after age 7 years – most likely to have DM
 - SGA had increased insulin sensitivity at birth but by 3 years were more insulin resistant than AGA

Reusens B et al. Current Drug Targets. 8:935, 2007.

Birth Weight and DM2 Risk Youth

- ◆ U-shaped curve for BW and risk of DM2 in childhood
- ◆ Both SGA and LGA are associated with DM2 later in life



Shaw J. Ped Diab: 8(Supp 9):7-15, 2007

Wei JN et al. Diab Care 26:343, 2003

Summary: Low Birth Weight

- ◆ **Low Birth Weight** leads to increased risk of DM2 and insulin resistance
- ◆ Low Birth Weight **followed by catch up growth and weight gain** lead to increased risk of DM and insulin resistance
- ◆ **Low and High Birth Weight** both associated with DM2 in childhood

Thrifty Phenotype Hypothesis

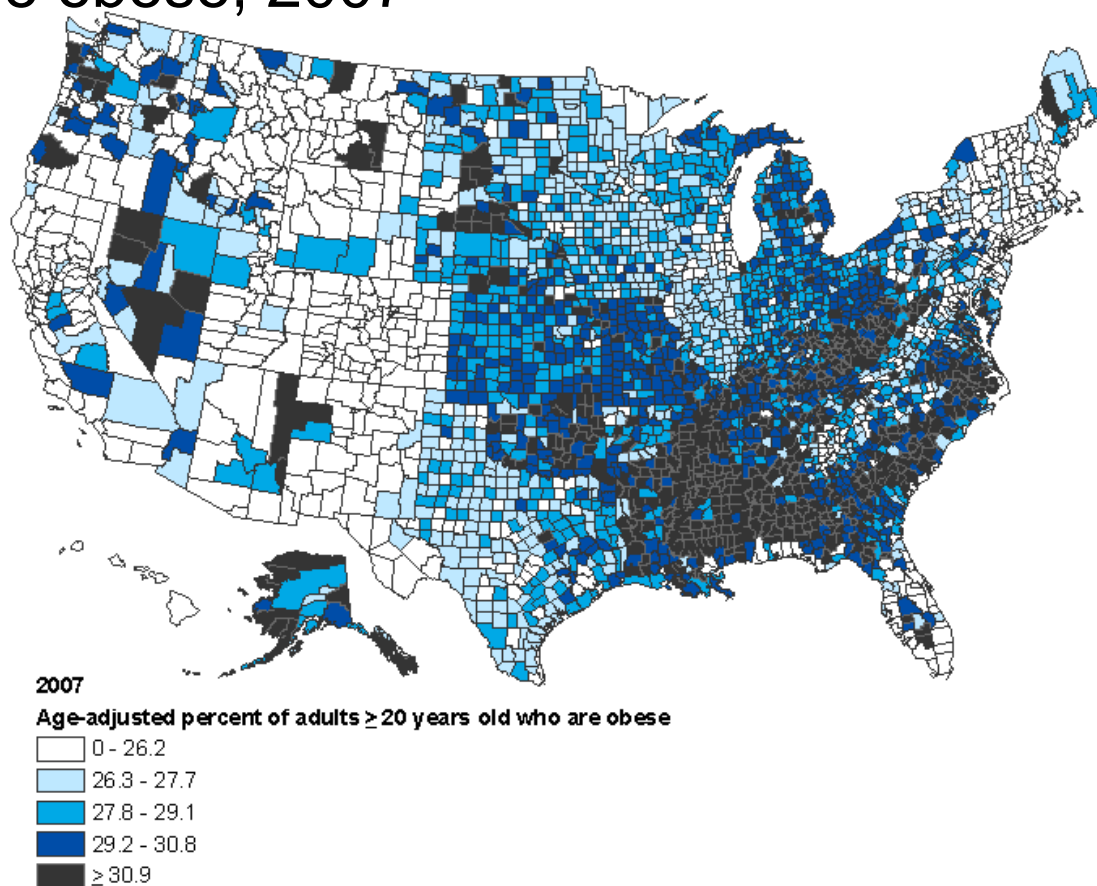
- ◆ Two essential elements
 - Poor fetal nutrition resulting in changes of key organs beneficial to survival in conditions of poor postnatal nutrition.
 - Postnatal adequate or excessive nutrition causing these otherwise beneficial adaptations to result in adult diseases (DM2, hypertension, and ischemic heart disease.) Reusens B et al. *Current Drug Targets*. 8:935, 2007.



What We Already Know

About Obesity and Diabetes

Age-adjusted percentage of adults aged ≥ 20 years who are obese, 2007



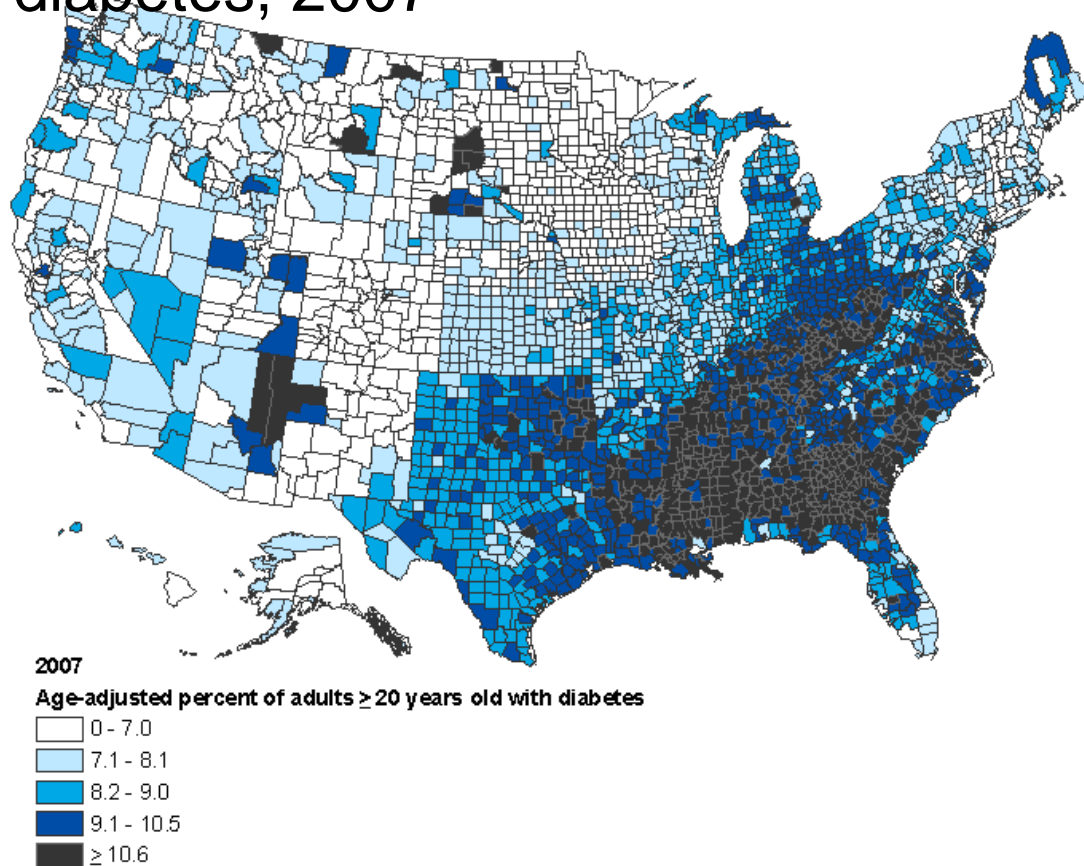
MMWR 58:1259-1263, 2009



CDC's Division of Diabetes Translation. National Diabetes Surveillance System available at <http://www.cdc.gov/diabetes/statistics>



Age-adjusted percentage of adults aged ≥ 20 years with diagnosed diabetes, 2007



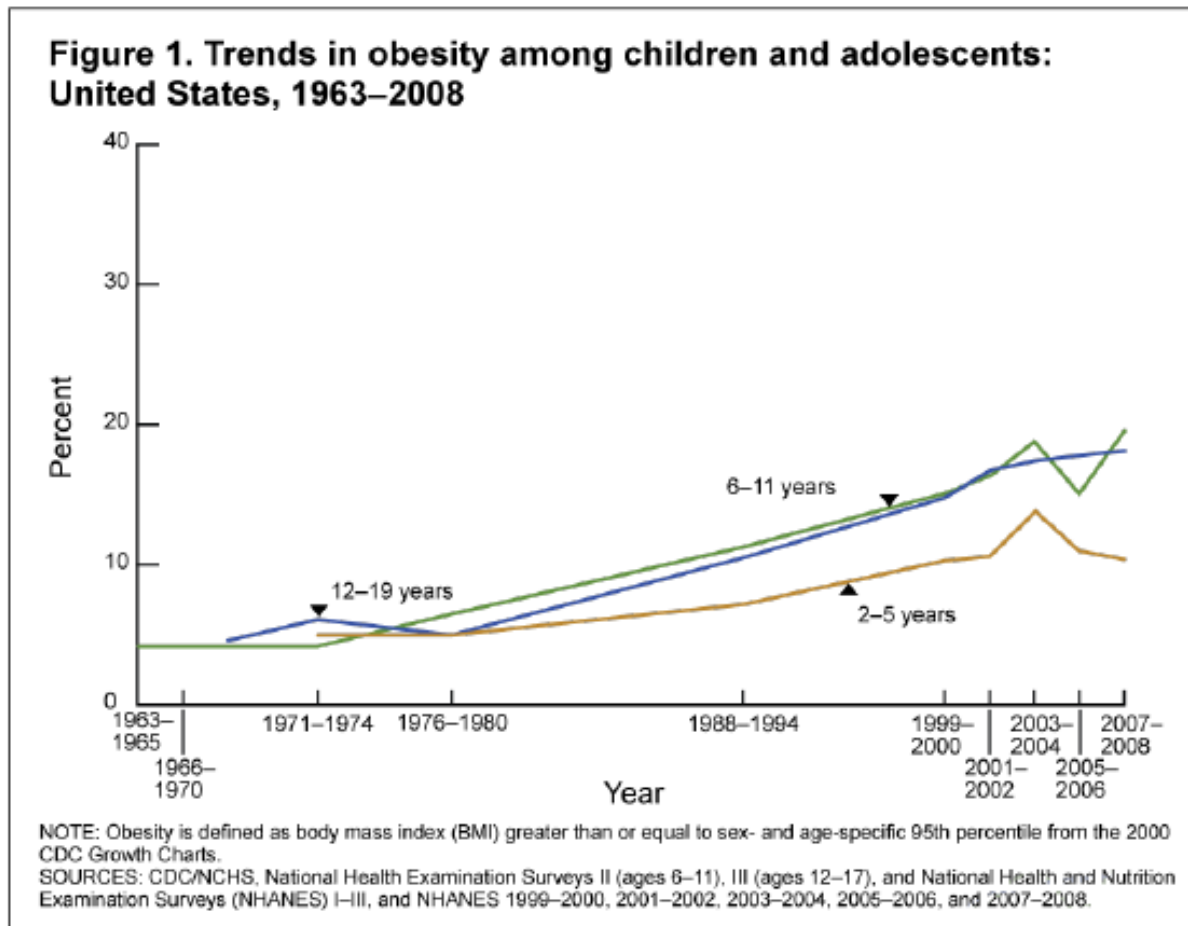
MMWR 58:1259-1263, 2009



CDC's Division of Diabetes Translation. National Diabetes Surveillance System available at <http://www.cdc.gov/diabetes/statistics>



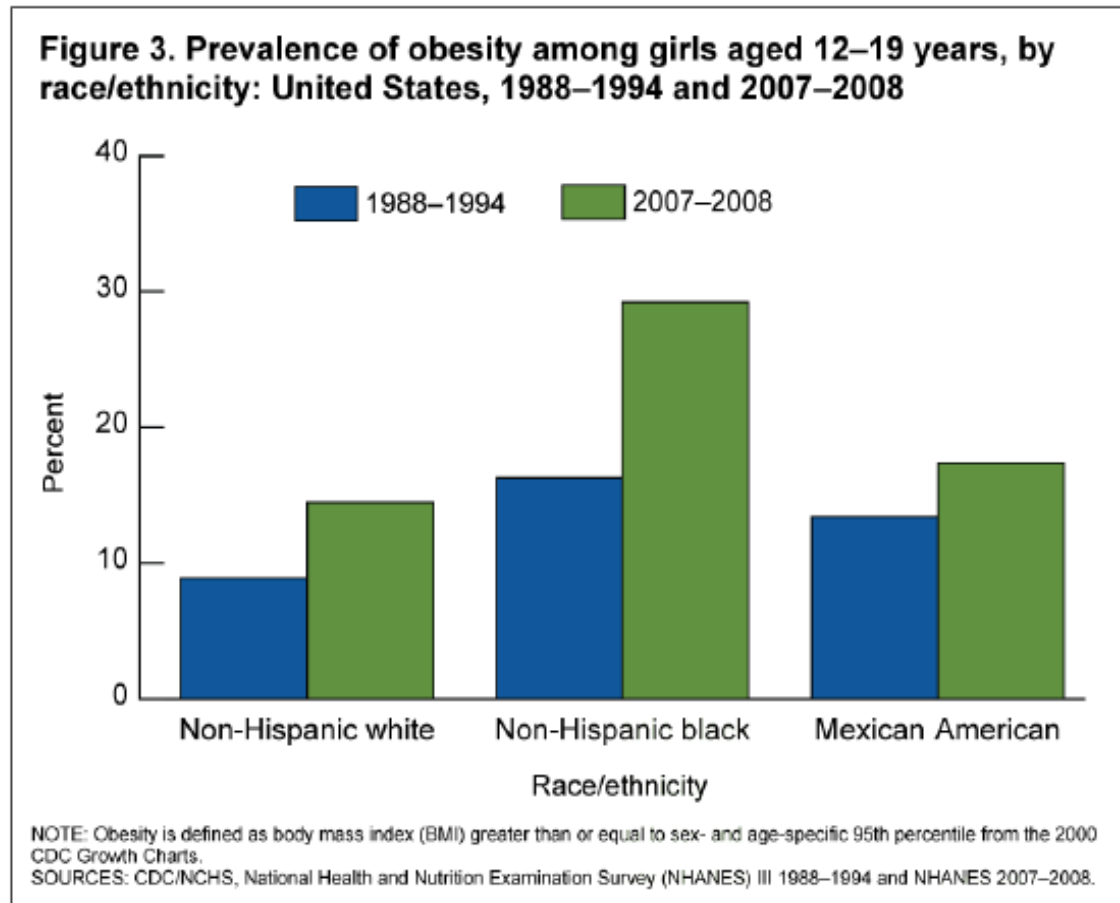
Trends in Obesity among Children and Adolescents and Adolescents



CDC's Division of Diabetes Translation. National Diabetes Surveillance System available at <http://www.cdc.gov/diabetes/statistics>



Prevalence of Obesity Among Girls 12-19 years old



CDC's Division of Diabetes Translation. National Diabetes Surveillance System available at <http://www.cdc.gov/diabetes/statistics>



The Effect of Maternal Obesity



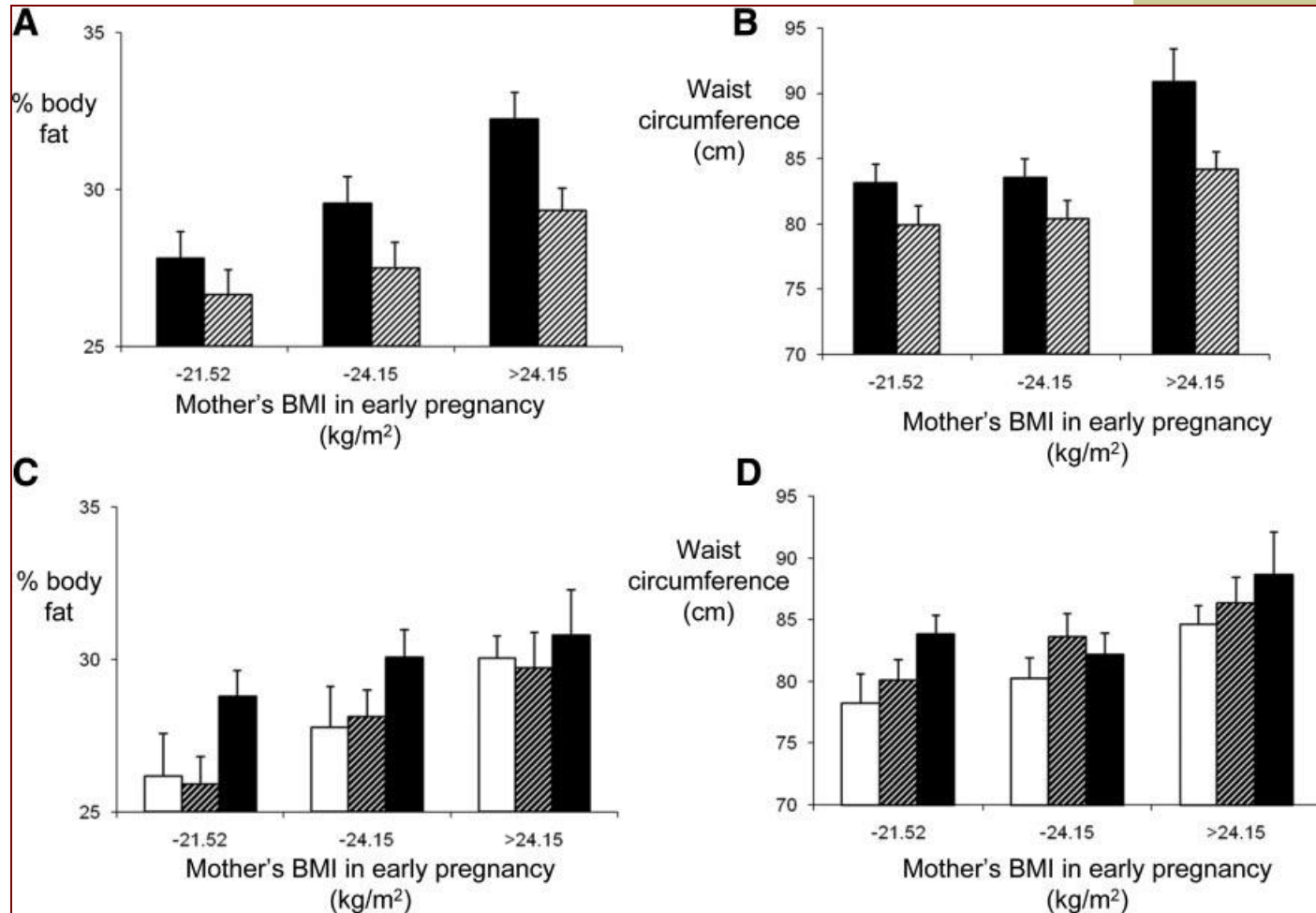
Obesity Leads to Obesity

- ◆ 800 mothers and offspring
- ◆ Best model to predict obesity
 - Childhood (4-5 years):
 - Birthweight
 - Weight gain in infancy
 - Delivery type
 - Adolescence (9-14 years):
 - Maternal smoking status
 - Gestational weight gain
 - Weight gain during infancy
 - Young Adult (19-20 years):
 - Maternal smoking status
 - Gestational weight gain
 - Birth weight

◆ Maternal obesity is the strongest predictor of obesity at all times studied

Rooney BL Matern Child Health J 2010
Oct 7 epub ahead of print

Maternal Obesity and Offspring Adiposity in Young Adults



Maternal Obesity and Offspring Adiposity in Young Adults

- ◆ 276 adults. Age 27-30
- ◆ Greater offspring % body fat and waist circumference were independently associated with:
 - Higher maternal BMI
 - Greater gestational weight gain
 - First born (even though BW is less)
- ◆ Adiposity in adulthood is influenced by prenatal influences independently of current lifestyle factors.
- ◆ **Impact of maternal adiposity on offspring obesity risk persists into adulthood.**

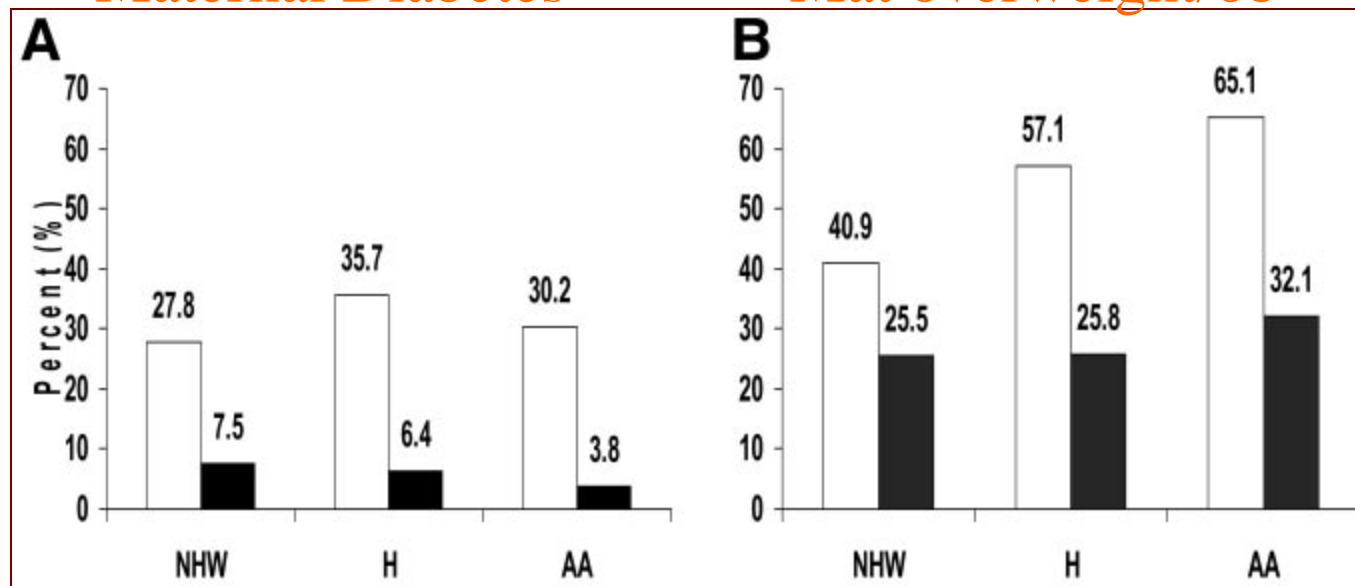
Reynolds JCEM 95:5365-69, 2010

Intrauterine Exposure of DM2 Youth to Maternal DM2 and Ob

Percentage of youth exposed in utero to:

Maternal Diabetes

Mat overweight/ob



White box DM2 Black box control

Intrauterine Exposure of DM2 Youth to Maternal DM2 and Ob

- ◆ Intrauterine exposures to maternal obesity are **strongly associated** with DM2 in youth independent of diabetes during pregnancy.
- ◆ Overall, 47.2% of DM2 in youth could be attributed to intrauterine exposure to maternal diabetes and obesity.
- ◆ **Prevention efforts** need to target, in addition to childhood obesity, the increasing number of pregnancies complicated by obesity and diabetes.

Dabelea Diab Care 31:1422-1426,
2008

Maternal Surgical Weight Loss

- ◆ Maternal Bariatric Surgery - biliopancreatic diversion.
- ◆ Studied children born after maternal surgery (AMS) compared to children born before maternal surgery (BMS)
- ◆ Recruited in Quebec from July 2007–January 2008
- ◆ Study cohort
 - Mothers 49
 - Children BMS 54
 - Children AMS 57

Maternal Surgical Weight Loss

- ◆ Maternal effects of bariatric surgery
 - Lower prepregnancy weight, BMI
 - Lower gestational weight gain
 - Lower glucose & lipids
 - Reduced pregnancy complications (GDM, HTN, and preeclampsia)
- ◆ Effects on children
 - AMS compared to BMS
 - Reduced birth weight (>4 kg, 1.8% cf to 14.8%)
 - Lower BMI (10.5% >98%tile cf to 35.2%)
 - Lower lipids
 - Lower markers of insulin resistance
 - Lower inflammatory markers
 - Higher ghrelin, lower leptin

Smith JCEM 94:4275-83, 2009

Summary: Maternal obesity

- ◆ Maternal obesity is the **strongest predictor of obesity** in child, adolescent, young adult
- ◆ Intrauterine exposure to maternal obesity are **strongly associated with DM2 in youth**
- ◆ Children born to obese mothers **after bariatric surgery** have lower BW and BMI than siblings born presurgery

The Effect of Maternal Diabetes

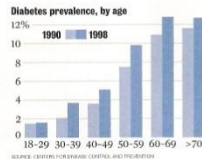
SOCIETY

An American Epidemic

Diabetes

The silent killer: Scientific research shows a 'persistent explosion' of cases—especially among those in their prime
BY JERRY ADLER AND CLAUDIA KALB

SOMETHING TERRIBLE WAS HAPPENING TO YOLANDA BENTEZ'S eyes. They were being poisoned; the fragile capillaries of the retina attacked from within and were leaking blood. The first symptoms were red lines, appearing vertically across her field of vision; the lines multiplied and merged into a haze that shut out light entirely. "Her blood vessels inside her eye were popping," says her daughter, Jannette Roman, a Chicago college student. Bentez, who was in her late 40s when the problem began four years ago, was a cleaning woman, but she's had to stop working. After five surgeries, she has regained vision in one eye, but the other is completely useless. A few weeks ago, awaking one night in a hotel bedroom, she walked into a door, setting off a paroxysm of pain and nausea that hasn't let up yet. And what caused this catastrophe was nothing as exotic as pesticides or emerging viruses. What was poisoning Bentez was sugar.



Heredity

Genes help determine whether you'll get diabetes. In many families, multiple generations are struck. But heredity is not destiny—especially if you eat well and exercise.

FAMILY PLAQUE: Bentez (left) and Roman. Bentez's mother and two brothers died from complications of the disease.



DM2 – The Role of Maternal Inheritance

- ◆ Adults with DM2 had a higher prevalence of DM2 on the maternal side
- ◆ In women with GDM a higher frequency of diabetes was reported in the mothers
- ◆ In the UK and France, people with DM2 have twice as many mothers as fathers with DM2

Fetita, L et al. JCEM 91:3718, 2006.

Infant of a Diabetic Mother

- ◆ Large for gestational age
 - >4000 gm
 - Genetic and environmental risk of DM2 associated with high BW and maternal diabetes in pregnancy



Shaw J. Ped Diab: 8(Supp 9):7-15,
2007

<http://img87.imageshack.us/img87/7109/infantofdiabeticmother.jpg>

GDM – Offspring with Obesity

At 15-19 year of age 58% of offspring of DM2 mothers weighed 140% or more of their ideal weight compared to to 17% with no DM2.

Pettitt, DJ et al. NEJM 308:242, 1983

By 8 years old, 50% of offspring of DM mothers had weights >90%tile compared to offspring of non DM mothers.

Silverman BL et al. Diab 40:121, 1991

Range of Maternal Glycemia: Risk of Obesity in Childhood

- ◆ 9439 women in a large multiethnic US population (Hawaii and Northwest/Kaiser)
- ◆ 1995-2000
- ◆ Universally screened for GDM with 50 gm glucose challenge test (GCT)
- ◆ Weight measured in children ages 5-7 years

Hillier, Diabetes Care 30:2287-2292, 2007

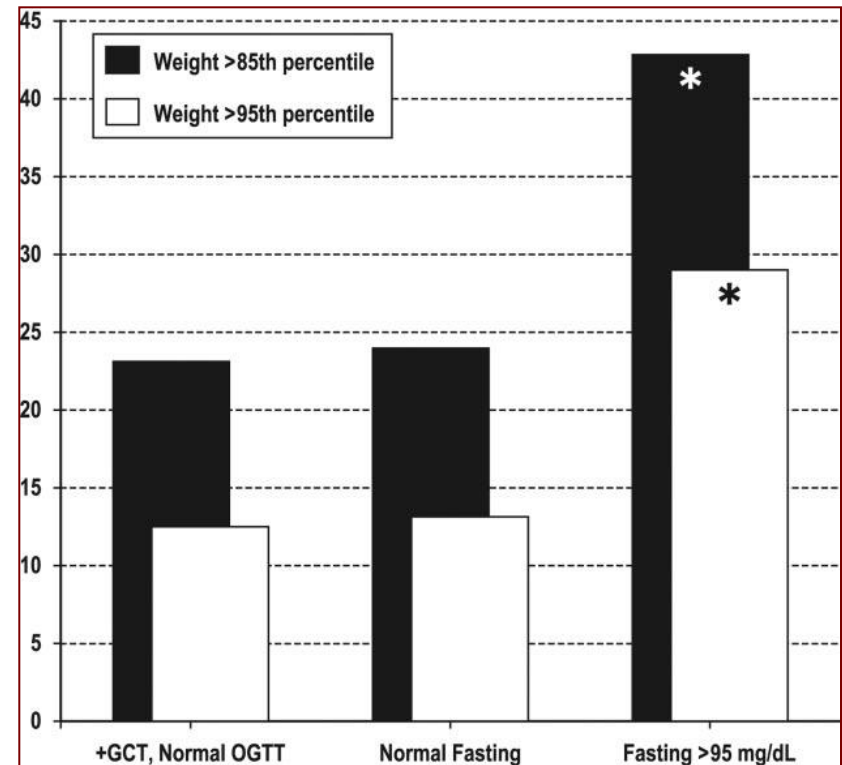
Range of Maternal Glycemia: Risk of Obesity in Childhood

◆ Results:

- Increasing maternal glycaemic level was associated with a greater prevalence of macrosomia
- Children who were macrosomic at birth had a higher prevalence of childhood obesity irrespective of maternal glycaemic level
- The highest quartile of hyperglycemia on GCT was associated with higher level of childhood obesity compared to lowest quartile ($P < 0.0001$)

Range of Maternal Glycemia: Risk of Obesity in Childhood

- ◆ The risk of childhood obesity was nearly double when mothers had FBG >95 mg/dl
- ◆ Increasing maternal hyperglycemia associated with increased childhood obesity was significant only among children who were **not macrosomic** at birth

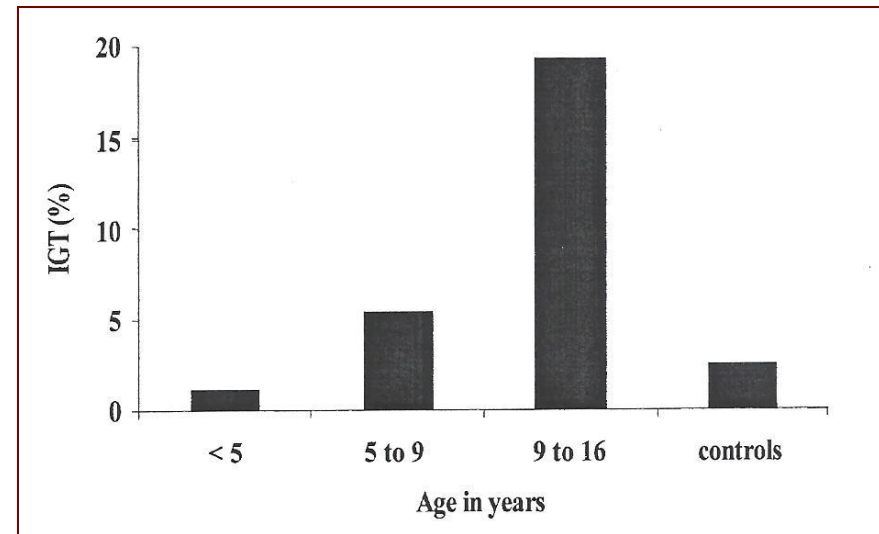


Summary: DM2 in pregnancy

- ◆ Adults with DM2 have **higher frequency of diabetes in mothers** compared to fathers
- ◆ Children **macrosomic** at birth had higher prevalence of childhood obesity
- ◆ When not macrosomic, the risk of childhood obesity nearly **doubled** when maternal **FBG >95 mg/dl**.

IGT in Offspring of Maternal DM (Multiethnic)

- ◆ Diabetes in Pregnancy Study at Northwestern Univ in Chicago
- ◆ **Prevalence of IGT** in offspring of diabetic mothers in three age groups and controls (age 10-16 yrs)



IGT in Offspring of Maternal DM (Multiethnic)

- ◆ Mothers had pregestational DM (PGDM) either DM1 or DM2 or gestational DM (GDM)
 - In PGDM the prevalence of IGT rose from 9.4% at 1-4 years old to 17.4% at 5-9 years old
 - In GDM, the prevalence of IGT rose from 11.1% at 1-4 years old to 20% at 5-9 years old

Plagemann A et al. Diabetologia 40:1094, 1997

- In PGDM or GDM , offspring had 36% prevalence of IGT at 16 years old.

Silverman BL et al. Diab Care 18:611, 1995

DM2 – Fetal Exposure to GDM

◆ Pima Indians

- Offspring of DM2 mothers had greater frequency of diabetes compared to those with DM2 fathers

Lindsay RS et al. Diab 49:445, 2000

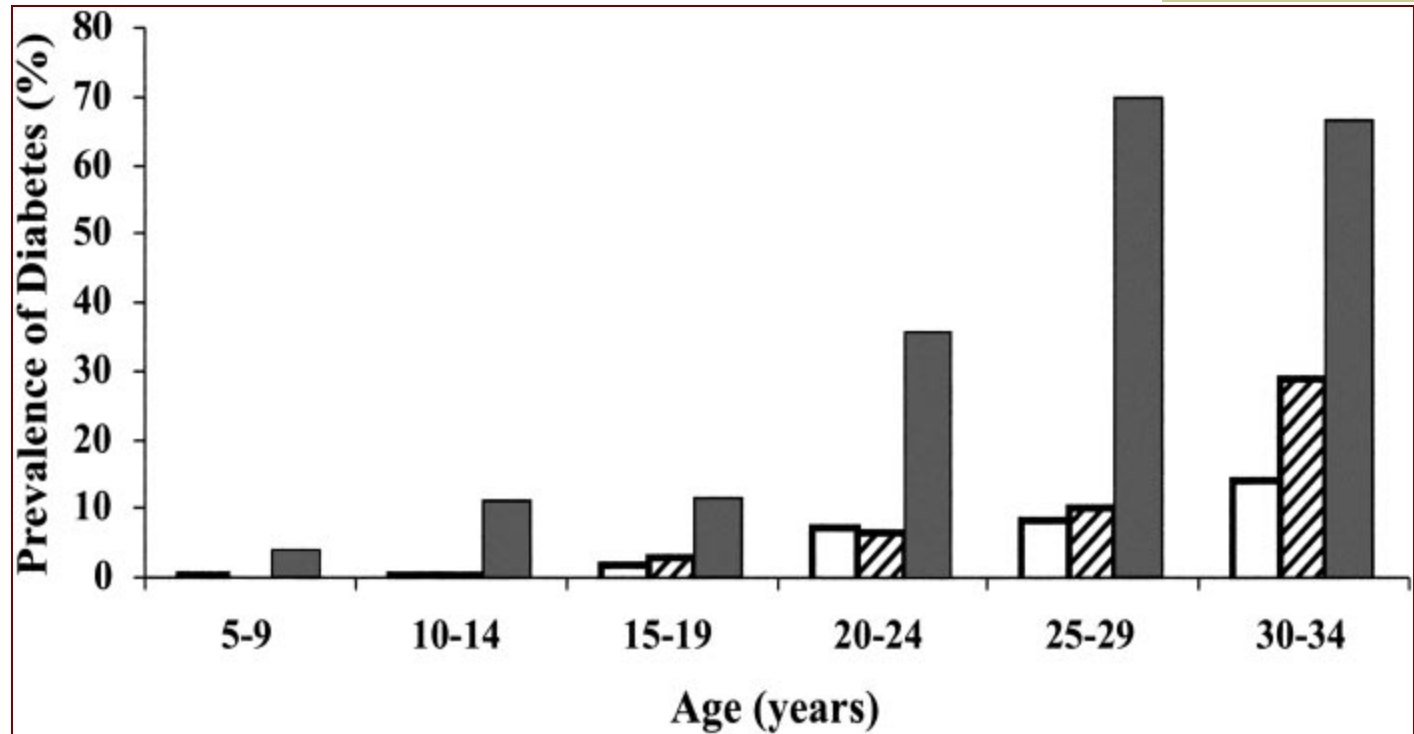
- At age 20-24 years, if mother had GDM, 45% had DM2 compared to 8.6% in PGDM and 1.4% in non DM.

Pettitt, DJ et al. Diabetes 37:622, 1988.

- At age 25-34 years, if mother had GDM, 70% had DM2 compared to 15% without GDM

Dabeala D et al. J Mat Fet Med 9:83, 2000

Prevalence of DM2 in Offspring of Maternal Diabetes



No diabetes (open)
Diabetes (solid)

PreDiabetes (hatched)
Dabelea J Pediatr Endoc 14:1085, 2001

Risk of DM2 in Maternal Diabetes

- ◆ Pima Nuclear Families with children born before and after Mom developed DM2
 - Compared to full siblings born **before** maternal DM2
 - **After** maternal DM2, 3.7 times higher risk of developing DM2
 - **After** maternal DM2, higher BMI

Dabelea D et al. Diabetes 49:2208, 2000. Fetita L et al. JCEM 91:3718, 2006

Risk of DM2 in Maternal Diabetes - Summary

- ◆ Conclusions: In Pima Indians
 - Intrauterine exposure to the diabetic environment increases risk of obesity and DM2 beyond that attributable to genetic factors. Fetita, L et al. JCEM 91:3719,2006.
 - The “epidemic” of DM2 in children “was almost entirely accounted for, statistically, by the increase in exposure to diabetes during pregnancy and the resultant increase in obesity”

Dabelea Diab Care 30:S169, 2007.

Summary: Pima Indians

- ◆ Offspring of Moms with GDM had **markedly increased** risk of DM2
- ◆ Children born to Moms with DM2 had **3.7X risk of DM2** and higher BMI
- ◆ Epidemic of DM2 in children “**almost entirely**” due to exposure to DM during pregnancy

Maternal DM2 and End-Stage Renal Disease in Young Adults

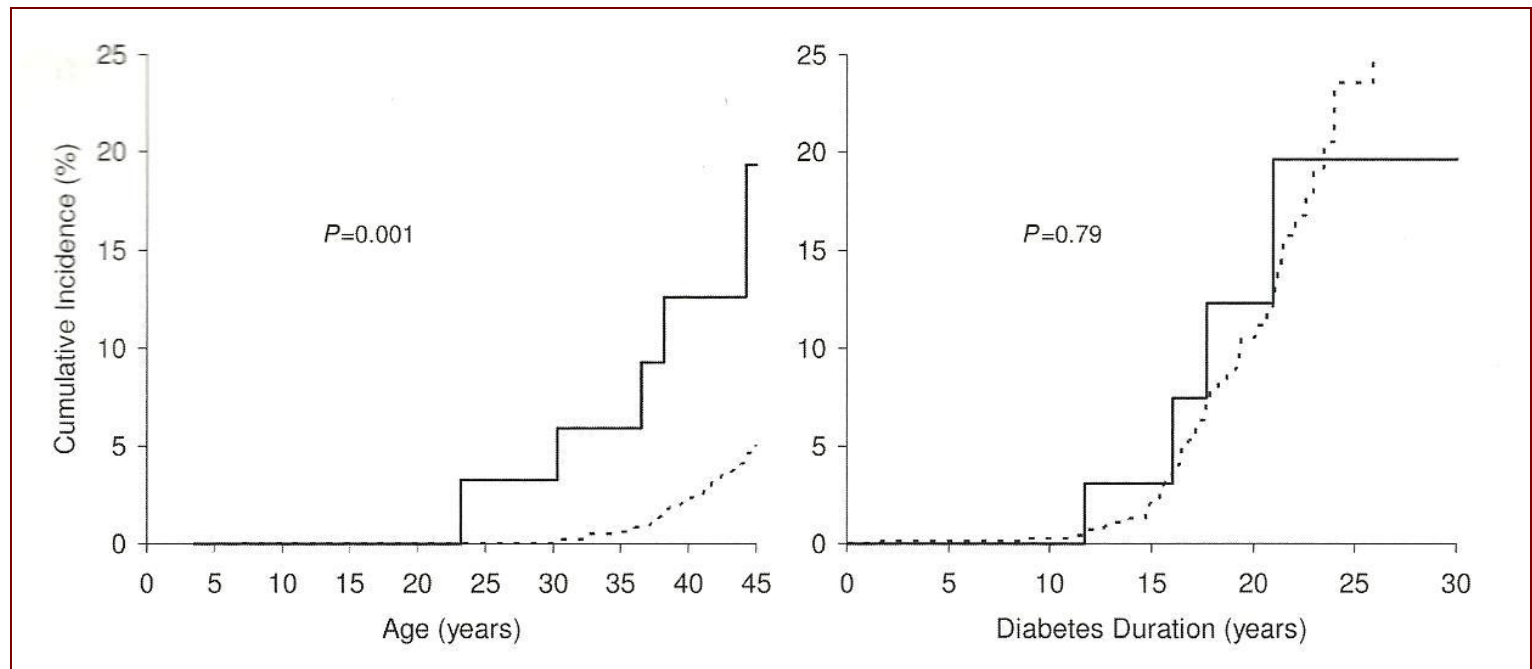
- ◆ Pima Indians – between 1965 and 2007 enrolled in study if >5 years old
- ◆ Diabetes defined as OGTT 2hr BG >200
- ◆ ESRD defined as initiation of renal replacement therapy or death
- ◆ 102 (5.5%) of 1850 persons with DM2 were offspring of diabetic mothers (IDE)
- ◆ ESRD occurred in 57, 5 of whom had IDE

Maternal DM2 and End-Stage Renal Disease in Young Adults

Cumulative incidence of diabetic ESRD

By age

Duration of Diabetes



Maternal DM2 and End-Stage Renal Disease in Young Adults

- ◆ Those exposed to DM2 intrauterine (IDE)
 - Were **younger at baseline** (17.5 yrs vs 34.2 yrs)
 - Exposure to IDE was associated with a **fourfold increase in the incidence of ESRD** in young adults with DM2 when adjusted for age and sex
 - This effect largely explained by their **earlier age of onset of DM2**. (With adjustment for age at DM2 onset, ESRD incidence was similar in the two groups)

Obesity and DM2 in Offspring of Mothers with Pediatric DM2

- ◆ Oji-Cree people - First Nation – Canada
- ◆ Offspring of the original cohort who were exposed to maternal DM2 in pregnancy
- ◆ Have unique polymorphism of the hepatic nuclear factor-1alpha(HNF-1alpha): glycine to serine substitution at codon 319
- ◆ Associated with a dose dependent decrease in age of onset of DM for each copy of the S319 allele

Obesity and DM2 in Offspring of Mothers with Pediatric DM2

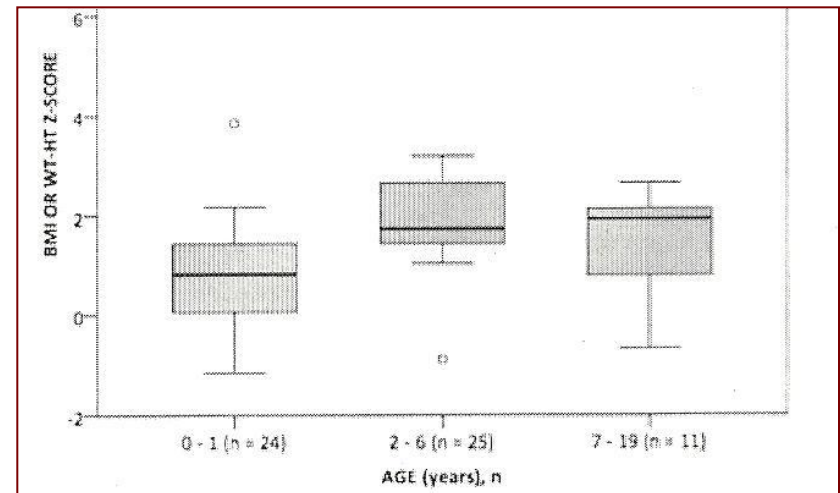
- ◆ Mutation in HNF-1alpha gene occurs in monogenic DM type 3 (MODY 3)
 - Single copy – lean with marked Beta cell deficiency and reduced insulin secretion
 - No homozygous reported ?lethal
- ◆ Oji-Cree youth heterozygous for S319, are obese at Dx and homozygous more closely fit the clinical description of MODY-3
- ◆ S319 polymorphism may cause a milder insulin secretory defect

Obesity in Offspring of Mothers with Pediatric DM2

◆ Mothers

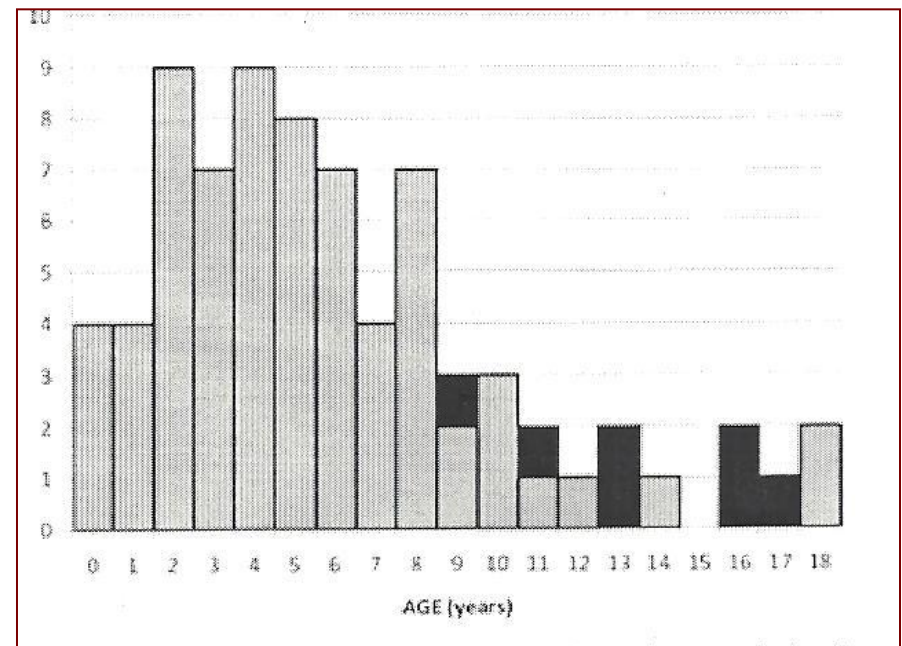
- Mean age Mothers at Dx of DM2 13.6 +/-2.2
- Mean age at birth of infant 22 +/- 3.9 years
- Mean duration DM2 8.6 +/- 4.6 years

- ◆ 32/36 children - 89% - age 2-19 were obese



DM2 in Offspring of Mothers with Pediatric DM2

- ◆ 76 offspring of 37 mothers with pediatric DM 2 <18 years old
 - 64% obese
 - 7/28 25% DM 7-19 yr
 - 6/14 43% DM 10-19 yr
- ◆ 5/7 obese all have 1 or 2 copies of G319S



Treatment of GDM

- ◆ 370/9439 multiethnic women in the US with GDM were treated with diet or diet/insulin
- ◆ Prevalence of obesity in 5-7 year olds
 - Maternal FBG >95 mg/dl was 20%
 - Treated GDM group was 17.3%
- ◆ Suggests treatment of GDM may modify the risk of obesity but needs further research

Hillier, Diabetes Care 30:2287-2292, 2007

Treatment of GDM

- ◆ 199 mothers with “mild GDM” (24-34 weeks gestation)
- ◆ Randomized controlled trial
- ◆ Treatment with diet or diet/insulin
- ◆ Measured BMI of 4-5 year old children
- ◆ Results:
 - Macrosomia
 - Treated 5.3%
 - Control 21.9%
 - Significant
 - BMI Z score of 4-5 year olds
 - Treated 0.49
 - Control 0.41
 - Not significant

IGT in Offspring of Maternal Type 1 DM

- ◆ Offspring of PGDM1 mothers without a family history of DM2 were studied
- ◆ Adult offspring are more likely to have impaired glucose tolerance (33%) and a deficient insulin secretory response to glucose
- ◆ There was no difference in adiposity or insulin resistance

Sobngwi 2003 Lancet 361:1861-65

Breast Feeding and Maternal Diabetes

- ◆ In maternal DM1, breast feeding has been linked to lower rates of DM1 in susceptible individuals
- ◆ In offspring of women with GDM, it is inconclusive whether breastfeeding reduces the risk of overweight, obesity and DM2.
- ◆ In offspring of Pima Indians with DM2, lower rates of DM2 may occur

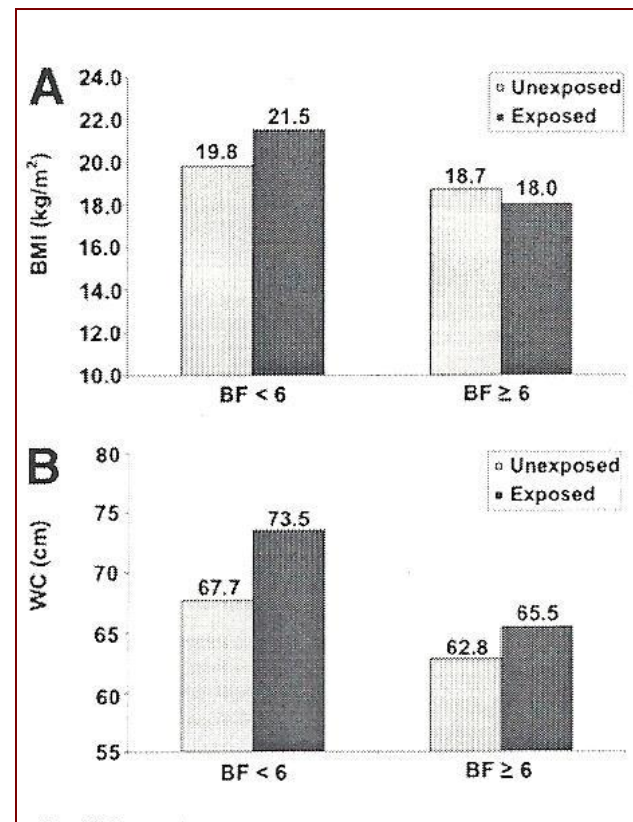
Breast Feeding and Maternal Diabetes

- ◆ Colorado 2006-2009
- ◆ Study group: 89 children of DM Moms
- ◆ 91% of Moms GDM
- ◆ Control: 379 children unexposed to DM
- ◆ Breastfeeding score
 - Breast 100% - 1
 - Formula 100% - 0
 - Mixed feeding
 - Breast>Formula 0.75
 - Breast = Formula 0.5
 - Formula>Breast 0.25
- ◆ Low <6 months
- ◆ Adequate >6 months

Breast Feeding and Maternal Diabetes

- ◆ Both maternal DM or none with adequate breast feeding had lower BMI, waist circ and abdominal fat
- ◆ “The macronutrient composition of breast milk...may influence metabolic programming and regulation of body fatness and growth rate”

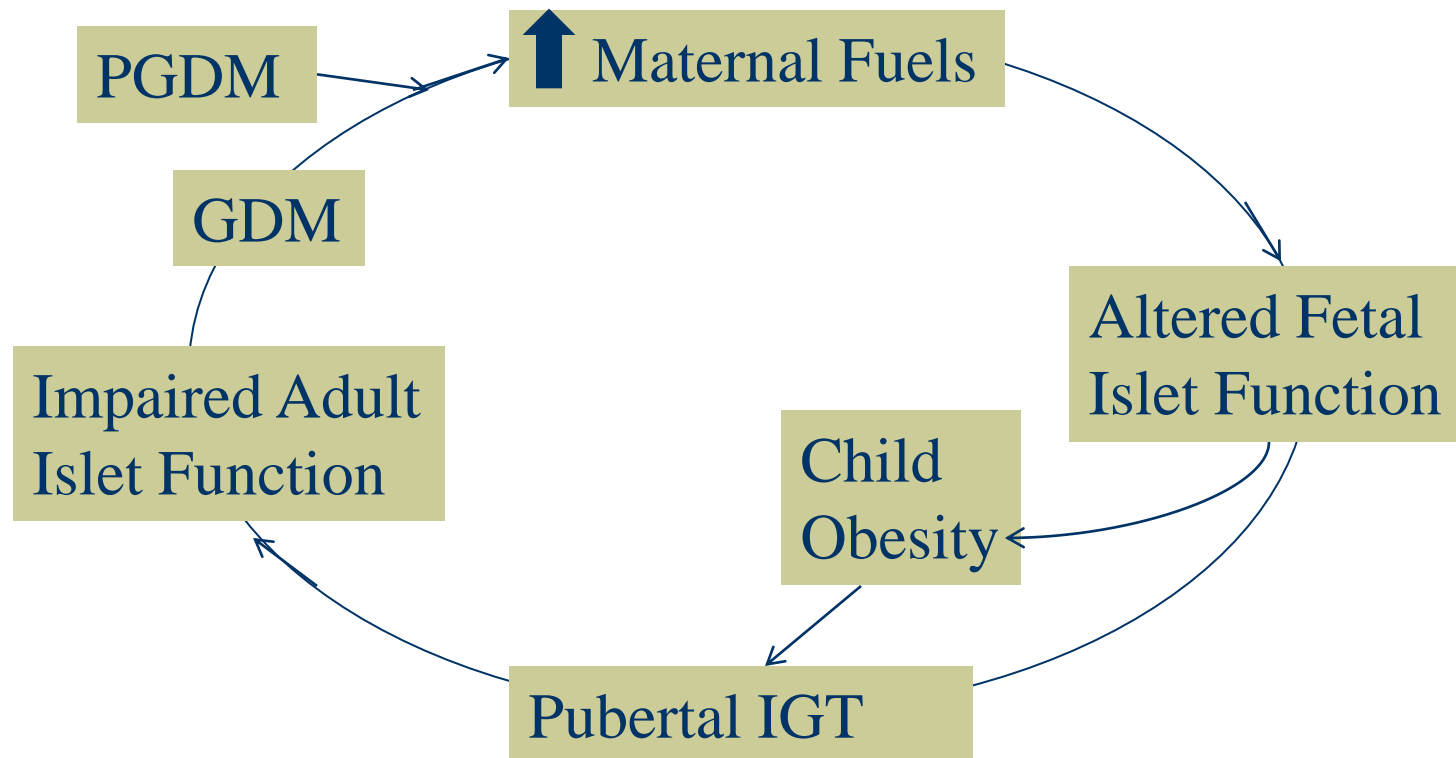
Crume, TL Diabetes Care 2011 34:641



The Perfect Storm

- ◆ **The Vicious Cycle**
 - Type 1 diabetes – 70% increase by 2020
 - Type 2 diabetes – 17-49/100,000 pt yrs in 15-19 yr olds
 - Gestational diabetes – 3.3% to 5.3% (2005) to 14.9% (Newport Beach)
- ◆ Increased infants of diabetic mothers
- ◆ Increased incidence of obesity
- ◆ Increased incidence of Type 2 diabetes

Diabetes Begets Diabetes



The Perfect Storm

- ◆ **Will this ever end? Can we do it? HOW?**
 - Must inform patients, medical staff, public
 - Must tighten management of GDM, DM1, DM2
 - Must prevent obesity in children who are Infants of DM
 - Must prevent obesity and metabolic syndrome in young female adolescents
 - Must decrease incidence of GDM and treat aggressively
 - Must encourage at least 6 months of breast feeding