Fetal programming – how much is "over" before it begins?

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Outline

- Developmental Origins of Health and Disease (DOHaD): Programming of adiposity
- Epigenetics as mechanism
  - → Evidence of transgenerational impact
- Challenges for epidemiologic studies

"Programming" of adiposity

- Prenatal factors associated with increased adiposity later in life
  - Maternal obesity
    - Siblings before and after maternal bariatric surgery
  - Maternal diet
    - High fat diet
  - Maternal hyperglycemia
    - Gestational diabetes
  - Growth restriction
    - Exacerbated by postnatal weight gain ("catch up" growth)
  - "Obesogens"
    - Environmental chemical exposures (e.g. DDT/DDE)

Kubo 2014; Plata 2014; Warner 2014; Poon 2013; Martin-Gronert 2012; Budge 2005

How much is over…?

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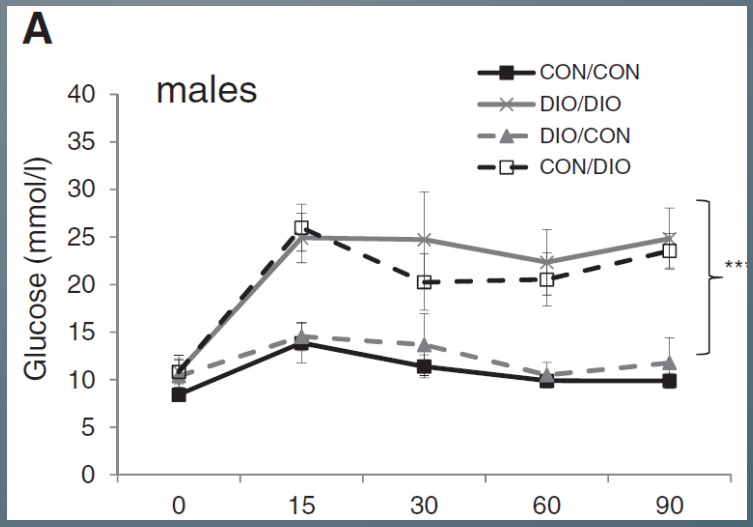
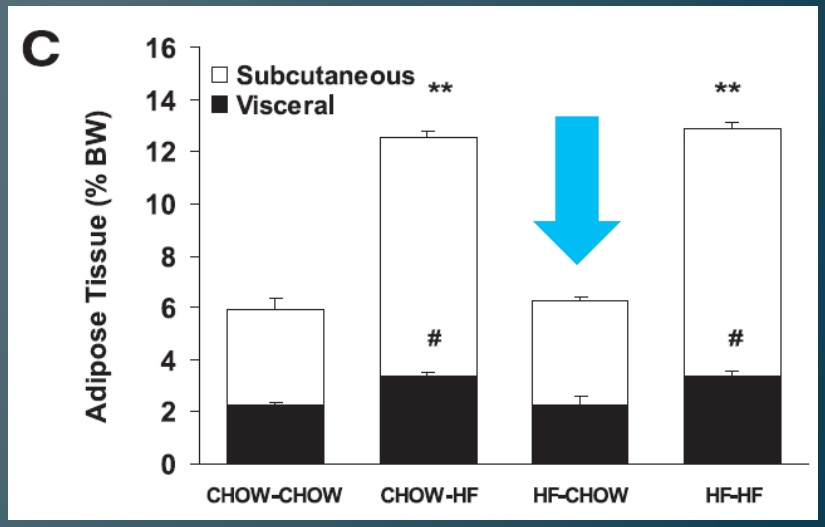
How much is over…?
Studies of pre- versus post- natal influences

- Postnatal diet influences more than prenatal
  - Diet induced obesity in mice after weaning affected offspring more than maternal over-nutrition (King 2014)
  - Pre- and post- natal exposure to maternal high fat diet (Sun et al. *Diabetes* 2012)





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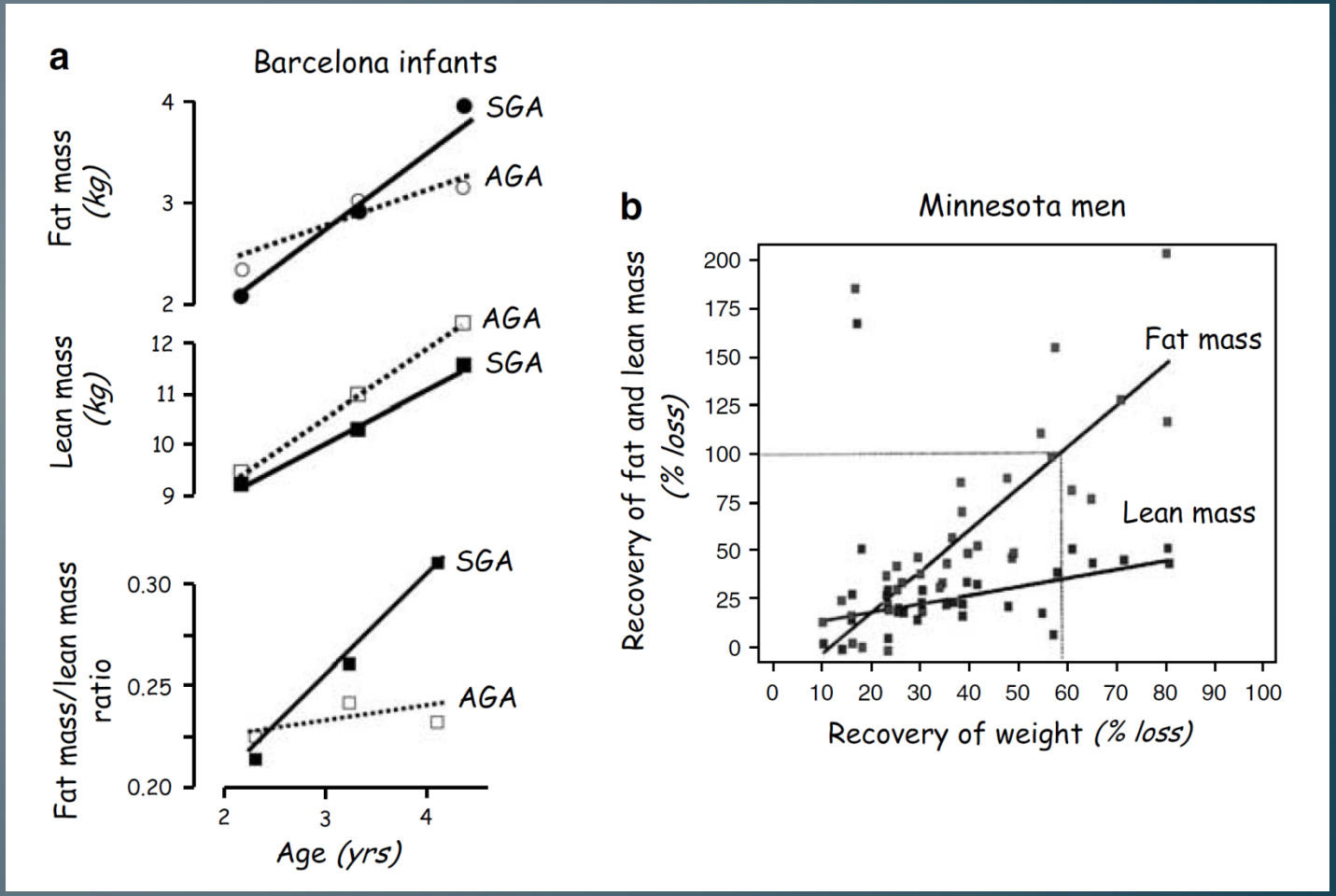
Catch-up "Fat"



Dullo 2006

How much is over…?

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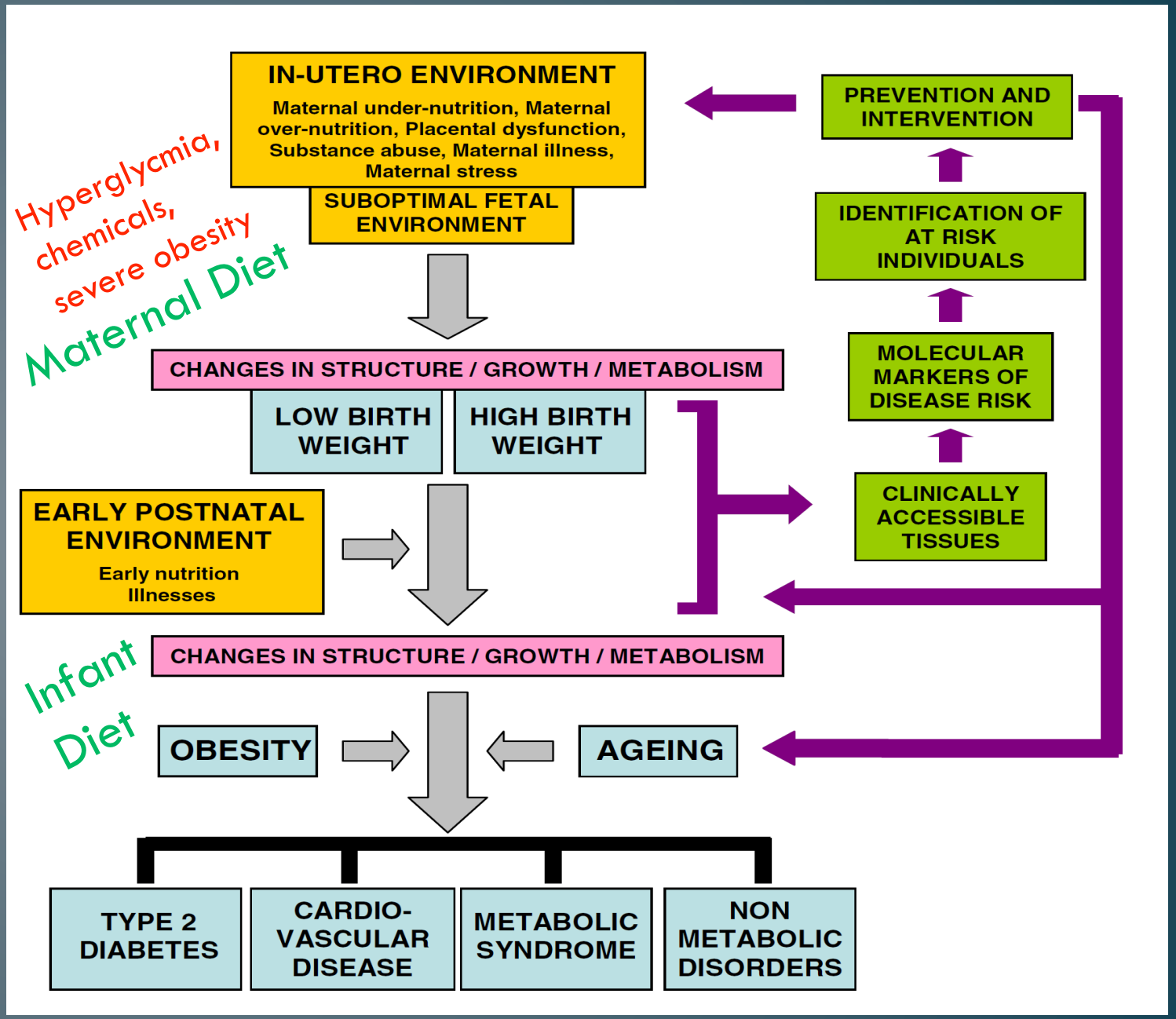
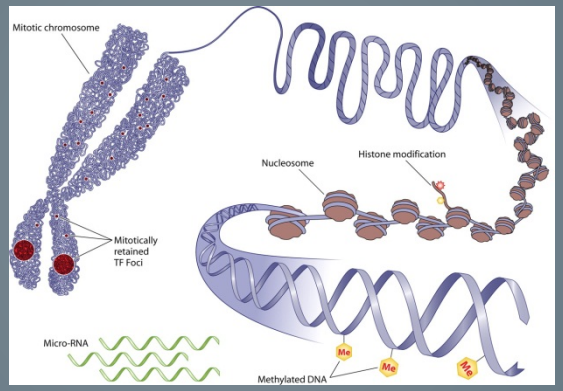
Unclear –
maybe not able
to amelierate

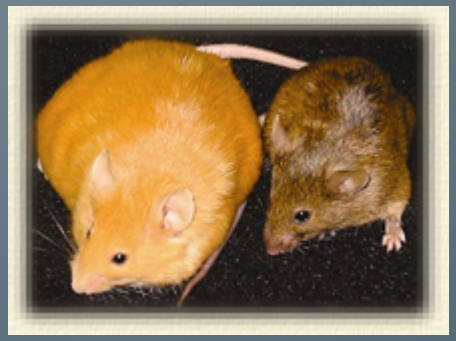


Martin-Gronert 2012

Epigenetics as DOHaD mechanism

- Histone modification
- mRNA
- DNA methylation





Early development

Exposure
- Early environment e.g. prenatal nutrition

Record
- Epigenetic change e.g. in DNA methylation
- Some loci are particularly sensitive

Propagate
- Inherited during cell division
- Tissue- or even soma-wide presence
- Blood may mark other tissues

Retain
- Stable maintenance unless age-related degeneration occurs

Adult phenotype

Express
- Persistent change in transcriptional potential contributing to disease risk

Transmit
- Transgenerational effects?

Wolff FASEB J 1998; 12(11):949-957; Heijmans et al. Epigenetics 4:8, 1-6; November 16, 2009

Trans-generation mechanism

- Epigenetic "erasure" occurs at 2 time points:
  - Preimplantation embryo
  - Primordial germ cells
    - E.g. epigenetic alterations (+50%) in mice conceived by use of intracytoplasmic sperm injection (ICSI) but not in their offspring
- Transgenerational epimutations: those not corrected at reprogramming of germline
  - E.g. tributyltin

McCarrey 2014; Chamorro-García 2013

Trans-generation effects
epidemiologic findings

Table 1 Summary of the historical transgenerational studies from Överkalix, Northern Sweden

Reference	Överkalix cohorts by grandchild's or proband birth year	Prior research question	Main findings	Comments
Bygren *et al*[27]	1905 (n=94)	Any link between ancestral food supply at two periods in childhood, the prepubertal spurt or the period just before and proband *longevity*?	*Paternal grandfather*'s food supply just *before prepubertal growth spurt* inversely associated with proband longevity	This study defined the mid-childhood 'slow growth period' as an exposure period associated with transgenerational effects
Kaati *et al*[28] Bygren *et al*[99 100]	1895 (n=107) 1905 (n=99) 1920 (n=111)	Any link between ancestral *mid-childhood* food supply and proband *cardiovascular and diabetes mortality*?	Father's poor, and mother's good, food supply in mid-childhood linked to *reduced proband cardiovascular mortality*. Paternal grandfather's good mid-childhood food supply linked to *increased proband diabetic mortality*	Diabetic mortality was included as a prior hypothesis based on possible role of imprinted genes. Each diabetic proband had a different paternal grandfather (Bygren *et al.* 2006)
Pembrey *et al*[29]	1895 (n=107) 1905 (n=99) 1920 (n=111)	Any *sex-specific* link between (grand) parental mid-childhood food supply and proband *mortality rate ratio*?	*Paternal grandfather*'s food supply linked to *grandson*'s mortality; *paternal grandmother's* food supply to *granddaughter's* mortality	Stratification by sex of the proband suggested by early ALSPAC results of paternal smoking effects (Northstone *et al.* 2014[39]). Exposure-sensitive period in mid childhood but not (pre)puberty confirmed
Kaati *et al*[30]	1895 (n=107) 1905 (n=99) 1920 (n=111)	Any link between (grand) parental mid-childhood food supply and proband *early-life circumstances and sex-specific longevity*?	Grandparental sex-specific transgenerational effects (as above) persisted. Parental effects now revealed as well	Taking proband's early-life circumstances into account revealed a father to son effect on longevity
Bygren *et al*[31]	1895 (n=107) 1905 (n=99) 1920 (n=111)	Any link between *sharp change* in grandparental food supply in childhood (0—13ys) and proband *cardiovascular mortality*?	Sharp change in food supply of *paternal grandmother* linked to increased cardiovascular mortality in *female* probands	Prior hypothesis—transgenerational effects of change in supply as the demonstrated effects from gestation to adulthood (Bygren *et al.* 2000)[101]

Pembrey 2014

Challenging epidemiologic methods

- Confounding by parental/familial behaviors/exposures
  - Can take the animal off an environmental influence after birth
- Exposure measurement
- Human growth and development
- Sex-specific differences
- Tissue specific alterations to epigenome

Summary

- How much is over…?
  - There are opportunities to overcome some prenatal influences
    - E.g. maternal versus early childhood diet
  - Pregnancy remains an important window for interventions to interrupt longer term effects
    - E.g. obesogen exposure
    - Other outcomes not discussed today may be more so "determined" at birth (e.g. vascular stiffness, cognitive development)
  - Trans-generational exposures much more difficult to evaluate but much longer impact