UNIVERSITY OF Southampton

Institute of Developmental Sciences and DOHaD Centre

British Heart Foundation

Healthy Cardiovascular Ageing: the life course perspective

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DOHaD International Society for Developmental Origins of Health and Disease

Unlike communicable diseases, globally everyone is at risk of non-communicable diseases (NCDs)

- NCDs account for >60% all global deaths (*but tackling them was not part of the Millennium Development Goals!*)
- Risk is partly established during early development
- Risk is passed across generations, by processes which are not simply genetic
- 'Mismatch' later amplifies the risk of NCDs established during development
- A life course model suggests that early prevention is needed and indicates periods to intervene
- Addressing this challenge is the greatest public health opportunity since germ theory

A widely believed "*fact*"

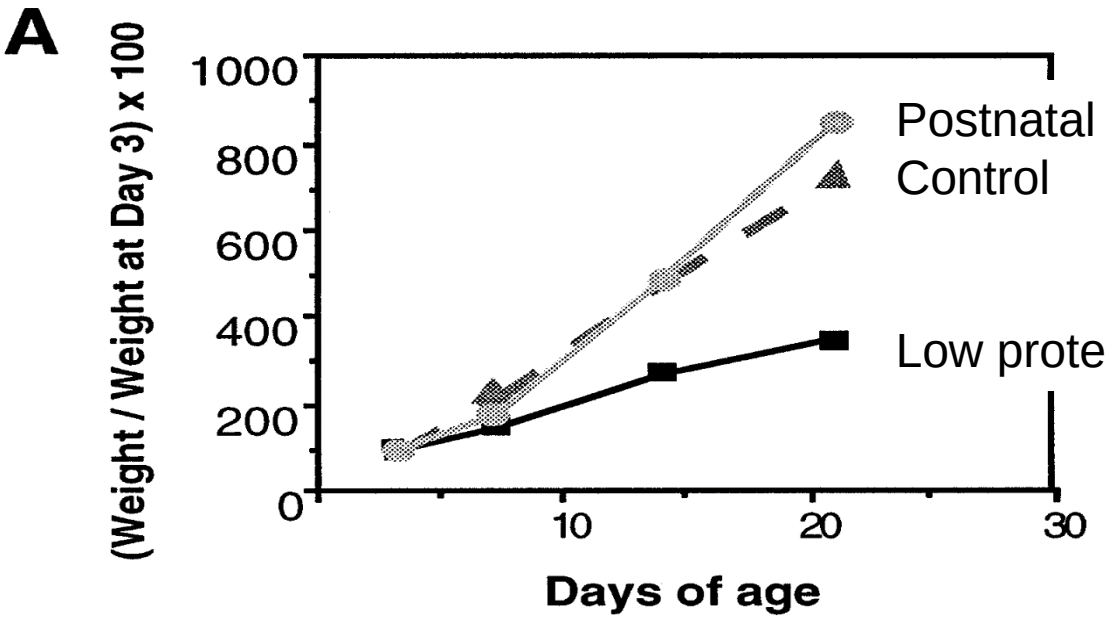
Noncommunicable disease risk = genetic predisposition + bad adult lifestyle

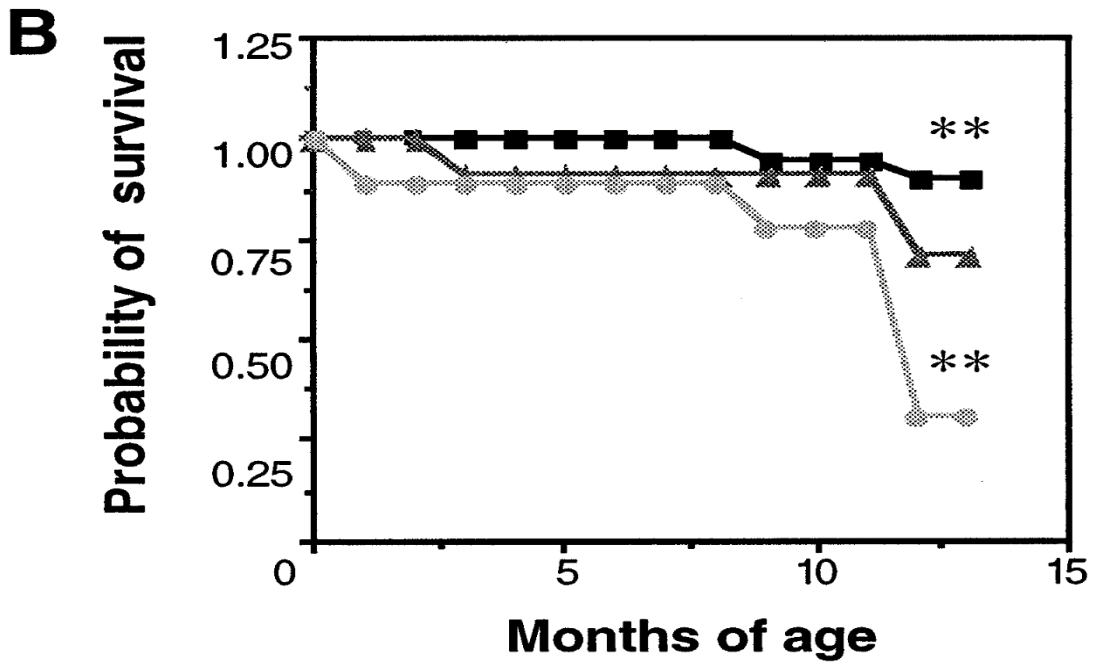
Shuldiner AR, Roden M, Barroso I, et al. with Morris AP, Voight BF, Teslovich TM et al., Wellcome Trust Case Control Consortium, MAGIC Investigators, GIANT Consortium, AGEN-T2D Consortium, SAT2D Consortium.

Large-scale association analysis provides insights into the genetic architecture and pathophysiology of type 2 diabetes. Nature Genetics 2012;44(9):981-990.

GWAS study of 63 newly discovered and established autosomal loci found that together these **genetic variants accounted for only 5.7% of variance in Type 2 diabetes susceptibility in the general population**

Development casts a long shadow…….

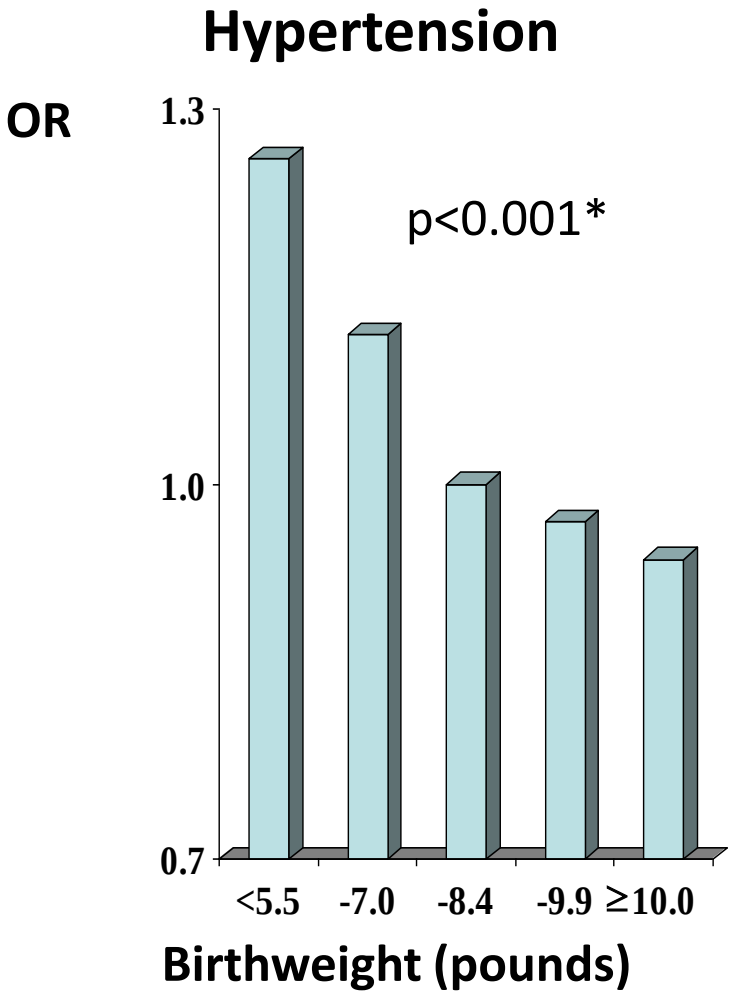


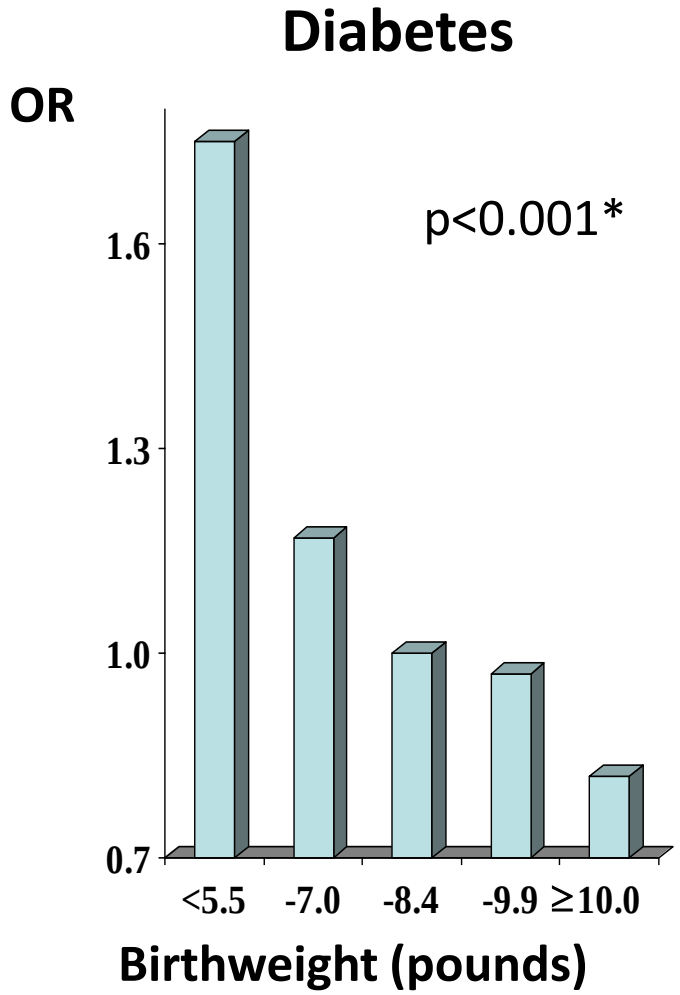


Jennings, B. J., Ozanne, S. E., Dorling, M. W., & Hales, C. N. (1999). Early growth determines longevity in male rats and may be related to telomere shortening in the kidney. *FEBS letters*, *448*(1), 4-8.

Odds ratios for hypertension and diabetes

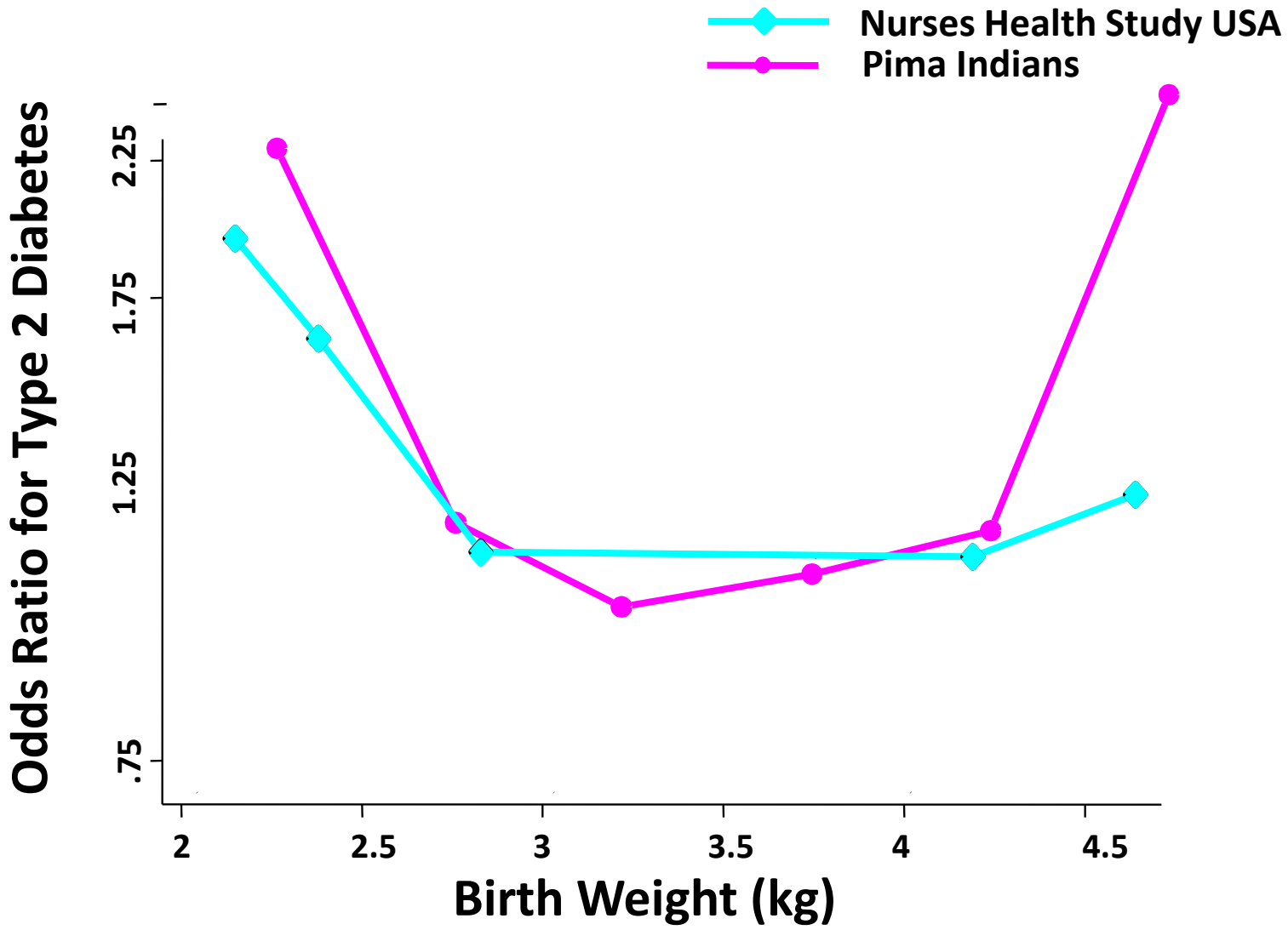
22,846 US men aged 48-83 years





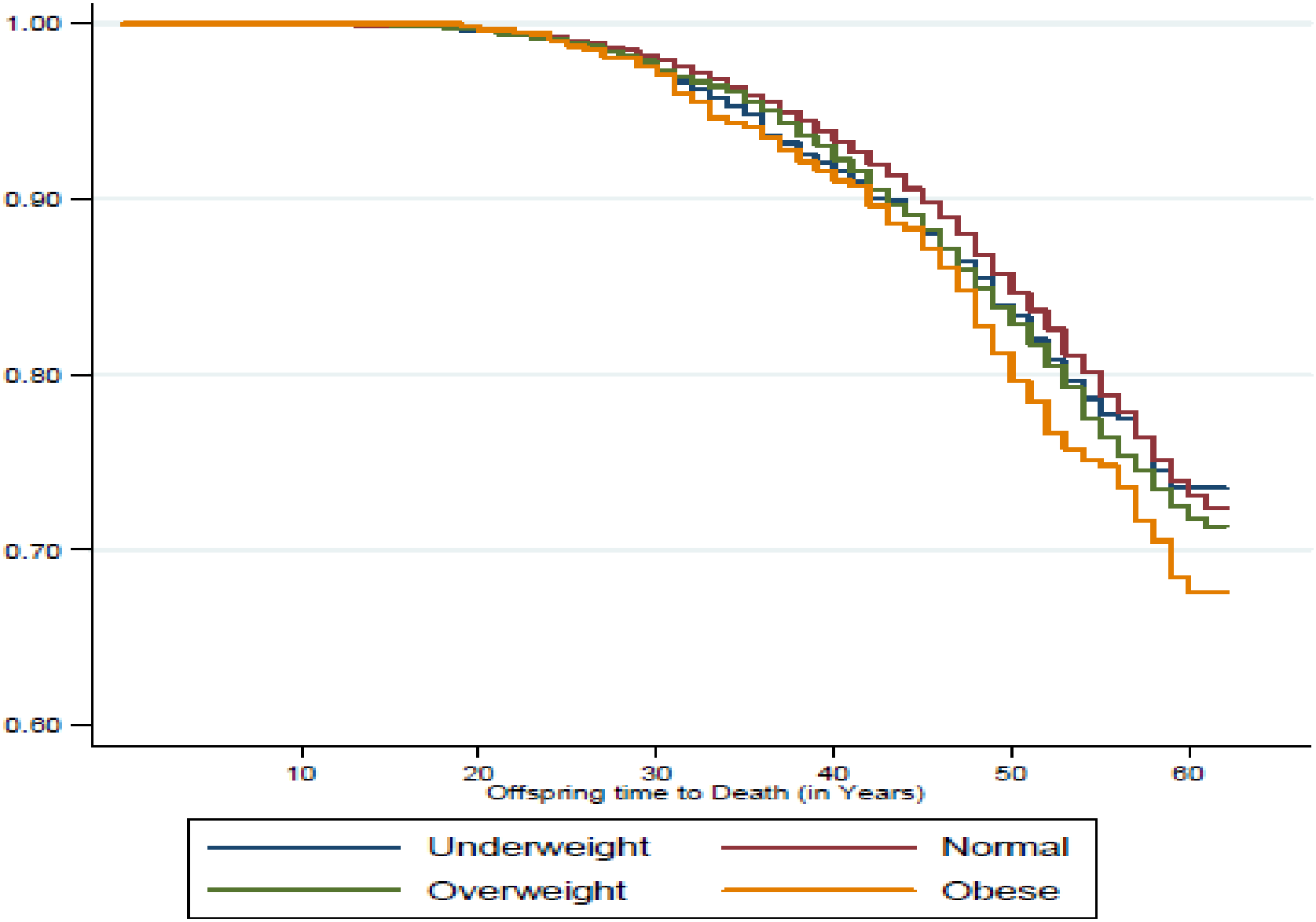
*p adjusted for age only

Birthweight and type 2 diabetes



Earlyread collaboration JAMA 2009

Survival (or death from CVD) of population according to maternal BMI categories

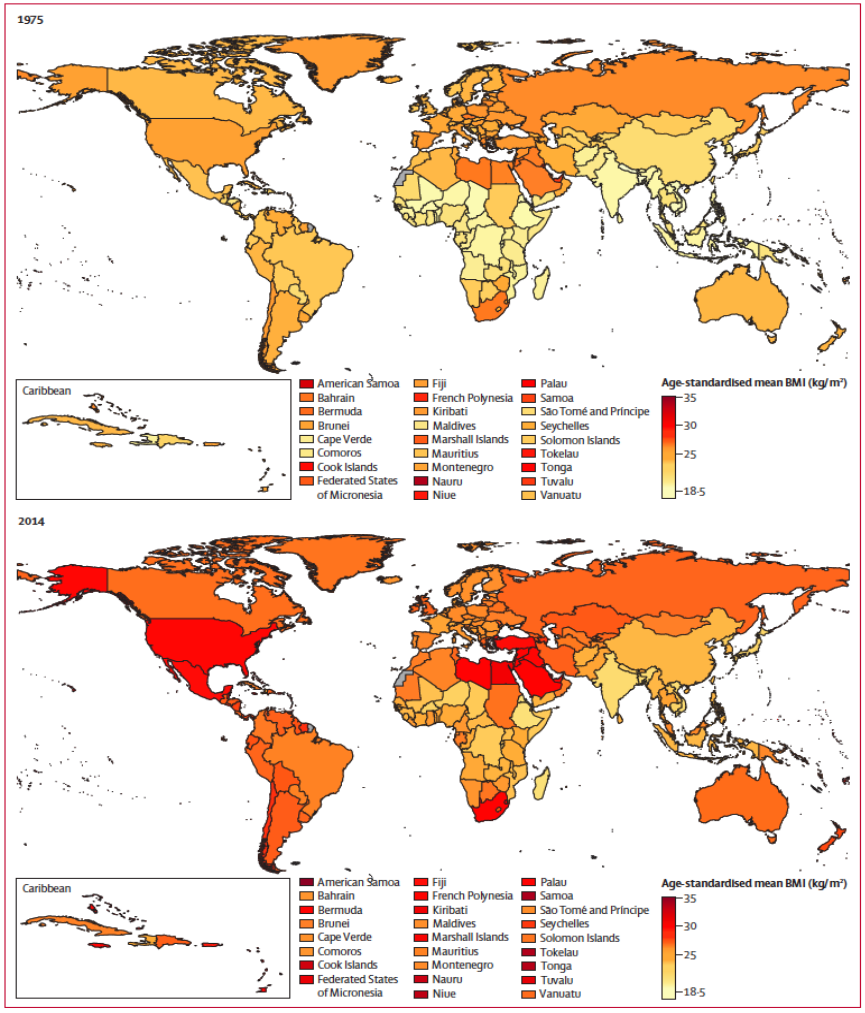


From Reynolds RM et al BMJ 2013.

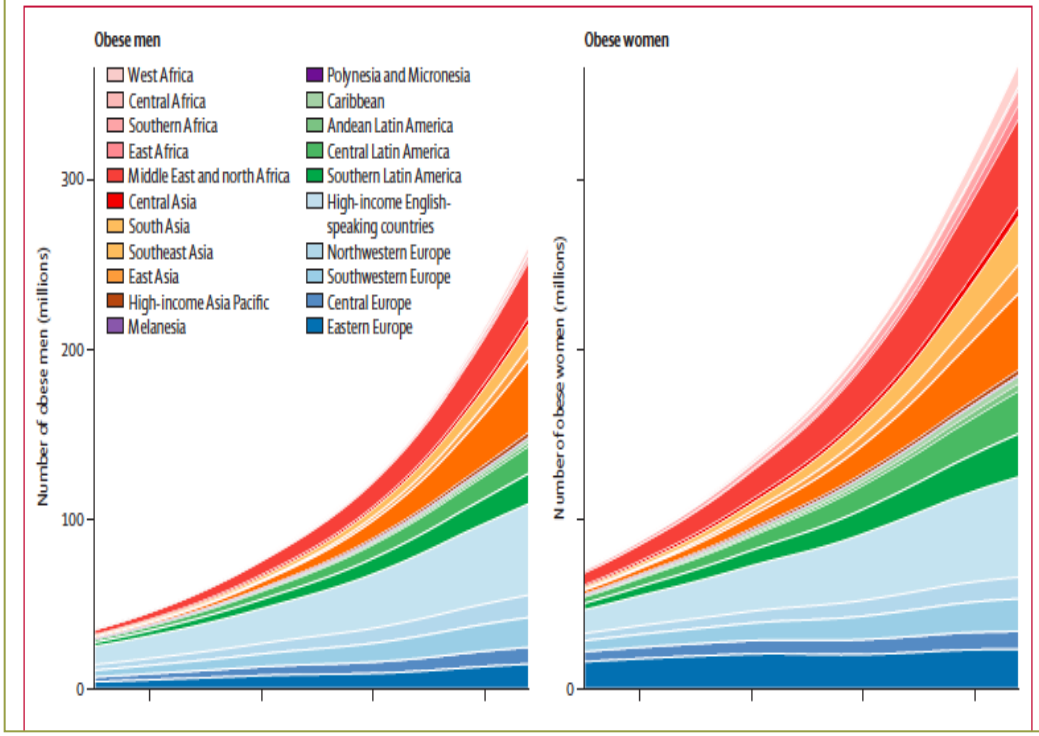
Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19·2 million participants

NCD Risk Factor Collaboration (NCD-RisC)*

Lancet 2016; 387: 1377–96



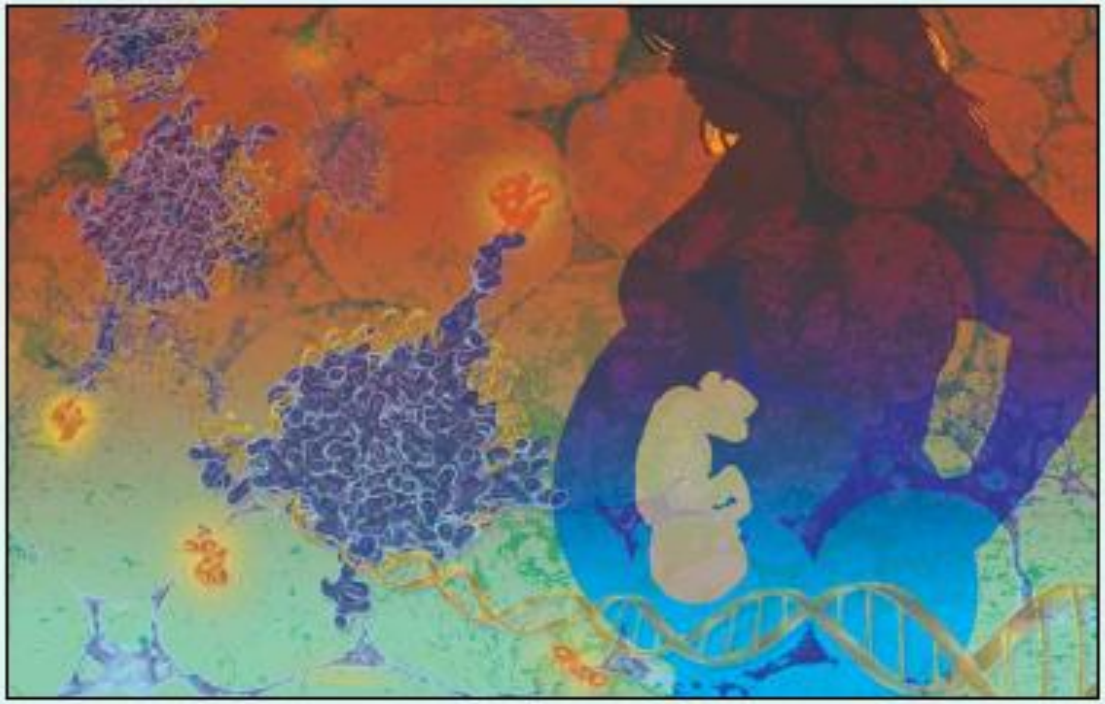
By 2025 more than 21% of women in the world will be obese



THE LANCET Diabetes & Endocrinology

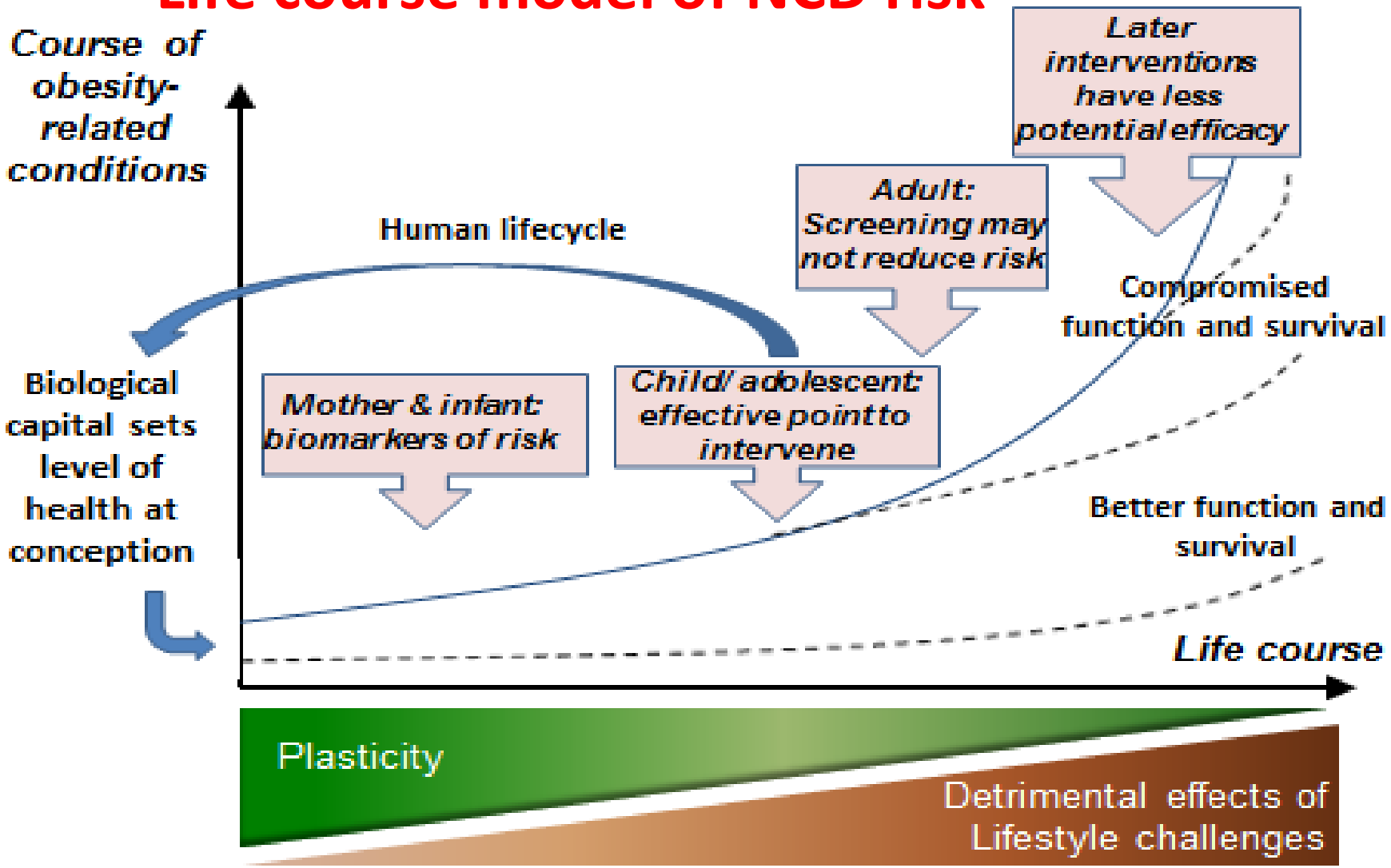
October, 2016 www.thelancet.com/diabetes-endocrinology

Maternal obesity

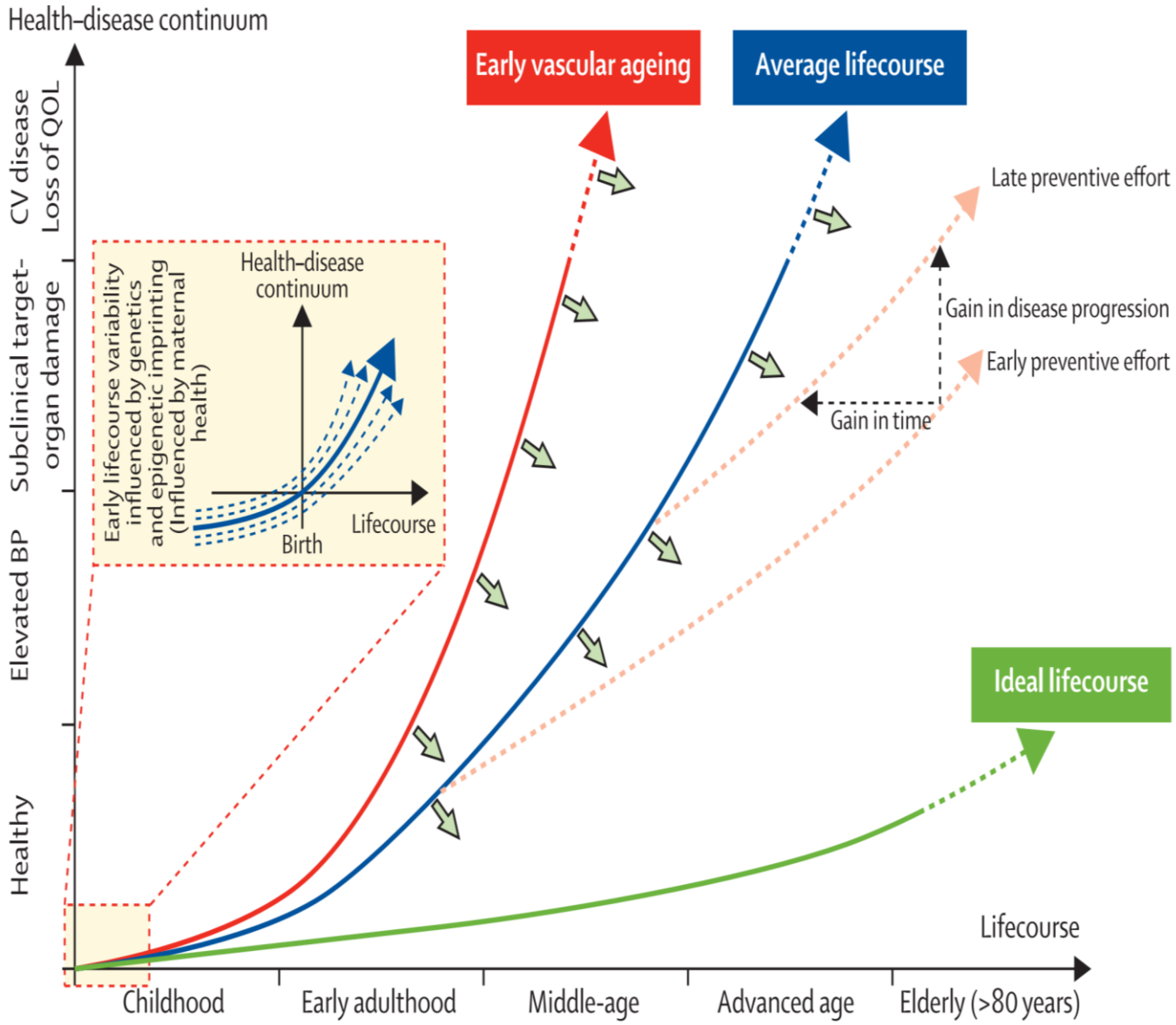


"Maternal obesity propagates intergenerational cycles of obesity and diabetes...interruption of these cycles before, during, or after pregnancy might help to stem the rising tide of non-communicable diseases worldwide."

Life course model of NCD risk

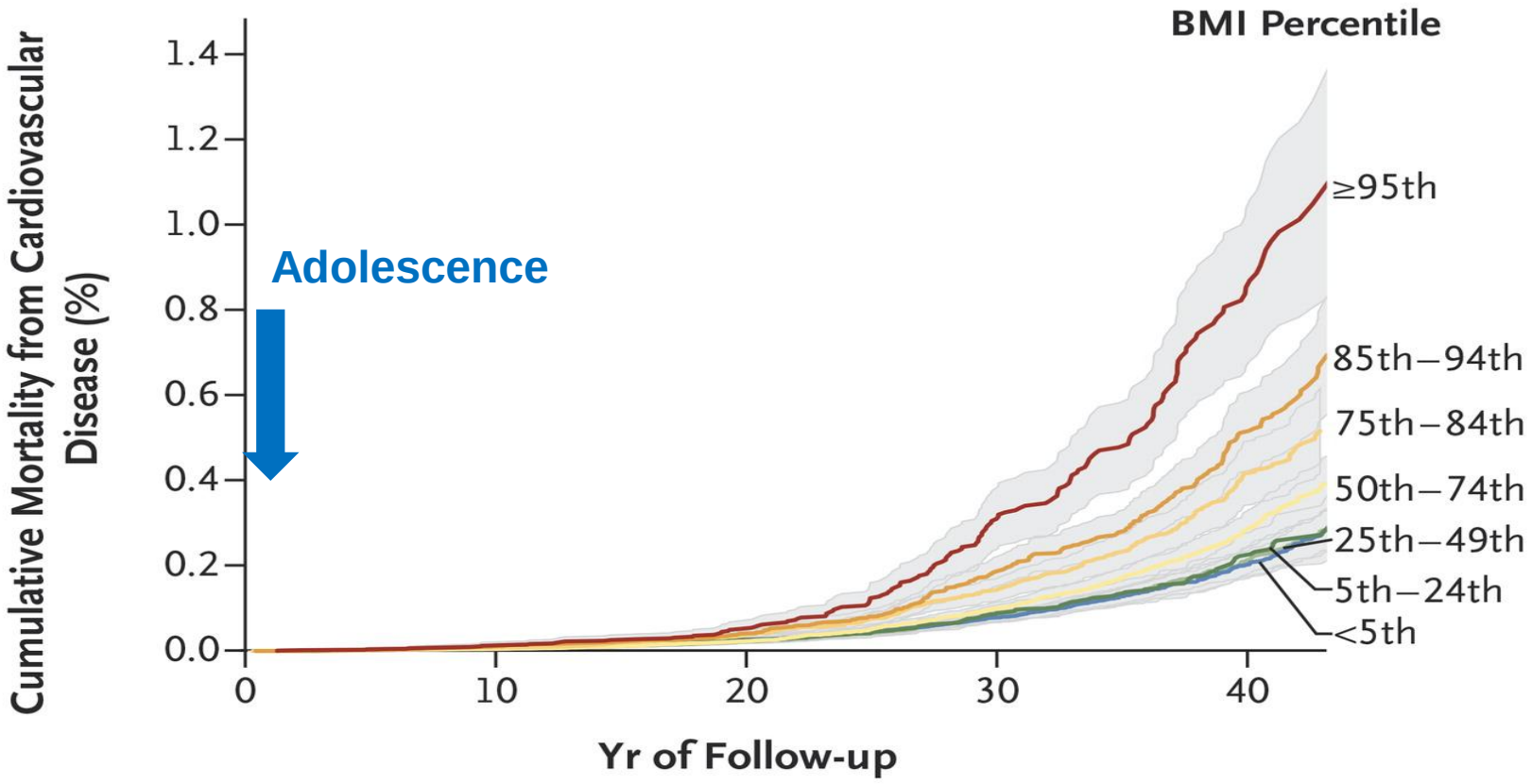


Lancet Commission: lifecourse strategy to address the global burden of raised blood pressure



Lancet 2016; 388: 2665–712

Body-Mass Index (BMI) during Adolescence and Subsequent Cardiovascular Mortality.

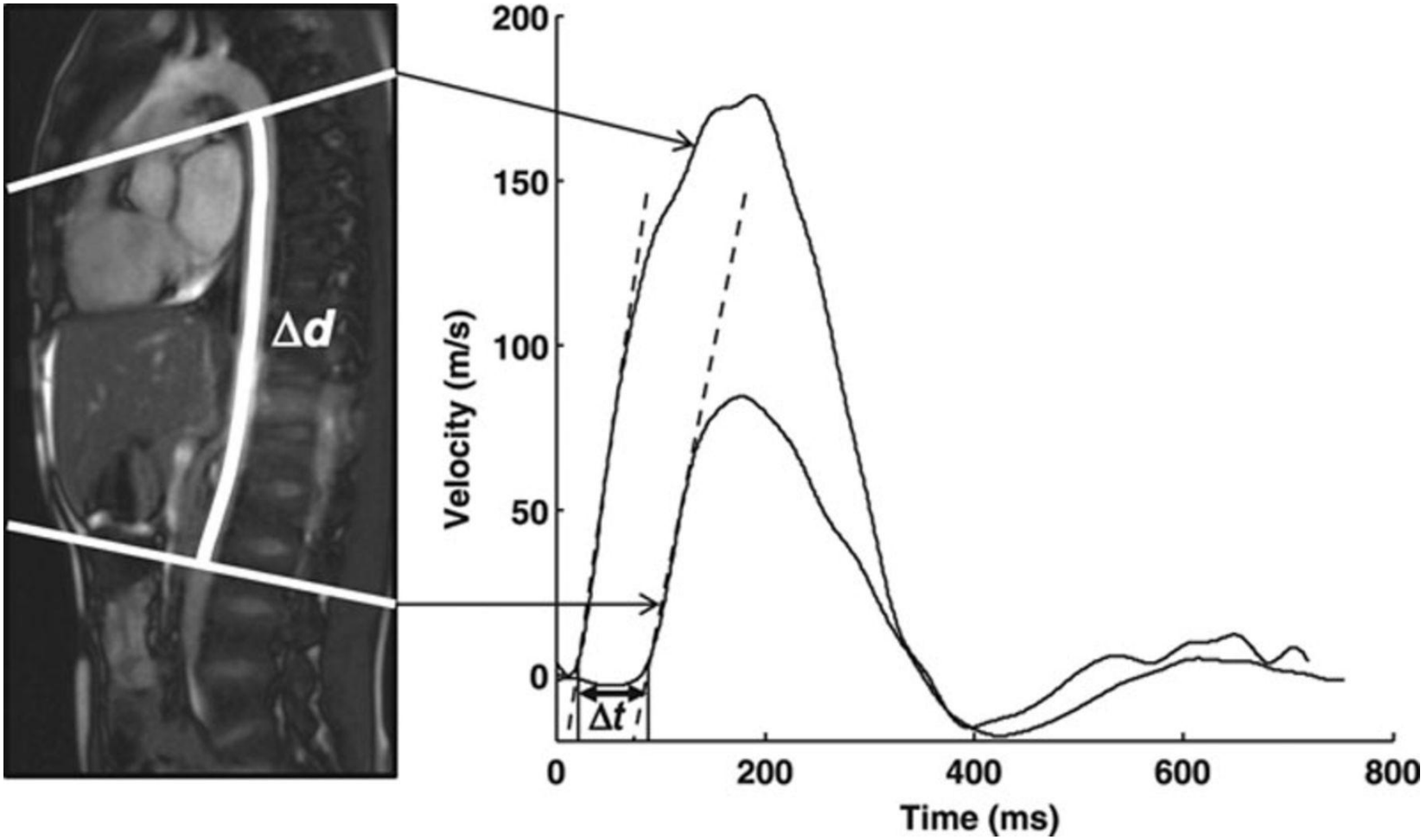


No. at Risk

Participants at risk	1,712,018	1,042,018	540,636	160,145
Cumulative person-yr	17,201,301	30,718,320	38,472,521	41,926,636
Cumulative cardio-vascular deaths	185	609	1,577	2,676

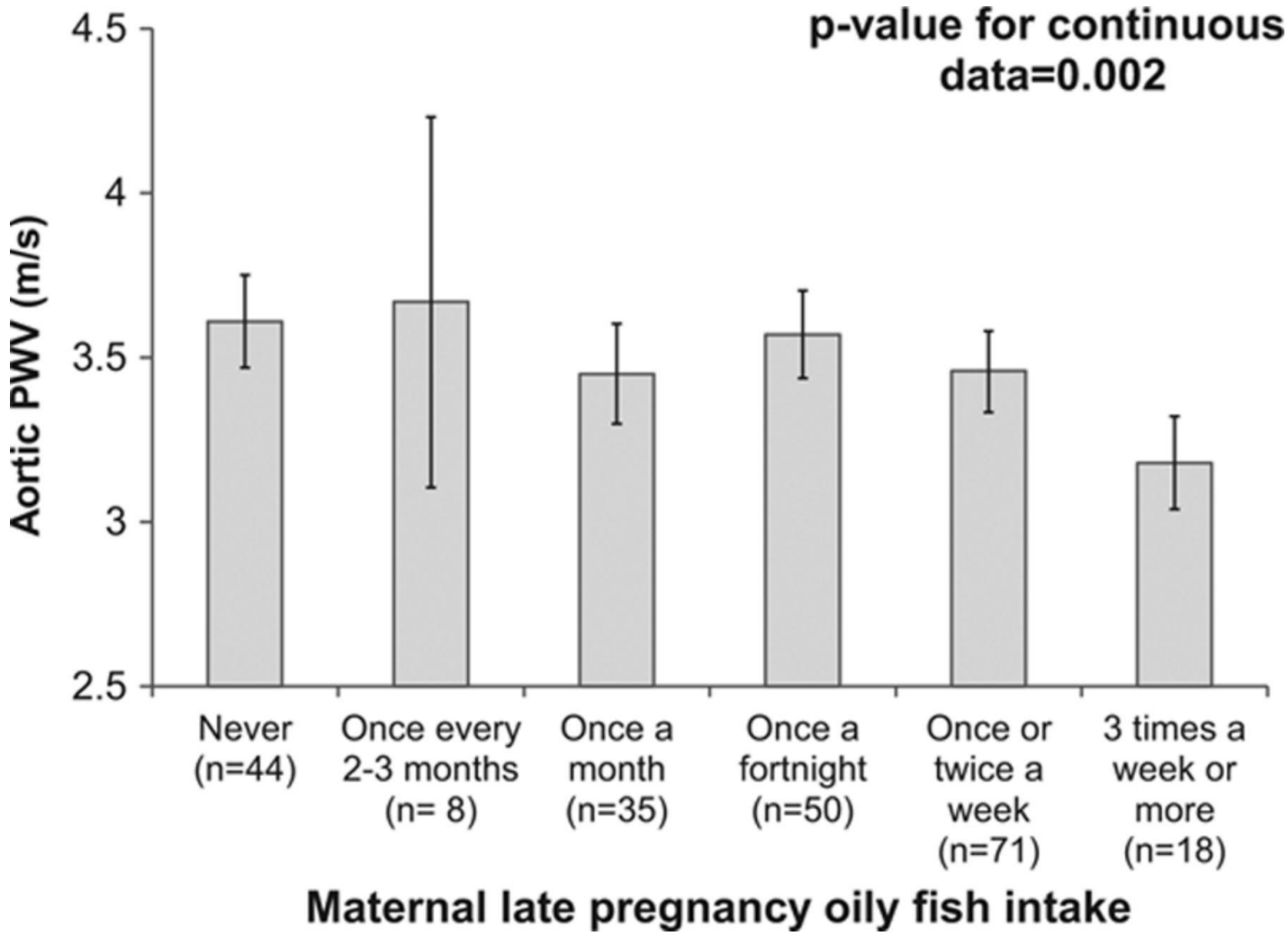
Twig G et al. N Engl J Med 2016. DOI: 10.1056/NEJMoa1503840

Aortic pulse wave velocity (PWV) as an early marker of cardiovascular risk in 9 year old children



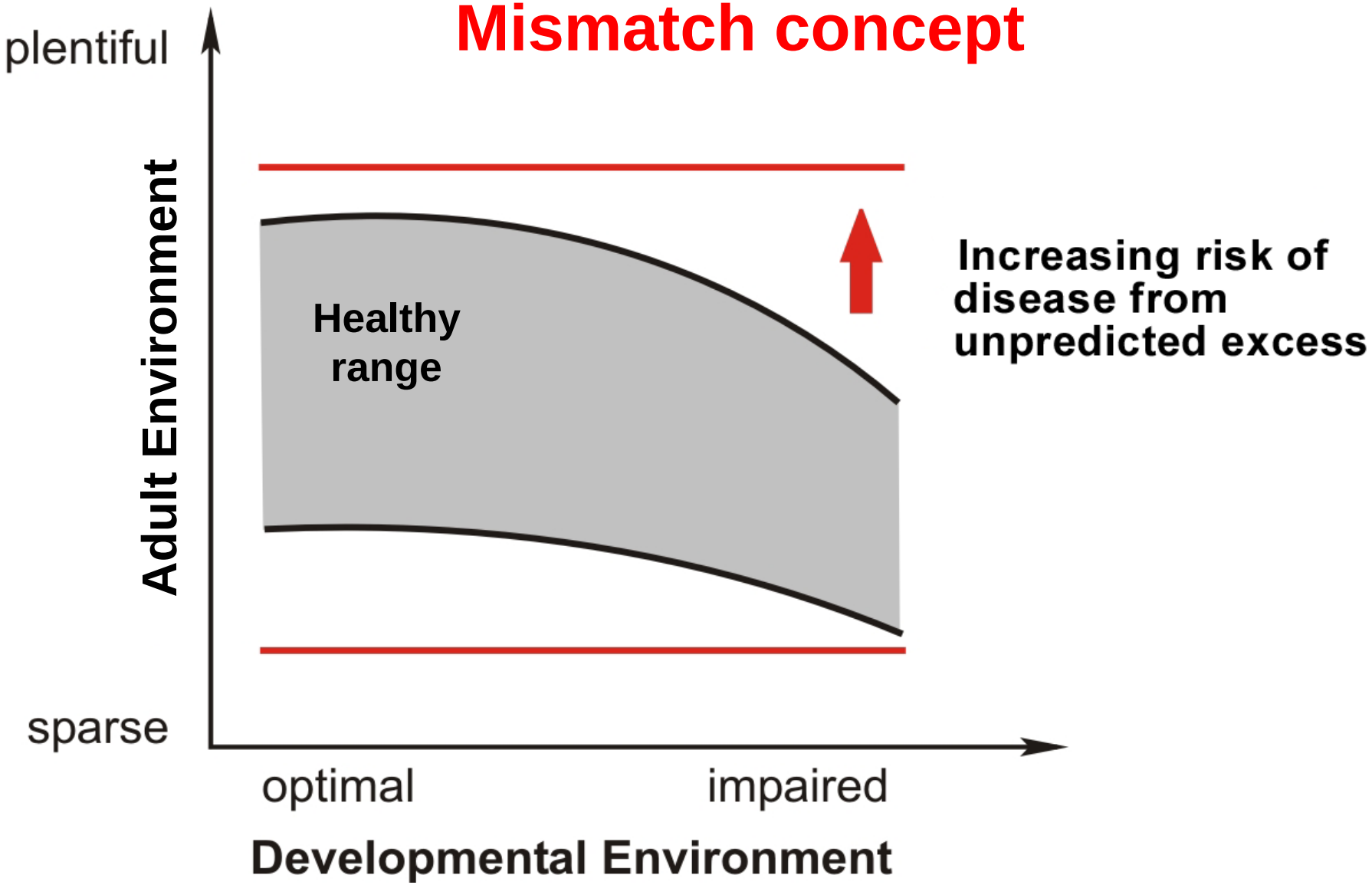
Bryant et al. Circ Res. 2015;116:1202-1205

Maternal oily fish intake in late pregnancy and child's aortic PWV.



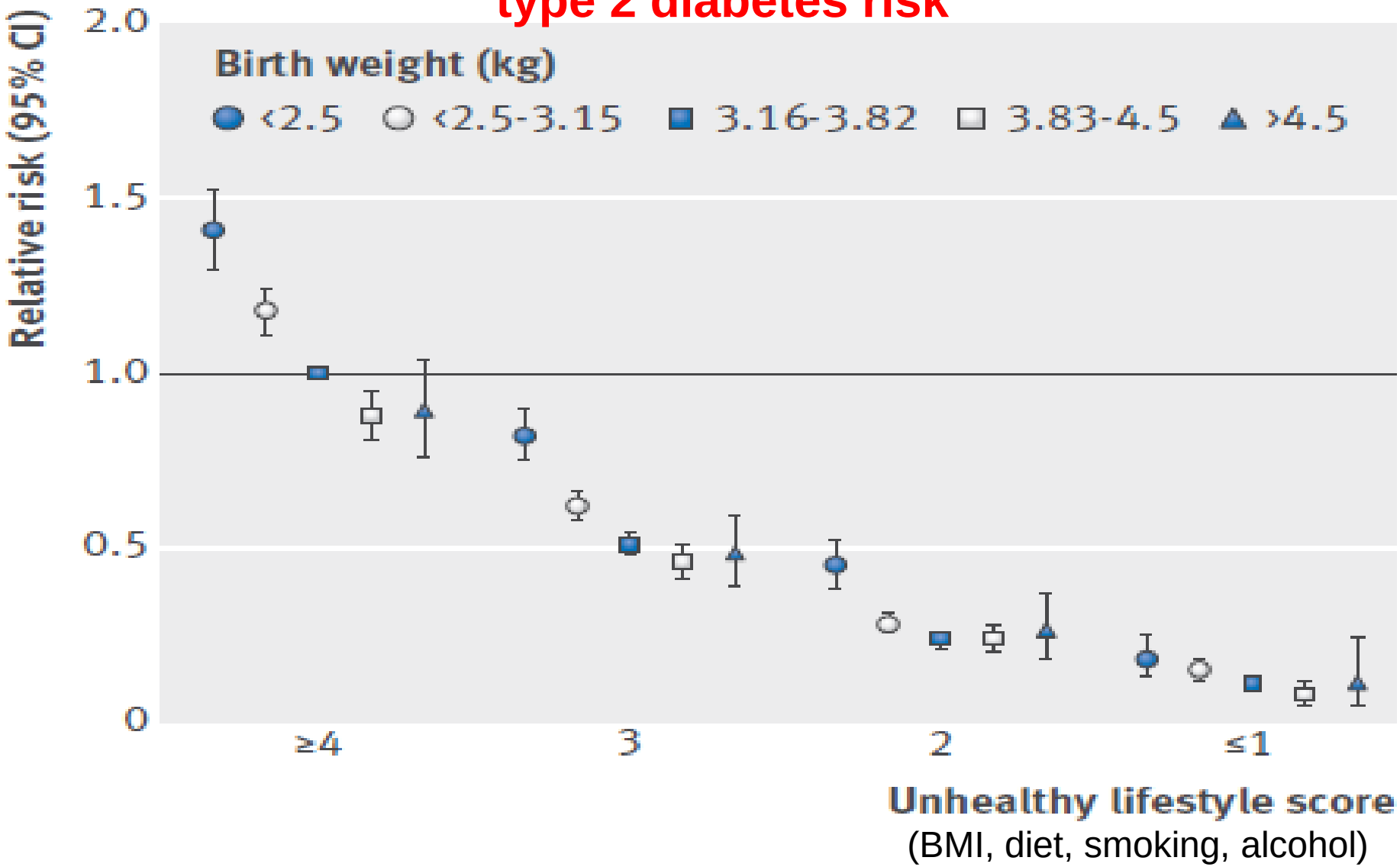
Jennifer Bryant et al. Circ Res. 2015;116:1202-1205

Mismatch concept



Modified from Gluckman & Hanson (2004) *Science* 305 (5691):1733-6

Developmental factors amplify effects of later lifestyle on type 2 diabetes risk



Li Y et al (2015). Birth weight and later life adherence to unhealthy lifestyles in predicting type 2 diabetes: prospective cohort study. BMJ 351: h36731

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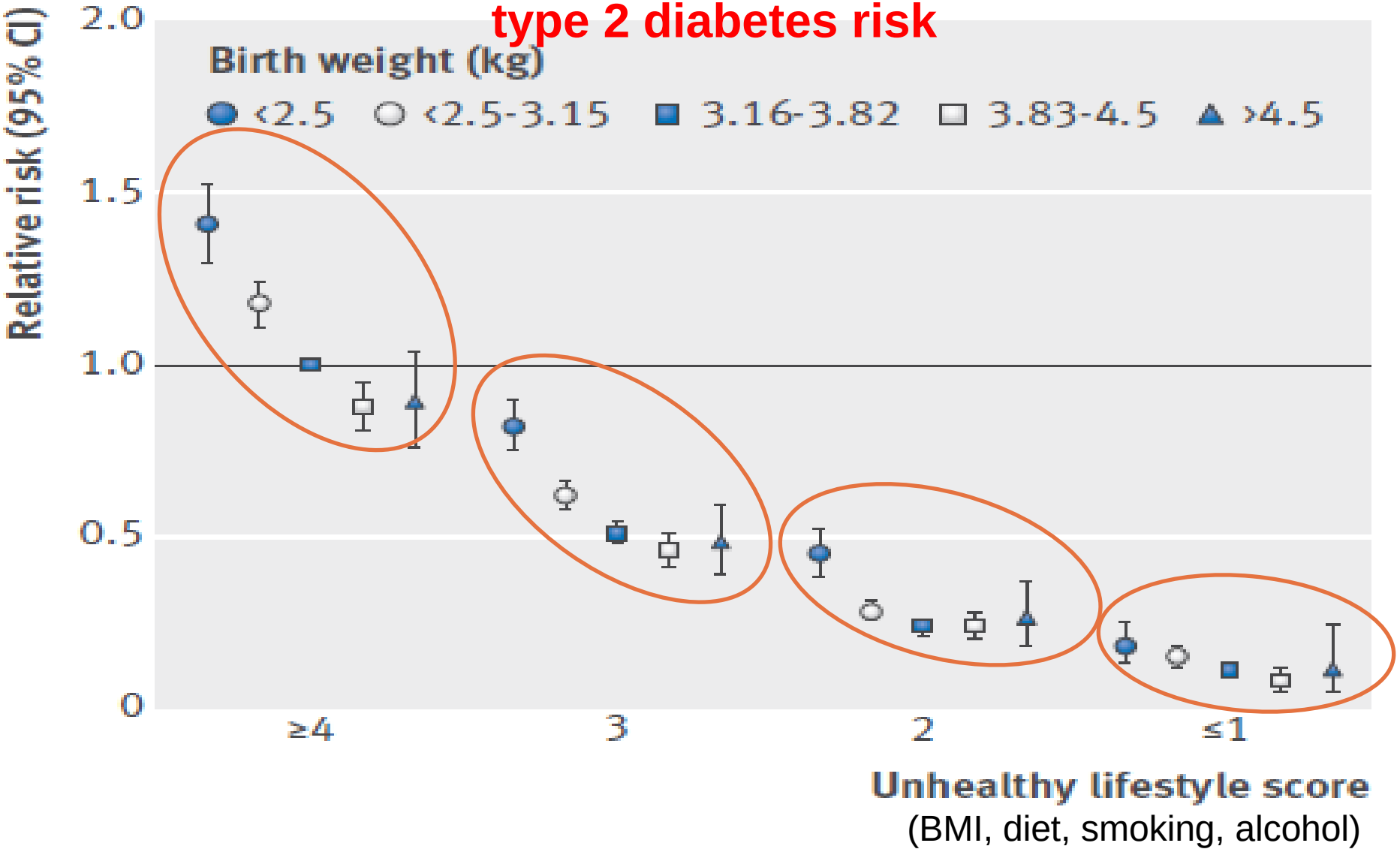
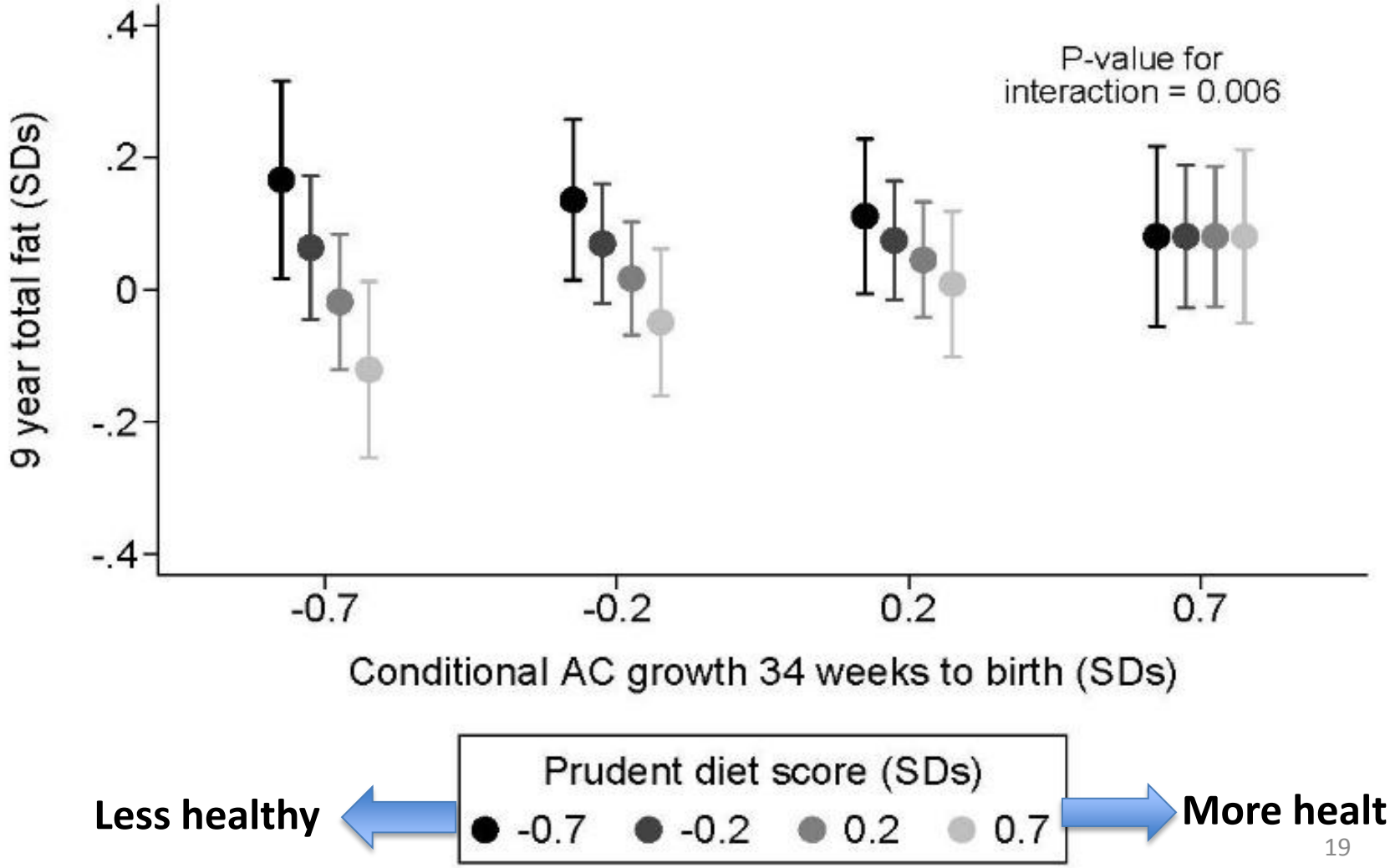


Li Y et al (2015). Birth weight and later life adherence to unhealthy lifestyles in predicting type 2 diabetes: prospective cohort study. BMJ 351: h36731

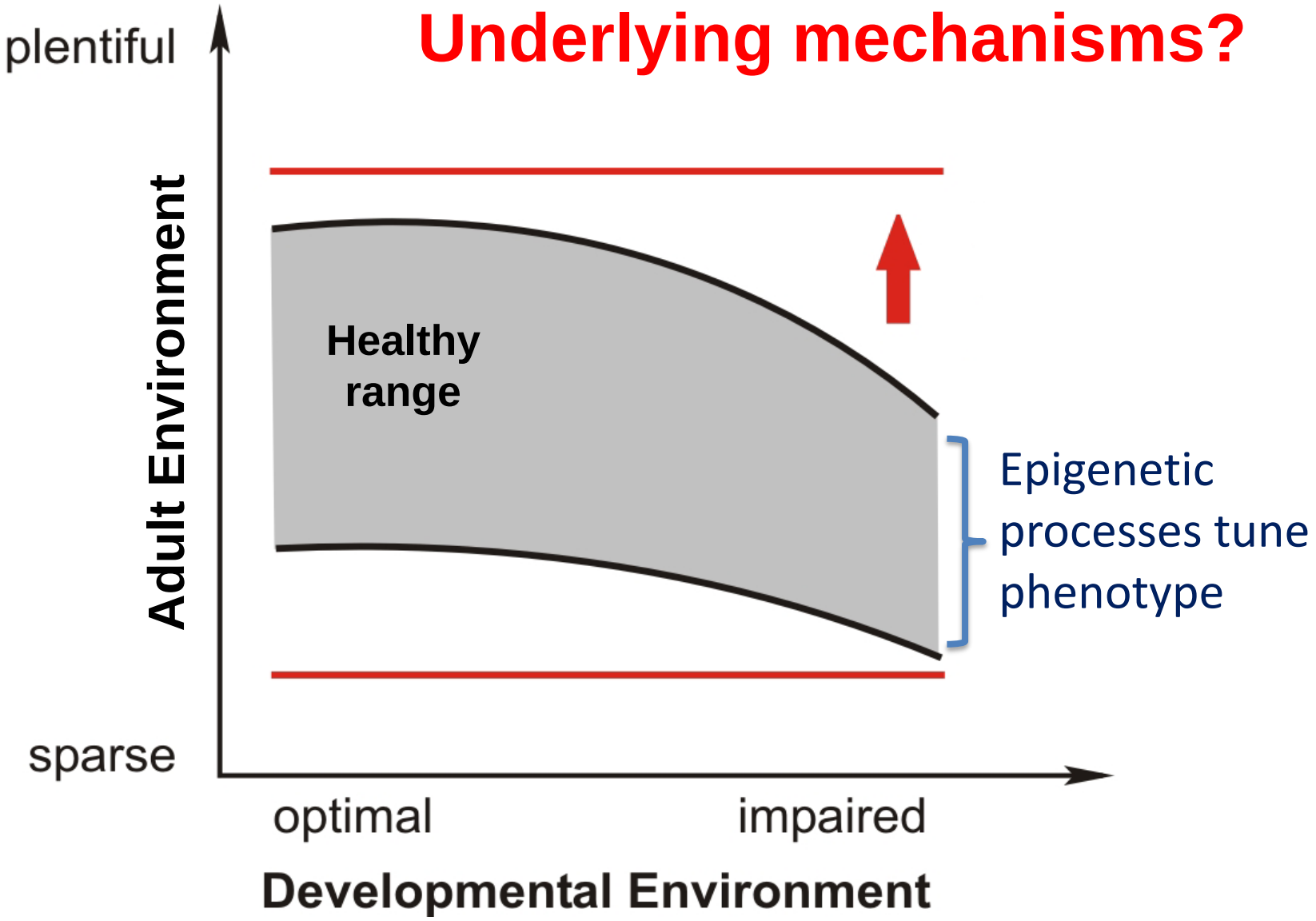
Testing the mismatch hypothesis:

Adiposity responses to unhealthy childhood diet depend on prenatal growth trajectory

S.R. Crozier, J. Bird, H.M. Inskip, N.C. Harvey, S.M. Robinson, C. Cooper, M. Hanson, K.M. Godfrey (DOHaD 2017)

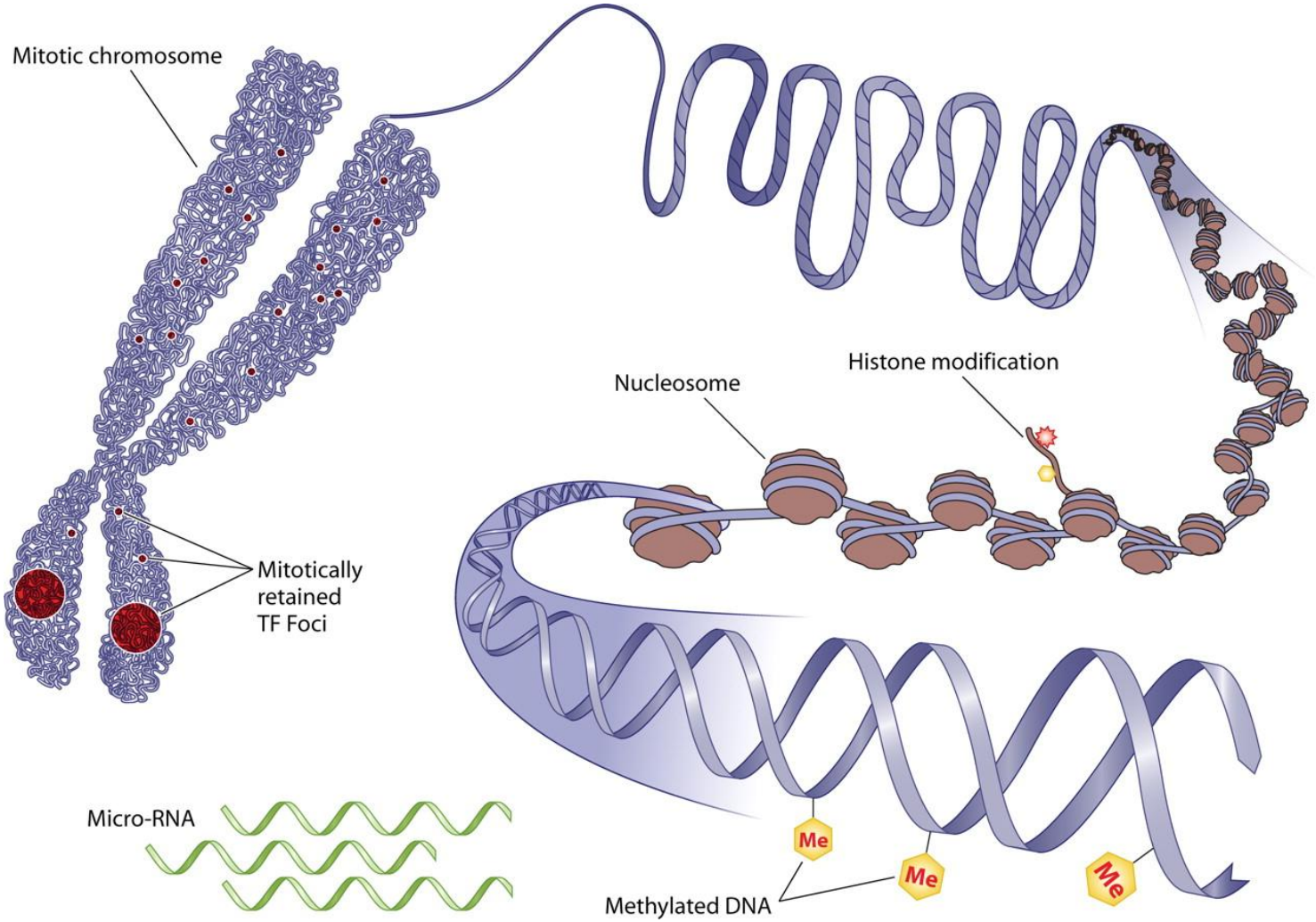


Underlying mechanisms?



Modified from Gluckman & Hanson (2004) *Science* 305 (5691):1733-6

Mechanisms of epigenetics



Zaidi S K et al. Mol. Cell. Biol. 2010;30:4758-4766

Molecular and Cellular Biology

Lillycrop K *et al*. ANRIL promoter DNA methylation: a perinatal marker for later adiposity. *EBioMedicine*. Apr 26 2017

- inter-individual DNA methylation differences in umbilical cord associated with child's adiposity at age 6 years. Search for DMRs
- level of CpG methylation at birth within the promoter of the long non-coding RNA ANRIL (encoded at CDKN2A gene) significantly related to childhood adiposity at age 6 years. Functionally plausible……..

- Association between ANRIL methylation and adiposity also observed in -
  - ethnically diverse neonates in Singapore (skinfolds at 1wk, ponderal index at 18mo
  - peripheral blood from adolescents
  - adipose tissue from obese vs. lean adults
- CpG methylation was associated with ANRIL expression *in vivo*
- CpG mutagenesis *in vitro* inhibited ANRIL promoter activity
- CpG methylation enhanced binding to an Estrogen Response Element within the ANRIL promoter.

The Sustainable Development Goals (SDGs)

In September 2015, the Sustainable Development Goals (SDGs) were adopted by the UN General Assembly and the international community, setting goals to achieve by 2030

Sustainable Development Goal 2.2

By 2030, end all forms of malnutrition, including achieving, by 2025, the internationally agreed targets on stunting and wasting in children under five years of age, and address the nutritional needs of adolescent girls, pregnant and lactating women and older persons

End hunger, achieve food security and improved nutrition and promote sustainable agriculture

Sustainable Development Goal 3.4

By 2030, reduce by one third premature mortality from non-communicable diseases through prevention and treatment and promote mental health and well-being

Ensure healthy lives and promote well-being for all at all ages

EVERY WOMAN
EVERY CHILD

THE GLOBAL STRATEGY FOR WOMEN'S, CHILDREN'S AND ADOLESCENTS' HEALTH (2016-2030)

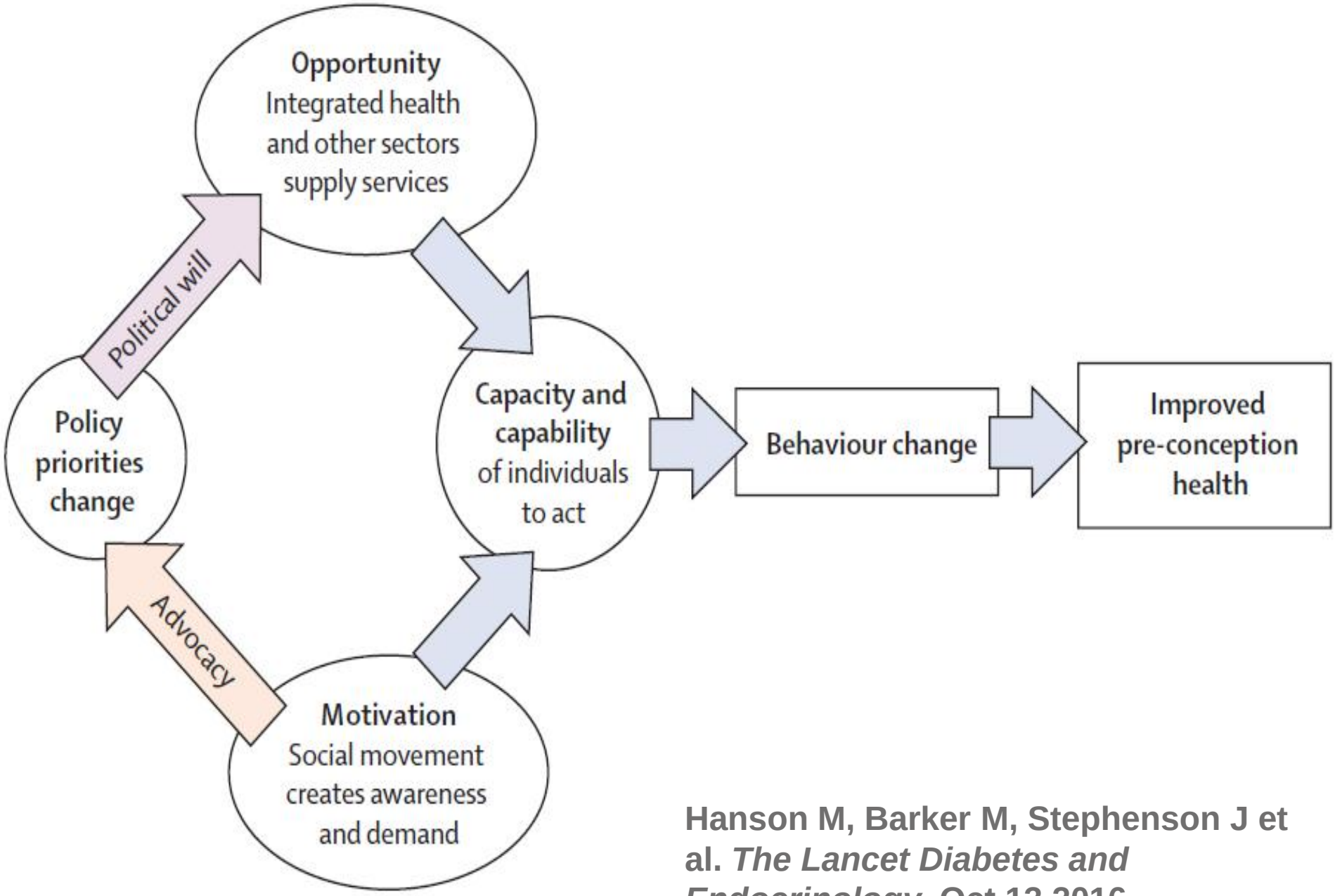
SURVIVE
THRIVE
TRANSFORM

SUSTAINABLE DEVELOPMENT GOALS

“Implementing the *Global Strategy* …
would yield tremendous returns by 2030:
at least a 10-fold return on investments in the health and nutrition of women, children and adolescents through better educational attainments,
workforce participation
and social contributions”

Why focus on pre-conception interventions?

- **Young people often do not know that they may be on a risky health trajectory, even if they appear healthy**
- **Many young people postpone adopting healthy lifestyles until some future date**
- **They do not realise that risk of NCDs can be transmitted to their future children by biological as well as environmental processes**
- **Many young people are not on primary health-care radar, and have poor levels of health literacy so are less likely to access services**
- **Whether pregnancy is planned or not, many women and their partners do not alter their lifestyles in preparation for it, nor indeed do so during pregnancy**
- **Women may not access health care until late in the first trimester of pregnancy – too late to prevent some risks for them and their children**



Hanson M, Barker M, Stephenson J et al. *The Lancet Diabetes and Endocrinology*, Oct 13 2016

Poor educational attainment
Poor diet
Take less exercise
Obese

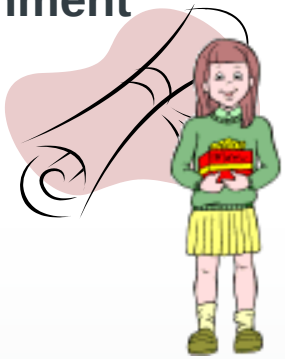
Ill-prepared for pregnancy.

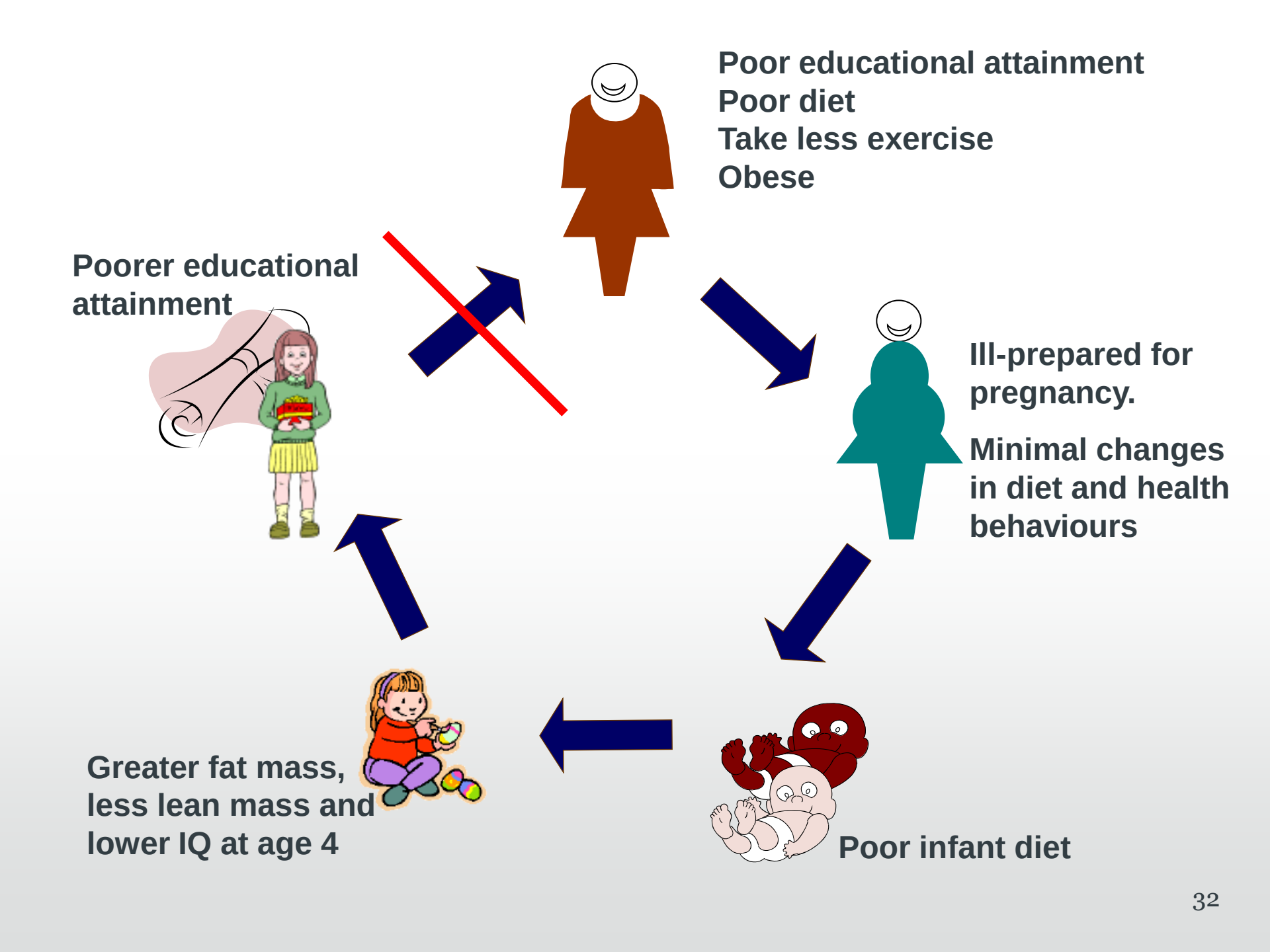
Minimal changes in diet and health behaviours

Poor infant diet

Greater fat mass, less lean mass and lower IQ at age 4

Poorer educational attainment

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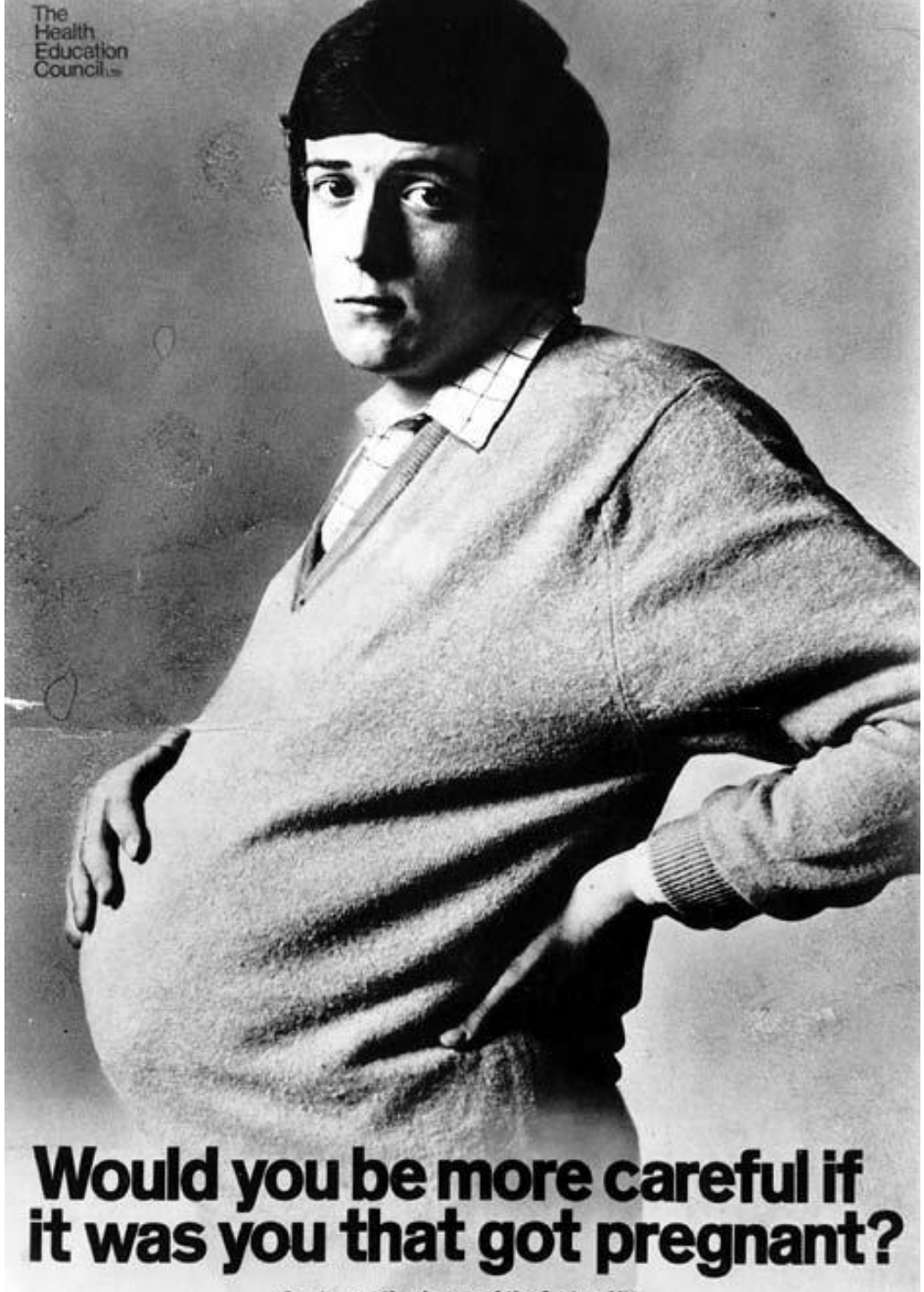
The
Health
Education
Council
Would you be more careful if
it was you that got pregnant?

Animal studies showing paternal epigenetic effects on offspring

- **Low paternal dietary folate alters the mouse sperm epigenome and is associated with negative pregnancy outcomes - Lambrot R et al *Nature Communications* 10 Dec 2013.**
- **Male rats fed a high fat diet have female offspring with altered pancreatic DNA methylation – Ng S-F et al (2010) *Nature* 467: 963-966**
- **Male mice fed a low protein diet have offspring with altered expression of cholesterol genes in liver – Carone BR et al (2010) *Cell* 143: 1084-96**
- **Male mice with pre-diabetes have abnormal sperm methylation and pass increased risk of diabetes to next two generations – Wei Y et al (2014) *PNAS* 111: 1873-78**

LIFELAB

The Healthy Generation

LifeLab: educating young people through science for their health and that of their future children

UNIVERSITY OF Southampton | University Hospital Southampton NHS
NHS Foundation Trust

First LifeLab RCT. Odds ratio of response to questions 12 months after LifeLab / no visit, relative to baseline response and adjusted for sex and deprivation score.

Question	Outcome response	OR	95%CI	P-value
At what age do you think our nutrition starts to affect our future health?	Before birth	**1.87**	(1.42,2.45)	<0.001
The food I eat now may affect my health in the future	Strongly agree or agree	**1.19**	(1.08,1.32)	<0.001
The food a woman eats when she is pregnant does not affect the health of her child	Strongly disagree or disagree	**1.62**	(1.20,2.20)	0.002
The food I eat now may affect the health of any children I have in the future	Strongly agree or agree	**1.43**	(1.17,1.74)	<0.001
The food a father eats before having a baby will affect the health of his children	Strongly agree or agree	**4.05**	(2.34,7.01)	<0.001
It is not important for me to eat healthy food now	Strongly disagree or disagree	**1.00**	(0.88,1.14)	0.9
At school I feel I have to eat and drink the same things as my friends	Strongly disagree or disagree	**1.12**	(0.90,1.39)	0.3

DOHaD 2017

15-18th October 2017
Rotterdam, The Netherlands

10th World Congress

DEVELOPMENTAL ORIGINS OF HEALTH AND DISEASE

www.dohad2017.org

Long-Term Persistence of Hormonal Adaptations to Weight Loss

Sumithran et al NEJM (2011) 365: 1597-604

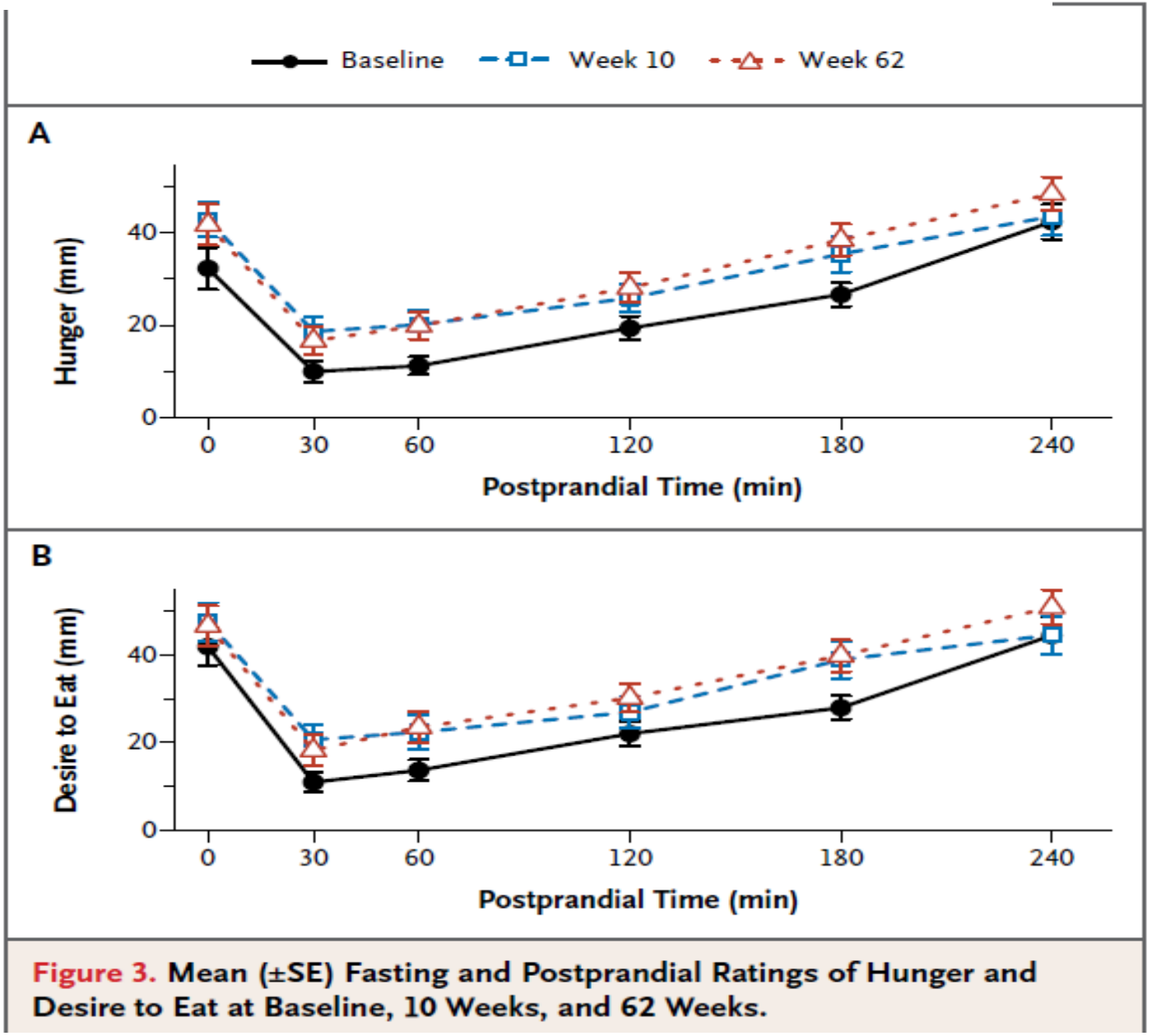

Figure 3. Mean (±SE) Fasting and Postprandial Ratings of Hunger and Desire to Eat at Baseline, 10 Weeks, and 62 Weeks.