

MATERNAL OBESITY AND OUTCOME OF OFFSPRING

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Objectives

- Describe outcomes of offspring of obese pregnant women
- Discuss potential mechanisms for various outcomes
- Describe the potential intergenerational impact of maternal obesity

Obesity

- Global epidemic
- NHANES 2009-2010 for US women aged 20-39¹:
 - 56% overweight or obese
 - 32% obese
 - 8% BMI ≥ 40 mg/kg²
- ~45% women were overweight or obese when becoming pregnant²

¹JAMA 2012;307(5):491-497

²Obstet Gynecol Clin North Am 2009;36:317-32, ix

Maternal Obesity

- ⦿ Known associated medical conditions
 - Hypertension
 - Type 2 Diabetes Mellitus
 - Obstructive Sleep Apnea
- ⦿ Increased pregnancy related complications
 - Preeclampsia
 - Gestational Diabetes

Stillbirth

- ~1 in 200 births in developed countries
- Maternal risk factors include advanced age, nulliparity, ethnic background, diabetes mellitus, hypertension, smoking, and obesity.

Obesity and Pregnancy

- The risk of stillbirth is at least 2 fold increased in obese women and is up to 4 fold increased in morbidly obese women as compared with lean women.

- Cedergren MI. Maternal morbid obesity and the risk of adverse pregnancy outcome. *Obstet Gynecol* 2004;103:219-24
- Cnattingius S, et al. Prepregnancy weight and the risk of adverse pregnancy outcomes. *NEJM* 1998;338:147-52
- Stephansson O, et al. Maternal weight, pregnancy weight gain, and the risk of antepartum stillbirth. *Am J Obstet Gynecol* 2001;184:463-9.
- Kristensen J, et al. Pre-pregnancy weight and the risk of stillbirth and neonatal death. *BJOG* 2005;112:402-8

Maternal Obesity & Stillbirth

- Meta-analysis of cohort and case controlled studies
 - Risk of stillbirth doubled in women with BMI ≥ 30 kg/m² as compared with BMI 18.5 -24.9 kg/m² (OR 2.07; 95% CI 1.59-2.74)
 - Risk of stillbirth in overweight women (BMI 25 – 29.9) increased to lesser degree (OR 1.47; 95% CI 1.08-1.94)

Maternal Obesity and Stillbirth

- Meta-analysis of 5 cohort studies found risk of stillbirth as compared with normal weight women
 - Obese women OR 1.63 (95% CI 1.35-1.95)
 - Overweight women OR 1.23 (95% CI 1.09-1.38)

Study	Population	Definition of stillbirth	Adjustment for covariates	OR for Obesity	OR for overweight
Tennant (2011)	UK 2003-2005 Regional multicenter 40,932 singleton deliveries	20 weeks	Maternal age, ethnicity, smoking. Preexisting diabetes and congenital anomalies excluded	2.3 (1.6-3.3)	1.3 (0.9-1.9)
Salihu (2007)	US 1978-1997 Regional multicenter 1,577,082 singleton deliveries	20 weeks	Maternal age, race, education, marital status, smoking, prenatal care, fetal sex, year of birth	1.5 (1.3-1.7)	-

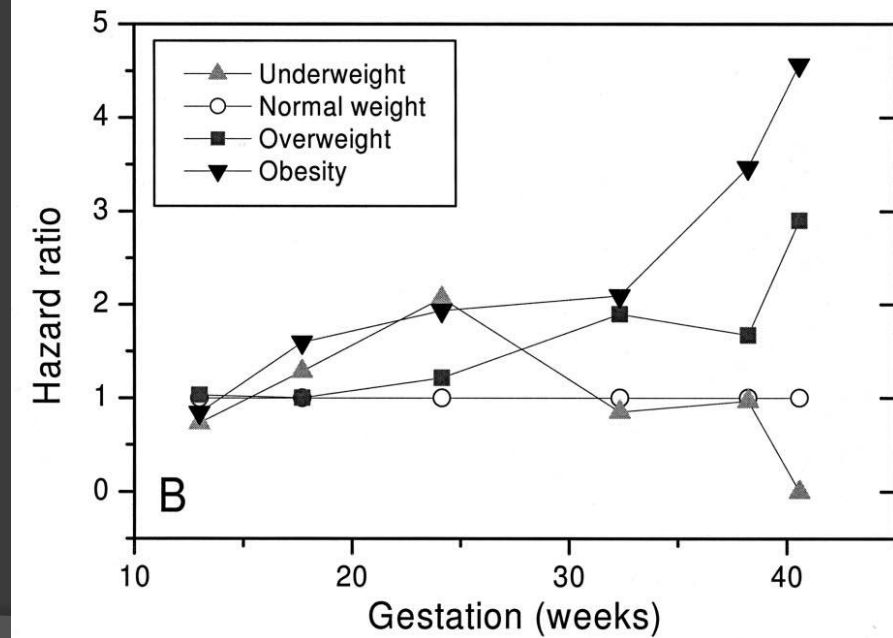
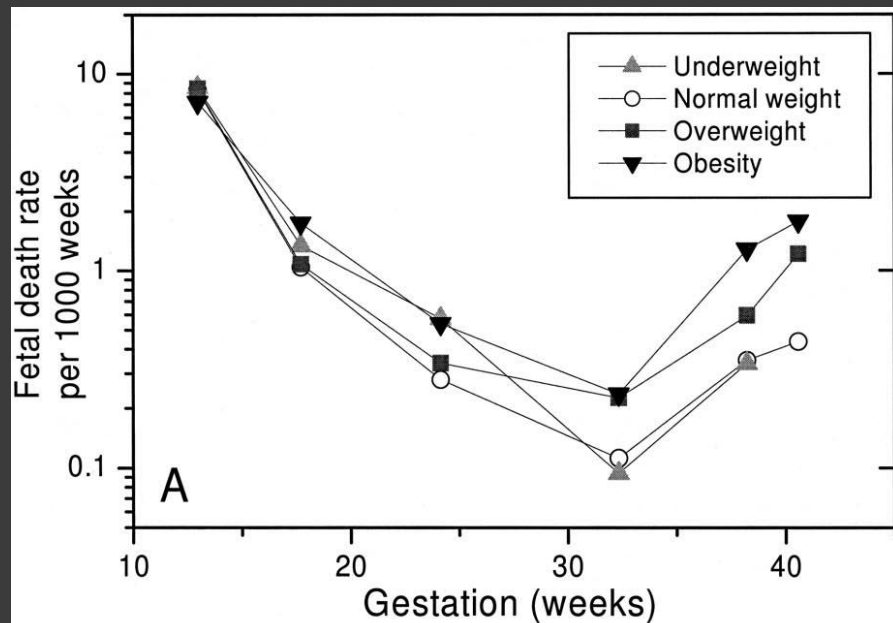


Fig. 1. A. Fetal death rate per 1,000 weeks by body mass index (BMI) category. Underweight, BMI 18.5; normal weight, 18.5 BMI 25; overweight, 25 BMI 30; obesity, BMI 30; n 54,505; 679 fetal deaths. B. Adjusted hazard ratio relative to normal-weight women by BMI category; n 54,133; 674 fetal deaths

Neonatal Mortality

- Obese women in 5 cohort studies increased neonatal mortality OR 1.6-2.6¹⁻⁵
- One study OR 0.89 (95% CI 0.61-1.3) but there was also a high neonatal mortality in women with normal BMI⁶

¹Human Reprod 2011;26:1501-11

²Obstet Gynecol 2004;103:219-24

³BJOG 2005;112:403-8

⁴Epidemiology 2009;20:74-81

⁵Obstet Gynecol 2007;110:1083-90

⁶Eur J Epidemiology 2009;24:697-705

Probability of fetal or infant death and pre-pregnancy BMI

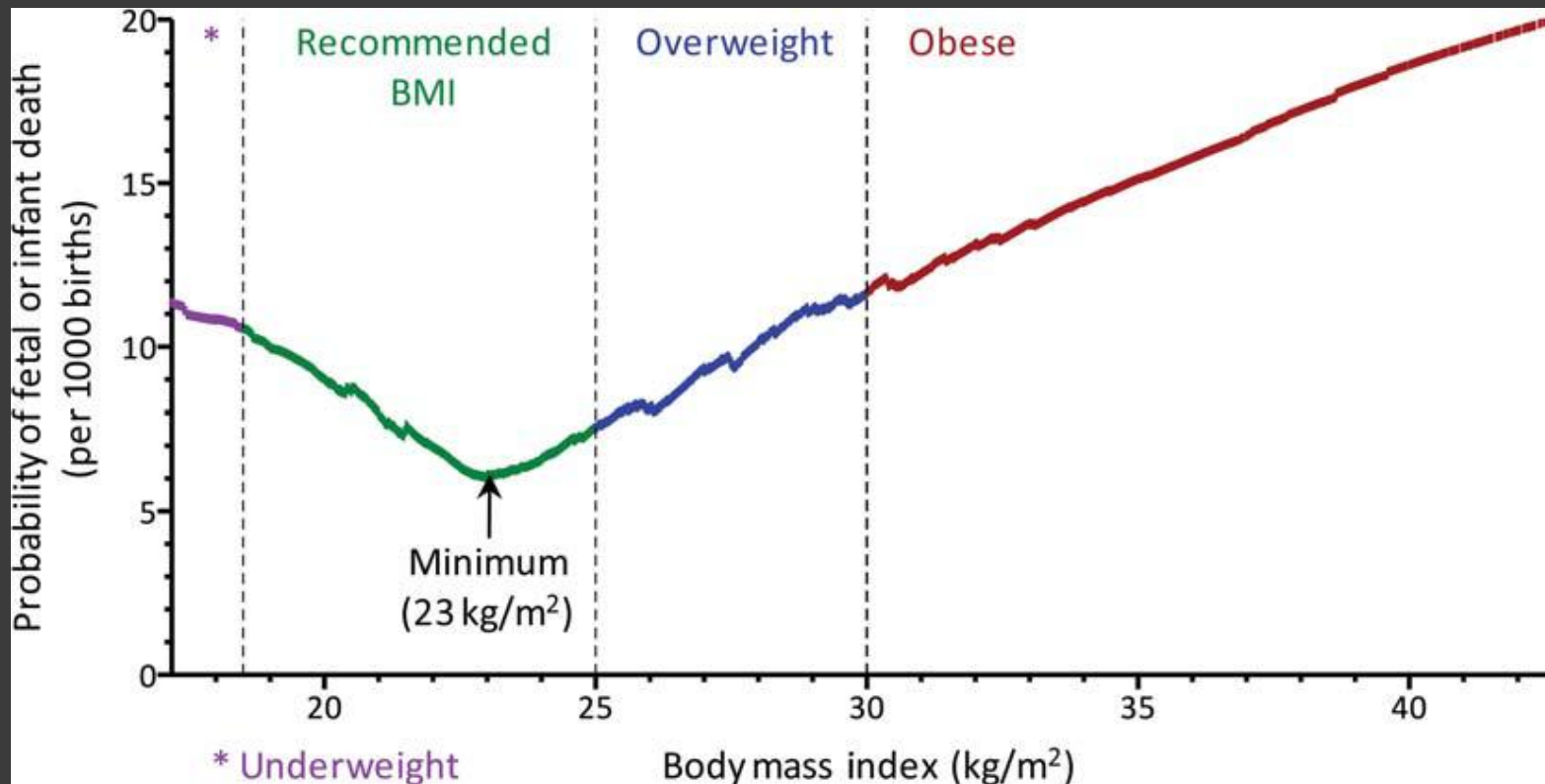


Figure 1 The association between maternal body mass index and the risk of a fetal or infant death, as estimated by locally weighted scatter plot regression.

Possible Mechanisms Fetal and Infant Mortality

- Associated morbidities: Preeclampsia, Diabetes
- Confounders such as poor socioeconomic conditions, dietary quality

Possible Mechanisms Fetal and Infant Mortality

- ⦿ Lower recognition of poor fetal growth/compromise
 - Lower detection of decreased fetal movement
 - Increased birth weight associated with hyperglycemia
- ⦿ Technical limitations ultrasound
 - Lower detection of congenital anomalies

Congenital anomalies

- Important cause of stillbirth and neonatal deaths
- Childhood morbidity

Obesity and Congenital anomalies

- Systematic review by Stothard, et al found that risk of congenital anomalies as compared to mothers with normal BMI
 - Cardiovascular abnormalities OR 1.30 (95% CI 1.12-1.51)
 - All neural tube defects OR 1.87 (95% CI 1.62-2.15)
 - Spina bifida OR 2.24 (95% CI 1.86-2.69)
 - Limb reduction anomalies OR 1.34 (95% CI 1.03-1.73)

- Stothard KJ, et al. Maternal overweight and obesity and the risk of congenital anomalies: a systematic review and meta-analysis JAMA 2009;301:636.

Obesity and Congenital Anomalies

- Meta-analysis by Rasmussen, et al found the risk of neural tube defects increased with maternal weight as compared with normal weight women
 - Overweight women OR 1.22 (95% CI 0.99-1.49)
 - Obese women OR 1.70 (95% CI 1.34-2.15)
 - Severely obese women OR 3.11 (95% CI 1.75-5.46)

- Rasmussen SA, et al. Maternal obesity and risk of neural tube defects: a metaanalysis. Am J Obstet Gynecol 2008;198:611.

Obesity and Congenital Anomalies

- ◎ Other reported associations:
 - Cleft palate, Cleft palate and lip
 - Anorectal atresia
 - Bilateral renal agenesis
 - Microtia

JAMA 2009;301:636-50

Am J Epidemiology 2008;168:1259-67

Am J Med Genet A 2010;152:2756-61

Obesity and Congenital Anomalies

- Potential mechanisms for increased congenital anomalies
 - Undiagnosed Type 2 DM or hyperinsulinemia without frank insulin dysregulation
 - Increased nutritional needs and nutritional deficits
 - Folic acid
 - Associated abnormal vascular and inflammatory process
 - Fat soluble substances
- Ultrasound less sensitive for detecting anomalies in obese women

Folate and Obesity

- Obese women of childbearing age in US have lower folate intake than leaner women.
- Inverse relationship between BMI and both serum and RBC folate levels even after controlling for differences in intake from diet and supplements

Folate and Obesity

◎ CMACE/RCOG 2010

- Women with BMI \geq 30 wishing to become pregnant should be advised to take 5mg folic acid supplementation daily, starting at least one month prior to conception and continuing during the first trimester of pregnancy

Maternal Obesity and Birth Weight

- High incidence of fetal growth restriction in nulliparous obese women not entirely explained by preterm delivery¹
- Increased risk of very low birth weight (<1.5 kg) in overweight and obese women apparently explained by preterm delivery due to preeclampsia²
- Maternal obesity and excessive weight gain during pregnancy are associated with LGA babies

¹AJOG 2009;200(4):395e1-9

²BMJ 2010;341:c3428

Risk of LGA or SGA in Singleton Pregnancy

Maternal BMI	SGA Adjusted OR* (95% CI)	LGA Adjusted OR* (95% CI)
19.8-26	Reference	Reference
29.1 - 35	0.98 (0.93-1.04)	2.20 (2.14-2.26)
35.1 - 40	1.02 (0.90-1.17)	3.11 (2.96-3.27)
> 40	1.37 (1.09-1.71)	3.82 (3.50-4.16)

*Adjusted for maternal age, parity, smoking, year of birth

Maternal BMI and Birthweight

BMI	Birthweight < 5 th percentile OR (99% CI)*	Birthweight > 90 th percentile OR (99% CI)**
20-25	Reference	Reference
25-30	0.80 (0.76 – 0.84)	1.57 (1.50 – 1.64)
>30	0.79 (0.73 -0.86)	2.36 (2.23 – 2.50)

*Adjusted for GDM, preexisting DM, preeclampsia, smoking

** Adjusted for GDM, preexisting DM

Influence of obesity and diabetes on prevalence of macrosomia

- 12,950 deliveries at urban center 1997-2001
- Risk of LGA
 - Pregestational DM OR 4.4 (2.9 – 6.7)
 - Pregravid BMI > 30 kg/m² OR 1.6 (1.4-1.9)

Influence of obesity and diabetes on prevalence of macrosomia

- Prevalence of diabetes 5%
- Prevalence of obesity/overweight 47%
- Maternal obesity and not diabetes appears to be the more important factor contributing to the population's increase in mean birthweight

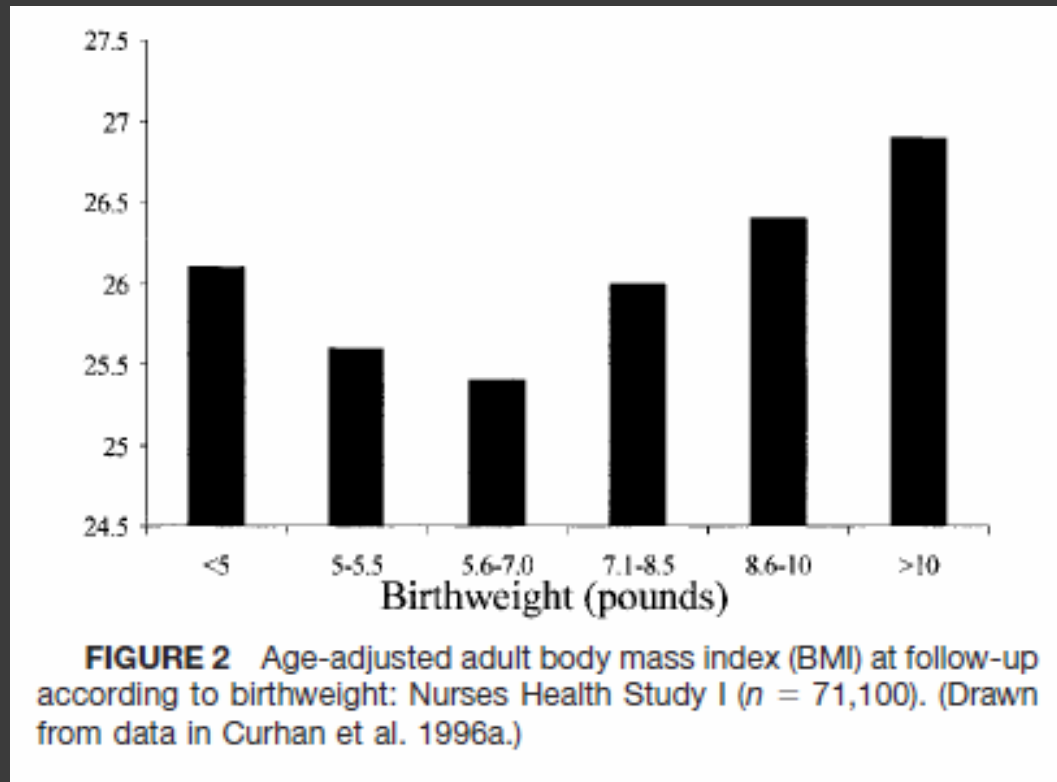
Maternal Obesity

- ⦿ Elevated maternal glucose concentrations → fetal hyperinsulinemia → increased fetal growth
- ⦿ Maternal obesity associated maternal insulin resistance and fetal hyperinsulinemia (even without diabetes)
- ⦿ Insulin resistance associated with elevated triglycerides → free fatty acid transfer to fetus
- ⦿ Amino acids → fetus

Offspring of Obese women

- Maternal obesity appears to influence the developing child in such a way that it increases the predisposition to obesity, insulin resistance, and diabetes later in life

Birth Weight and Offspring BMI



Higher birth weight is associated with higher BMI in adults

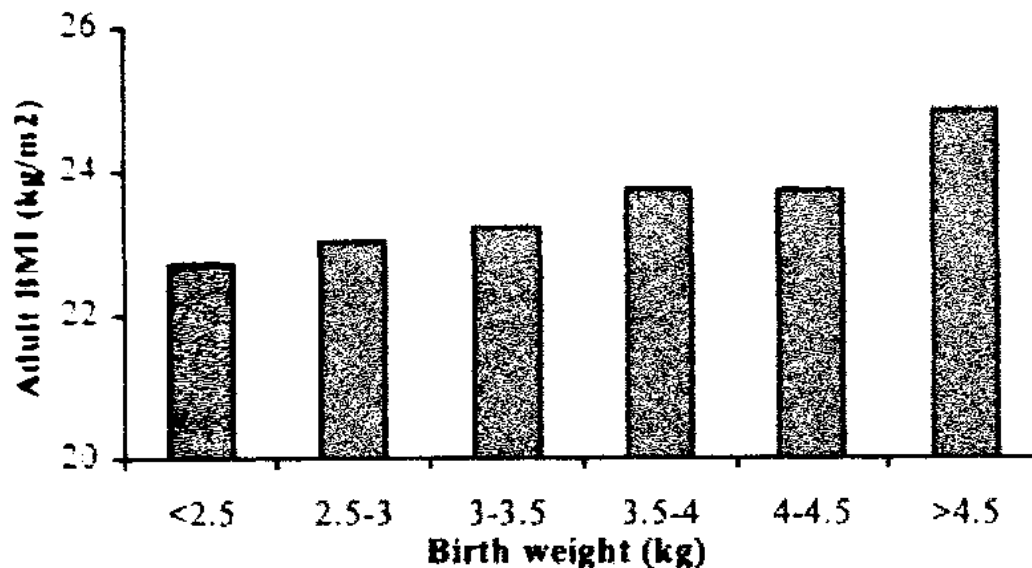


Figure 2: BMI at ages 18 to 26 years in Danish military conscripts by birth weight. Estimates are adjusted for gestational age, birth length, birth order, mother's marital status, age, and occupation. Adult BMI rises monotonically with birth weight (20).

Offspring of Obese Women

- ⦿ In childhood and young adulthood the offspring of obese women have more
 - Hypertension
 - Dyslipidemia
- ⦿ Largely driven by adiposity of offspring

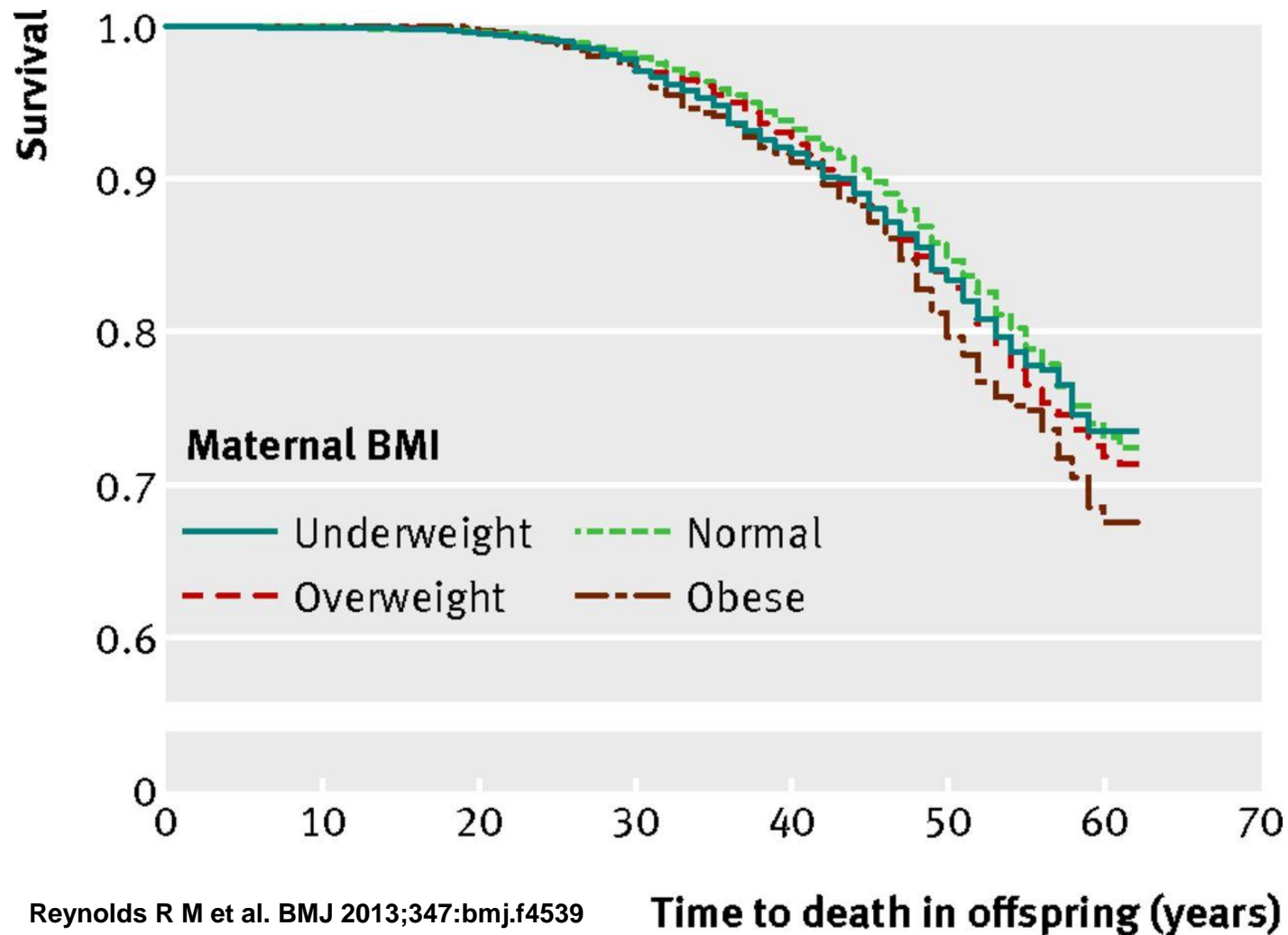
Maternal Obesity and Premature CV Events

- 37,709 people living in Aberdeen, Scotland with birth records from 1950 – present day
- Maternal prenatal records from 1950 - 1976
- Offspring records linked to General Register of Deaths, Scotland to identify specific cause of death and admissions for cardiovascular events

Maternal Obesity and Premature CV Events

- Offspring of obese mothers had increased risk of hospitalization for cardiovascular events (hazard ratio 1.29, 95% CI 1.06-1.57)
- Adjusted for maternal age at delivery, socioeconomic status, sex, current age, birth weight, gestation at delivery, and gestation at measurement of BMI

Fig 2 Kaplan-Meier curves for death rates in offspring according to maternal BMI category showing increased adjusted all cause premature mortality in offspring of obese mothers (BMI >30).



Reynolds R M et al. BMJ 2013;347:bmj.f4539

Time to death in offspring (years)

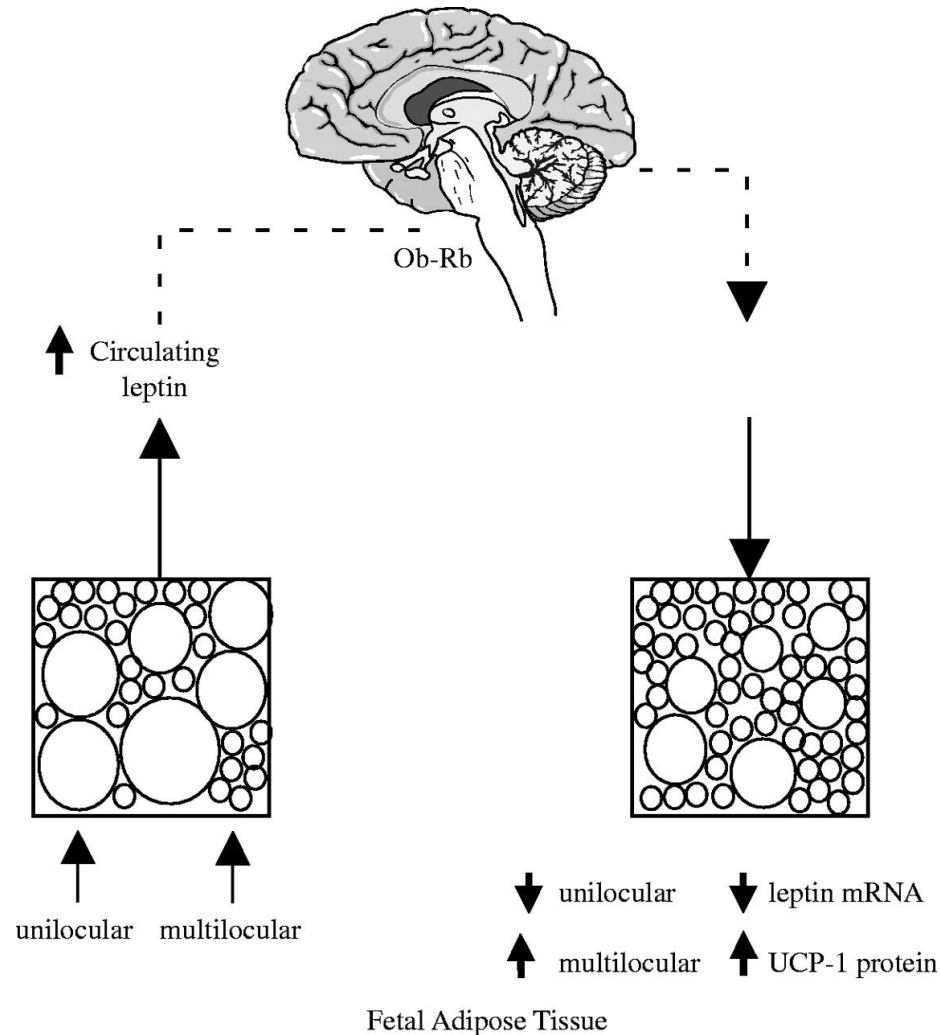
Maternal Obesity and Offspring Animal Models

- Offspring of overfed rats have reduced energy expenditure and greater taste for junk food. (Similar to offspring of obese mothers)
- Lambs of overfed ewes have changes in central appetite regulatory system, and altered gene expression in adipose tissue.

Maternal Obesity and Offspring Animal Models

- Overfeeding in pregnant animals is associated with:
 - changes in neuropeptide gene expression associated with appetite regulation
 - Higher numbers of hypothalamic neurons containing orexigenic neuropeptides
 - Changes in perinatal leptin levels (leptin appears to have important developmental role in the development of hypothalamic circuits controlling energy homeostasis)

Figure 3 Schematic diagram representing a summary of the potential effects of an increase in circulating leptin concentrations on the structural and functional characteristics of fetal adipose tissue (reprinted from Yuen et al.



Maternal Obesity and Offspring – Animal models

- Maternal obesity and nutrient excess induces changes
 - Decreased muscle mass
 - adipocyte differentiation
 - Hypertrophy and hyperplasia
 - Increased fat mass
 - Upregulation of inflammatory markers

Maternal Obesity and Offspring – Animal models

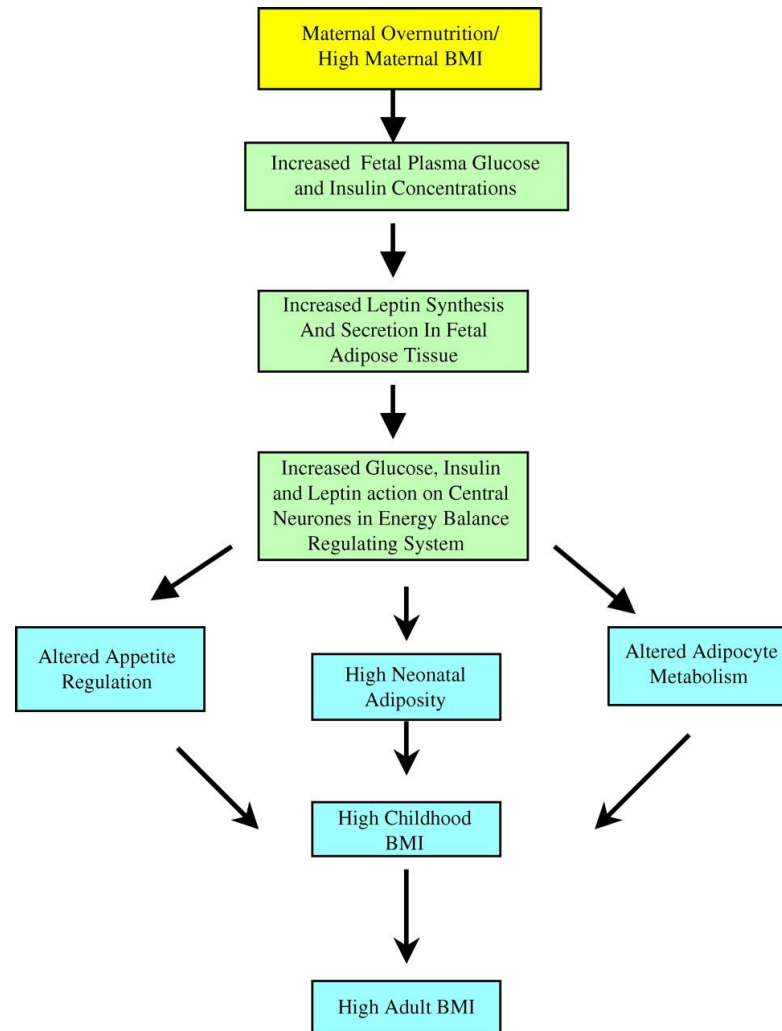
● Epigenetic Changes

- High fat maternal diet is associated with altered gene specific DNA methylation and histone modification
- Potential influence on expression of genes related to metabolism and accumulation of body fat

Maternal obesity and offspring

- Both maternal and paternal adiposity is associated with offspring birthweight but stronger for maternal
 - Postnatal environment?
 - Intrauterine environment?
 - Genetics?
 - Intergenerational environmental influences?

Figure 1 Potential pathways explaining the relationship between high birth weight and adult obesity.



McMillen I C et al. Reproduction 2006;131:415-427

“The Vicious Cycle”

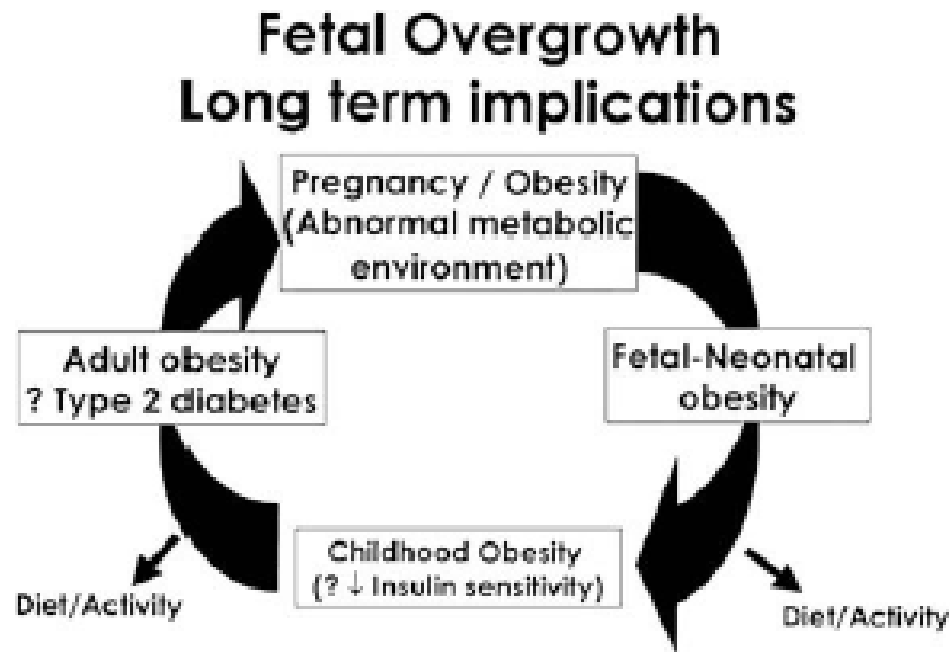


Fig. 5. Potential long-term implications of fetal overgrowth. (From Catalano PM. Obesity and pregnancy—the propagation of a viscous cycle? *J Clin Endocrinol Metab* 2003;88:3505–6; with permission.)

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