



Professor John Dixon

Head of Clinical Obesity Research
Baker IDI Heart and Diabetes Institute
Melbourne

Friday, August 09, 2019

(Plenary)

16:30 - 16:45 Genetic and Early Life Factors: The First Thousand Days

The determinants of obesity

Genetics and early life factors: The first 1000 days

Professor John B Dixon
Head of the Clinical Obesity Research Laboratory
Baker Heart and Diabetes Institute, Melbourne

South GP CME South Meeting
08 Aug 2019 - 11 Aug 2019

Disclosures: Professor John B Dixon



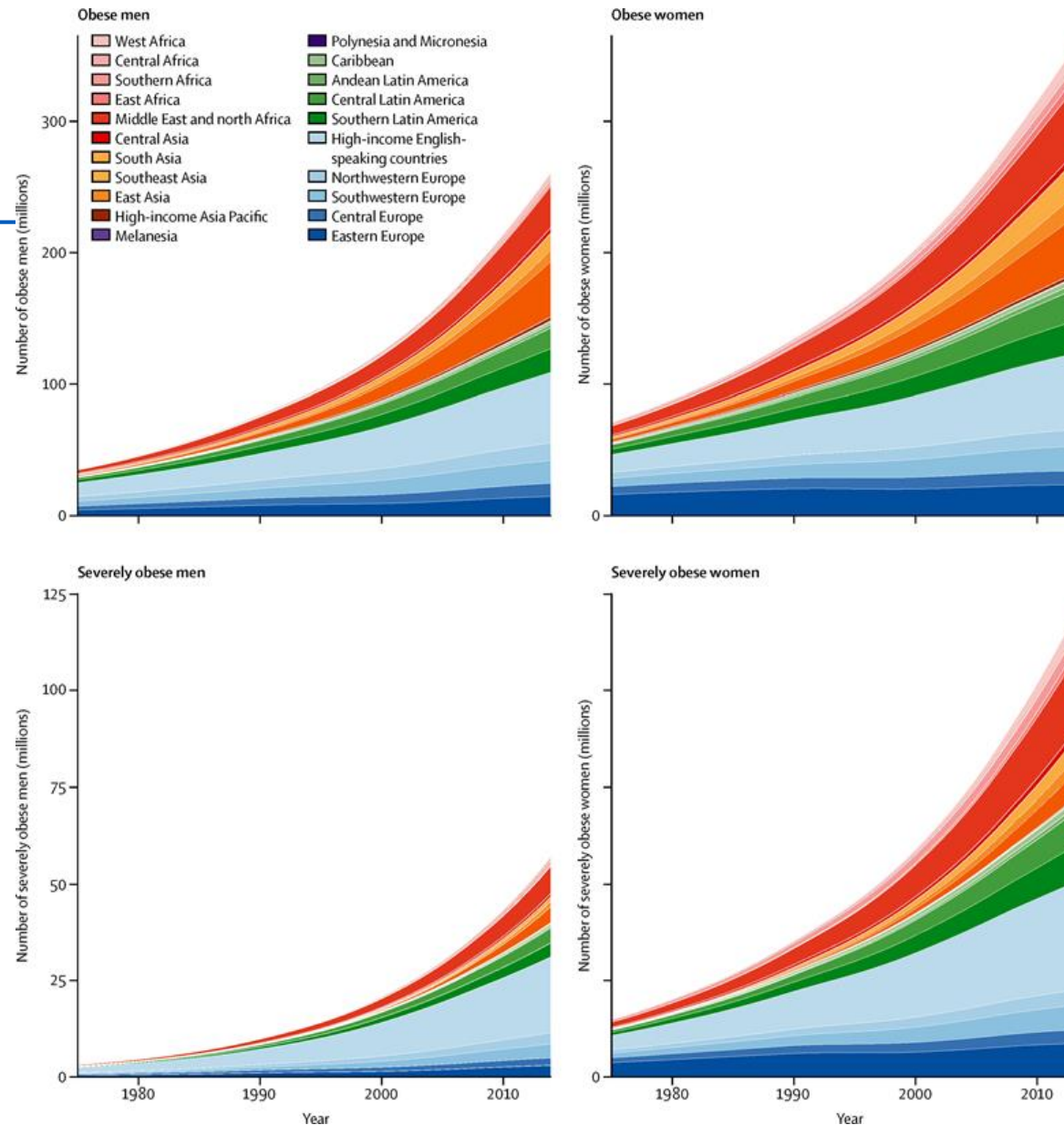
Bariatric Advantage	Consultant
BUPA	Research Support
I-Nova	Consultant
Nestle Health Science	Consultant
NACOS	Chair accreditation
NHMRC	Research Support
Nova Nordisk	Advisory board and speaker fees
MISS	Co-director US surgical conference
Obesity Australia	
RACGP	Research Support

Everything You Know About Obesity Is Wrong
For decades, the medical community has ignored mountains of evidence to wage a cruel and futile war on fat people, poisoning public perception and ruining millions of lives.

HUFFINGTON POST
SEPTEMBER 19, 2018

Global & Regional Obesity

High income
English speaking
Blue

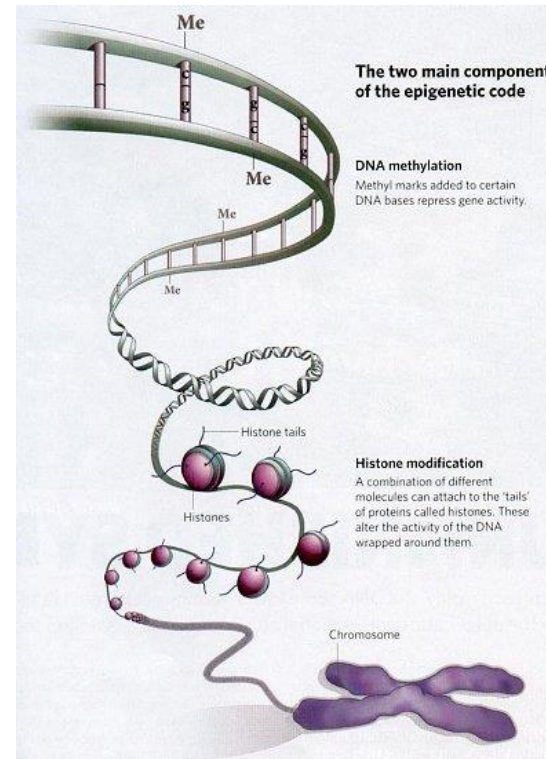


Global & Regional Severe obesity

Collaboration, N. C. D. R. F. (2016). "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." *Lancet* **387**(10026): 1377-1396.

The complex determinants of obesity: Nature and Nurture

Type	Correlation Men	Correlation Women
Monozygotic		
Reared apart	0.70	0.66
Reared Together	0.74	0.66
Dizygotic		
Reared Apart	0.15	0.25
Reared Together	0.33	0.27

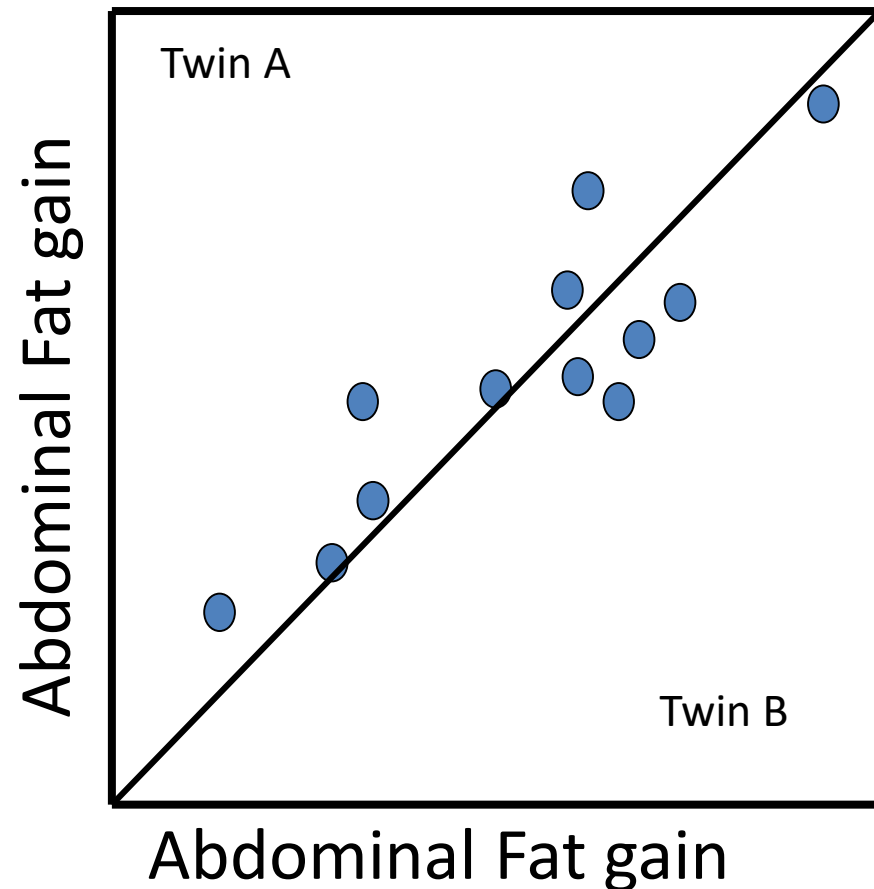


Stunkard AJ et al New Engl J Med 322:1483-7 1990



Early life programming is critical and we now focus on the first 1000 days following conception

Effect of 100 days of overfeeding in 12 pairs of identical twins



Bouchard C et al New Engl J Med 322:1477-82 1990

Genes are major determinants of our likelihood of becoming obese

Farooqi estimated the heritability of BMI at around 40% to 70% (35).

Farooqi IS, O'Rahilly S. New advances in the genetics of early onset obesity. *Int J Obes* 2005; **29**: 1149–1152.

Fetal origins of adult disease



“Barker” hypothesis: programming of function

During early life nutrient exposure sets metabolic behaviour and thereby determines the risk of chronic disease during adult life.



The evidence is presented in Barker's book Fetal and Infant Origins of Adult Disease (1992).

Epigenetics “The science of change”

Refers to changes in gene expression caused by environmental factors, not by changes in the underlying DNA sequence.

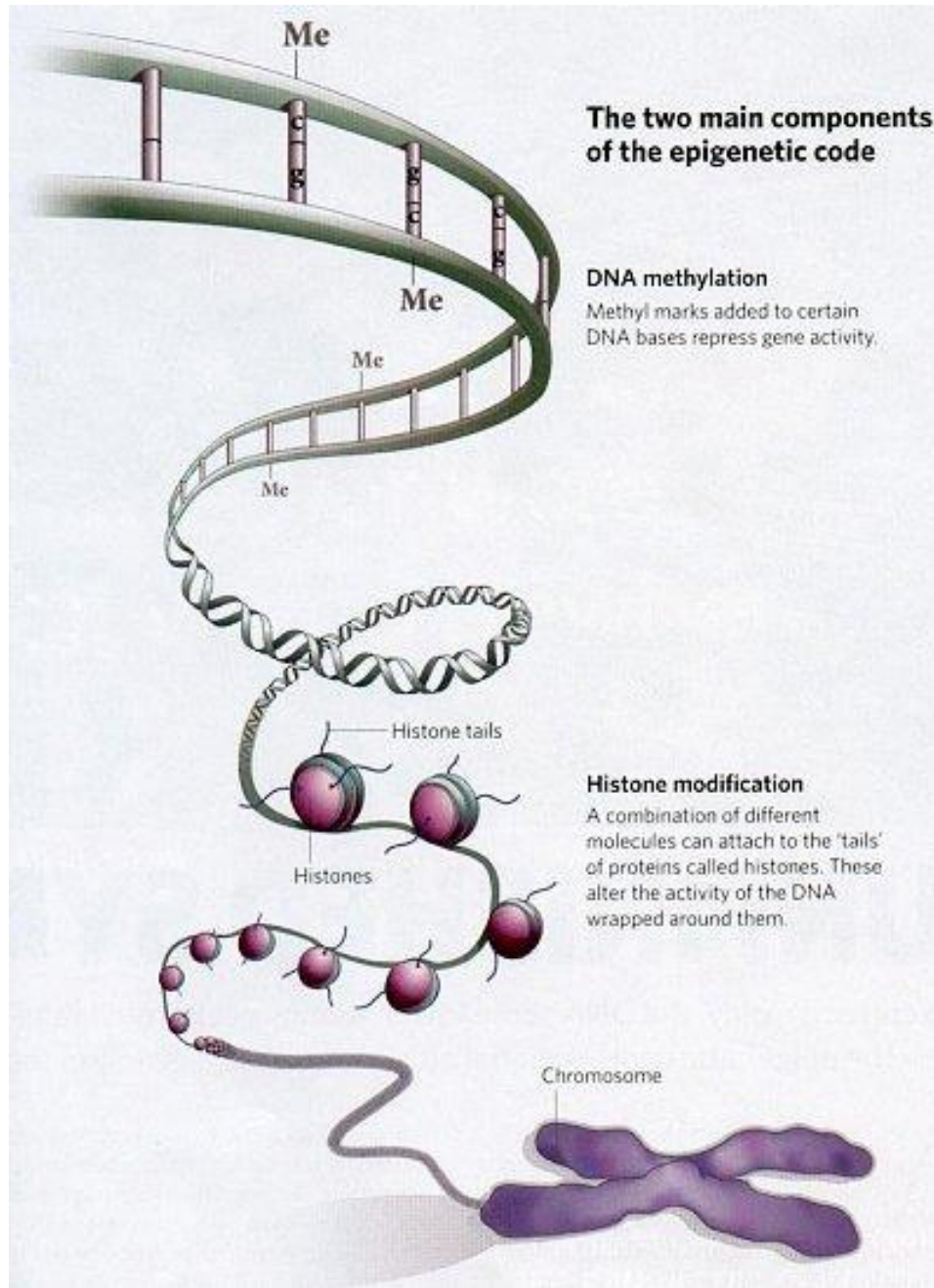
Changes may remain not just for the rest of that cell's life but through cell division continue to influence.

Sometimes the changes last for multiple generations.

Environmental factors cause the organism's genes to express themselves differently.

The mechanisms are complex

Changes are usually prenatal and early post natal



Environmental influences on one generation may last for generations

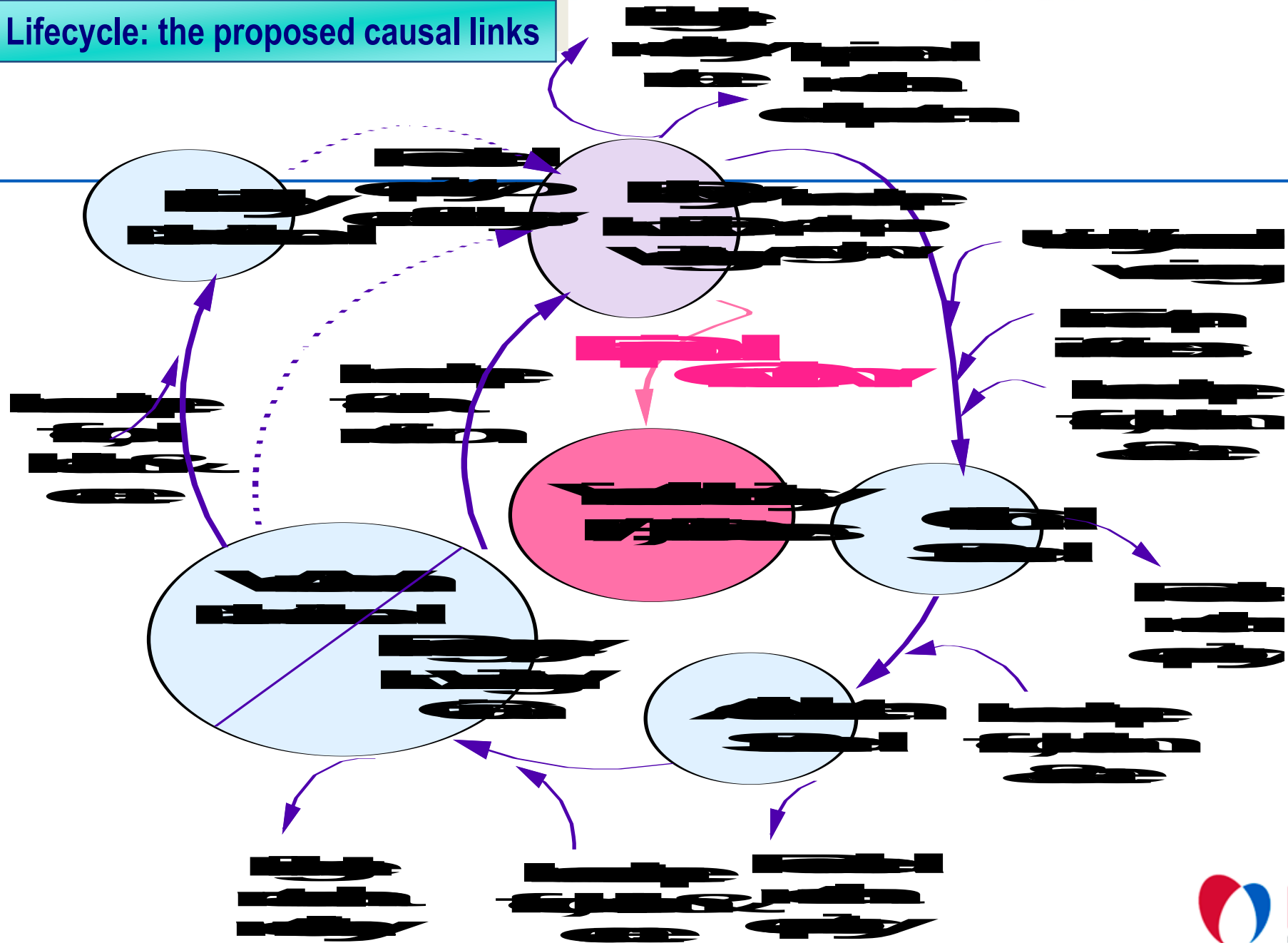
DNA methylation

Histone modification

**Patterns of micro RNAs
are also readily changed
by the environment**

**Small non-coding RNA
from oocyte and sperm**

Lifecycle: the proposed causal links



Epigenetics “the science of change”

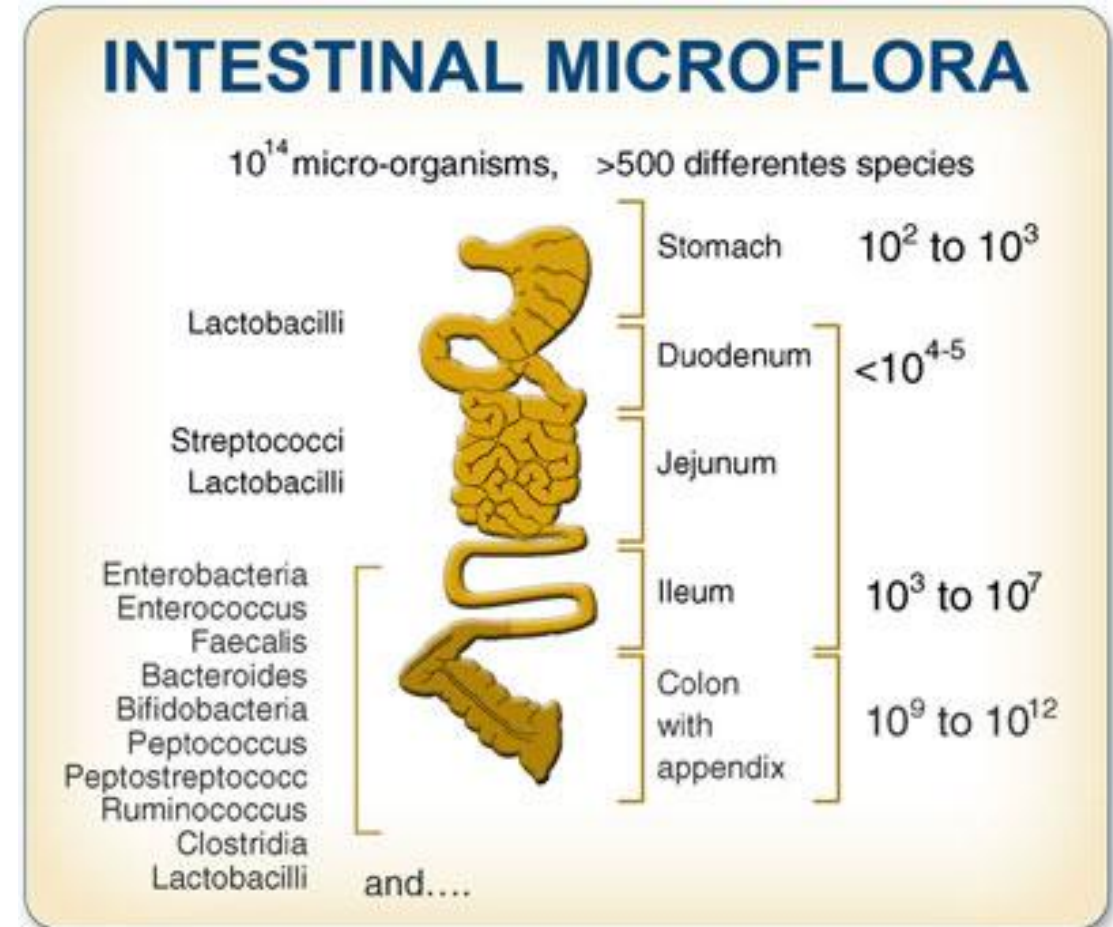
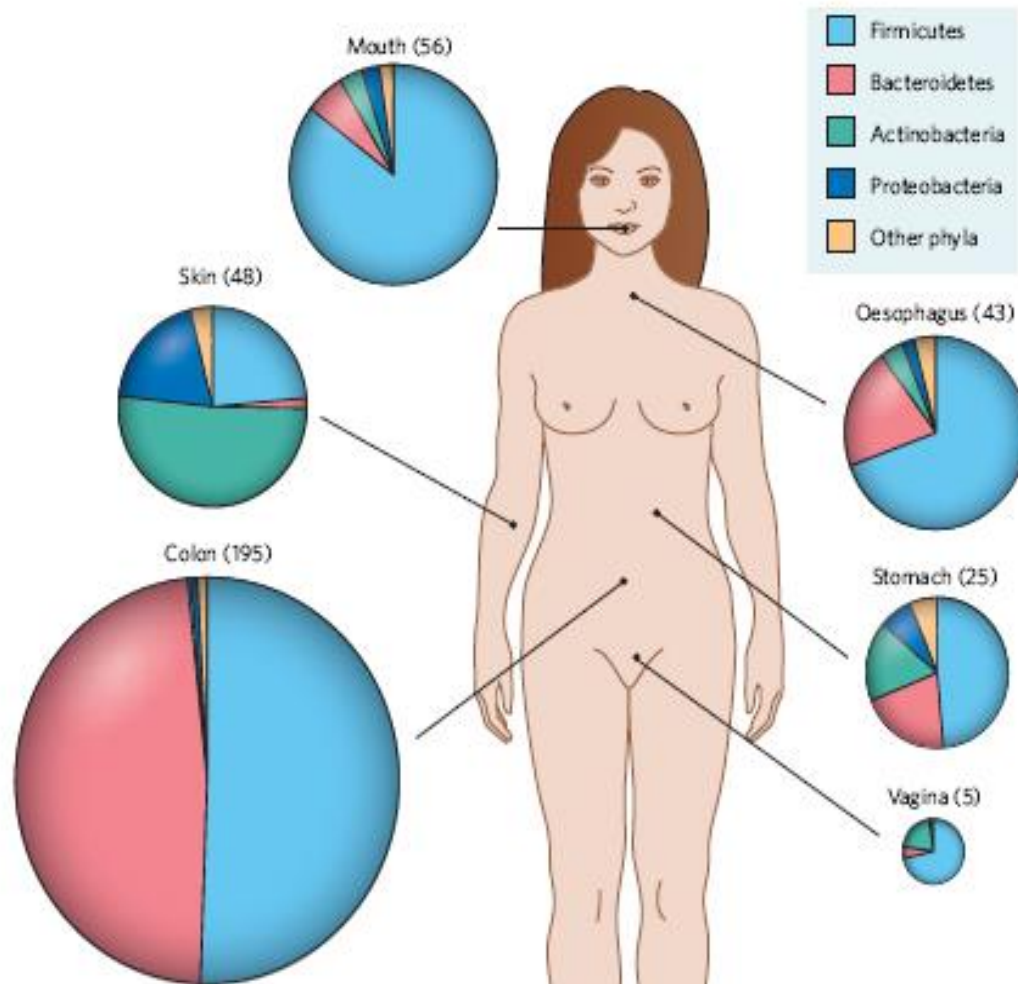
But her developing ova
are also programmed
And it can take several
generations to reverse



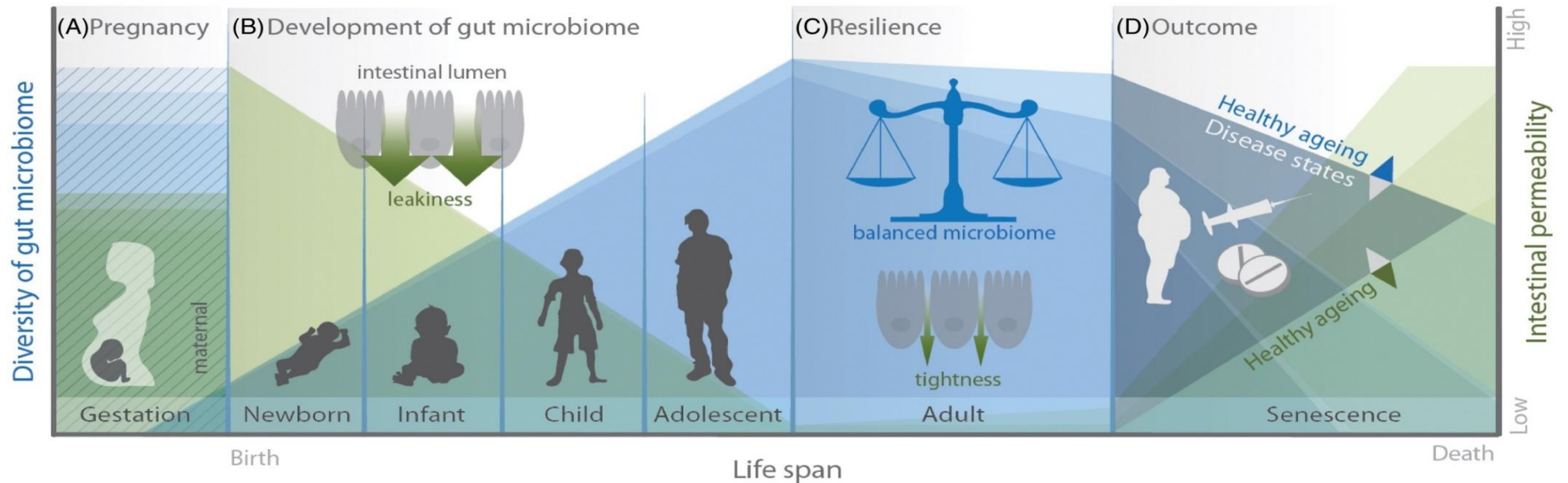
Telltale traits. Differences in the size and color of offspring are epigenetic effects of genistein consumption (via a high-soy diet) by mouse moms.

Color by Soy- Genistein Linked to Epigenetic Effects
Weinhold, Envir Health Perspect, Dolinoy, EHP 2006

The proportion of phyla vary with site, are robust within sites, and patterns are highly specific to an individual



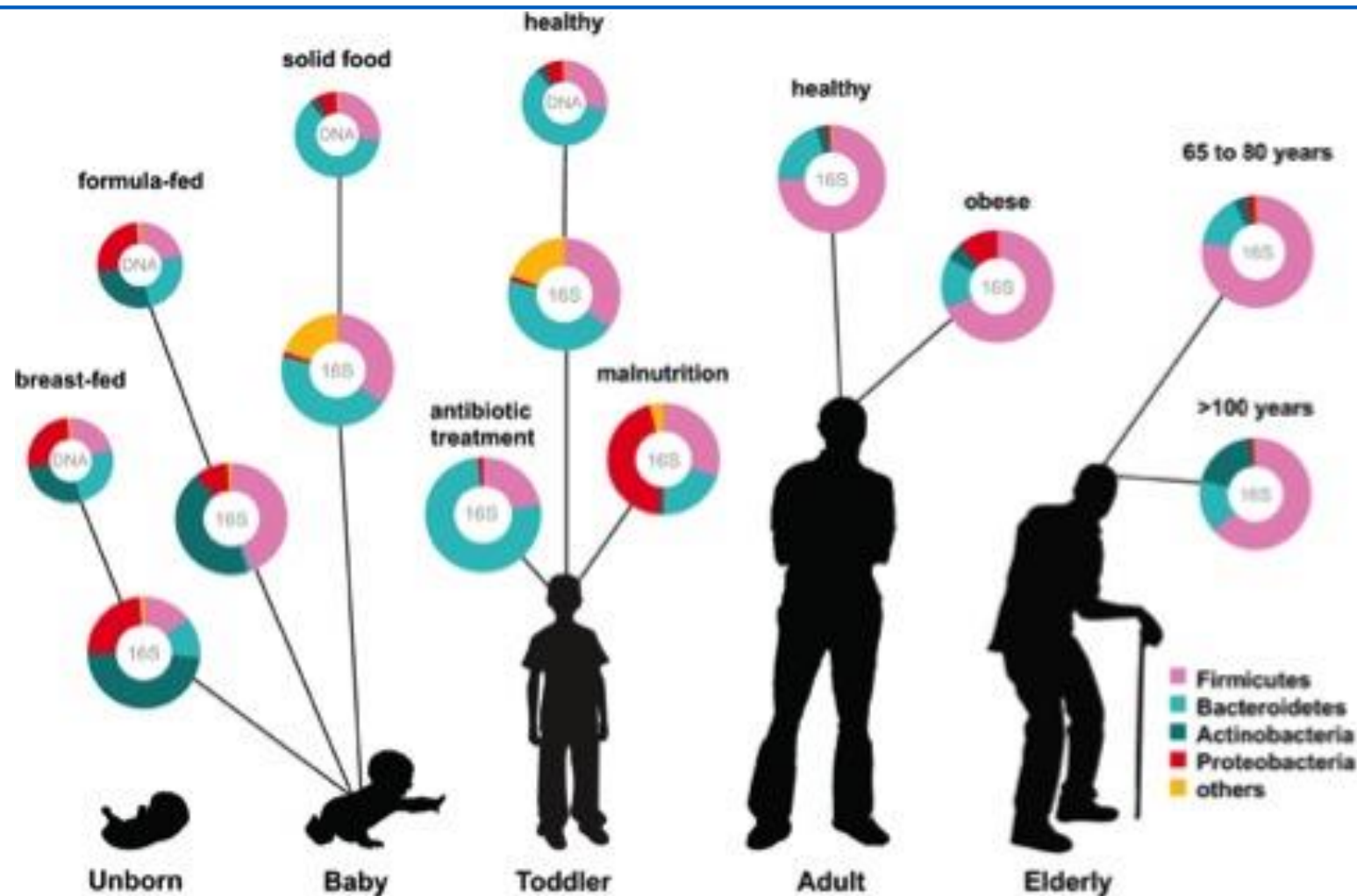
The development of a healthy gut microbiome



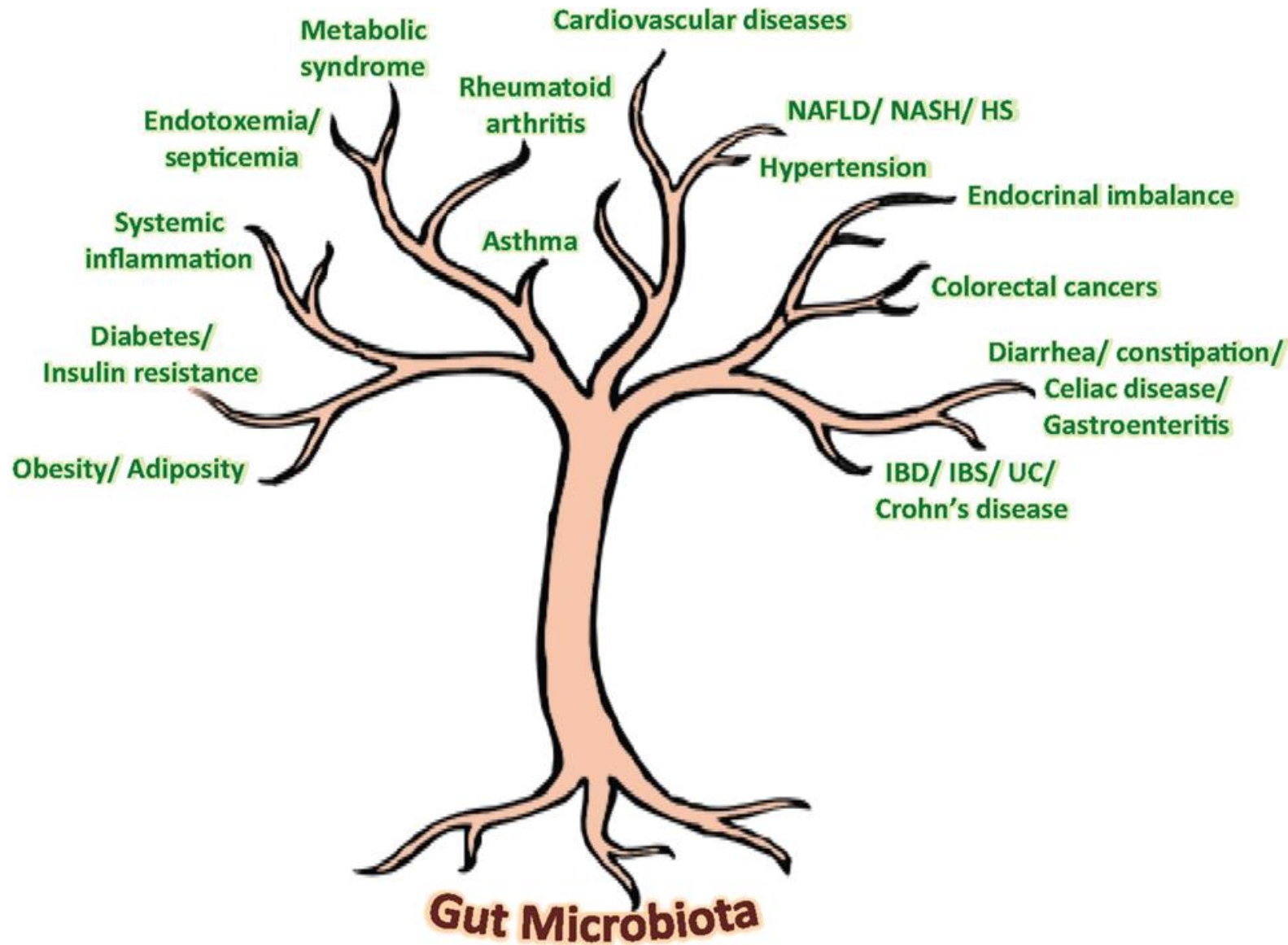
Green is the level of permeability and blue a balanced resilient microbiome

The gut microbiome and health throughout the life cycle

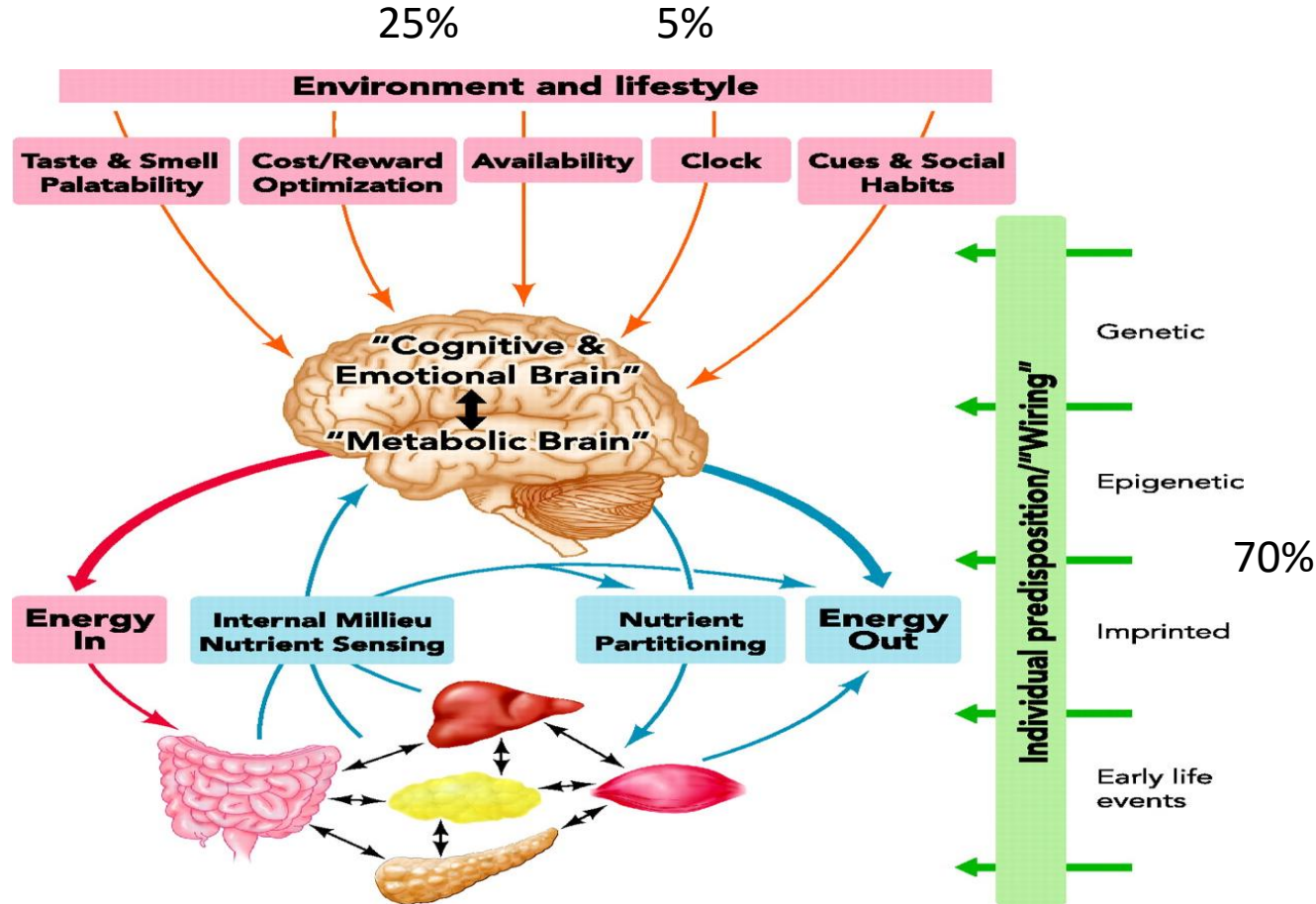
Change throughout the human life cycle



Ottman N, et al, (2012) Front. Cell. Inf. Microbio. 2:104. doi: 10.3389/fcimb.2012.00104.



Schematic diagram showing the major factors determining neural control of appetite and regulation of energy balance



The first 1000 days of life are critical in determining weight trajectory for life

Unfortunately a rise in weight (fat) is defended just as a rise in blood pressure is defended

Contributors beyond the BIG TWO



Reduced smoking rates

Infection and obesity

Epigenetic

Intrauterine and
intergenerational effects

Maternal age

Non-random mating

Sleep debt

Endocrine disruptors

Iatrogenic

Ambient temperature



Ten Putative Contributors to the Obesity Epidemic

EMILY J. McALLISTER,¹ NIKHIL V. DHURANDHAR,¹ SCOTT W. KEITH,²
LOUIS J. ARONNE,³ JAMIE BARGER,^{4,5} MONICA BASKIN,⁶ RUTH M. BENCA,⁷
JOSEPH BIGGIO,⁸ MARY M. BOGGIANO,⁹ JOE C. EISENMANN,¹⁰
MAI ELOBEID,¹¹ KEVIN R. FONTAINE,¹² PETER GLUCKMAN,¹³
ERIN C. HANLON,¹⁴ PETER KATZMARZYK,¹⁵ ANGELO PIETROBELLI,¹⁶
DAVID T. REDDEN,¹¹ DOUGLAS M. RUDEN,¹⁷ CHENXI WANG,¹⁸ ROBERT A. WATERLAND,¹⁹
SUZANNE M. WRIGHT,³ and DAVID B. ALLISON¹¹

The Putative 104 Causes of Obesity

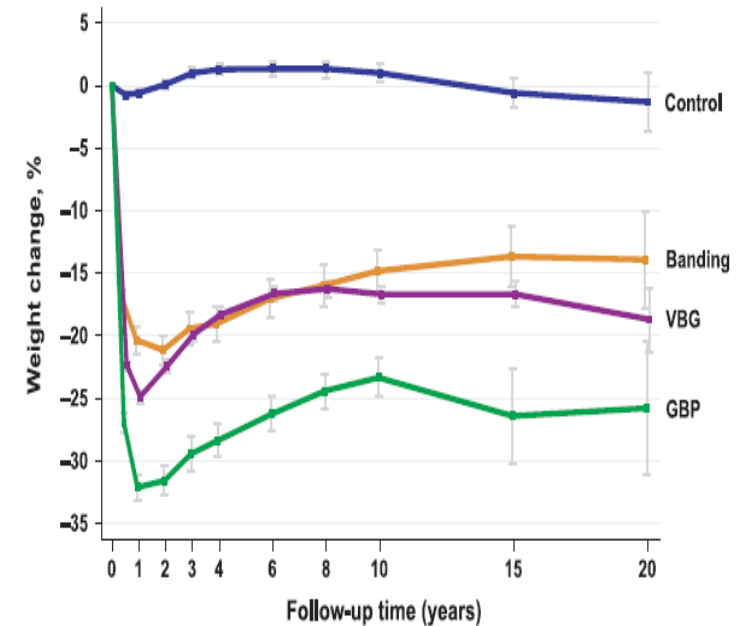
Update October 22nd, 2015 by Morgan Downey

1. agricultural policies 2. air conditioning, 3. air pollution, 4. antibiotic usage at early age, 5. arcea nut chewing, 6. artificial sweeteners, 7. Asian tiger mosquitos, 8. assortative mating, 9. being a single mother, 10. birth by C-section, 11. built environment, 12. celebrity chefs, 13. chemical toxins, (endocrine disruptors) 14. child maltreatment, 15. compulsive buying, 16. competitive food sales in schools, 17. consuming skim milk in preschool children, 18. consumption of pastries and chocolate (in Burkina Faso), 19. decline in occupational physical activity, 20. delayed prenatal care, 21. delayed satiety, 22. depression 23. driving children to school 24. eating away from home 25. economic development (nutrition transition) 26. entering into a romantic relationship, 27. epigenetic factors, 28. eradication of Helicobacter pylori, 29. family conflict, 30. family divorce, 31. first-born in family, 32. food addiction, 33. food deserts, 34. food insecurity, 35. food marketing to children, 36. food overproduction, 37. friends, 38. genetics, 39. gestational diabetes, 40. global food system, (international trade policies) 41. grilled foods, 42. gut microbioata, 43. having children, for women, 44. heavy alcohol consumption, 45. home labor saving devices, 46. hormones (insulin, glucagon, ghrelin), 47. hunger-response to food cues, 48. high fructose corn syrup, 49. interpersonal violence, 50. lack of family meals, 51. lack of nutritional education, 52. lack of self-control, 53. large portion sizes, 54. living in crime-prone areas, 55. low educational levels for women, 56. low levels of physical activity, 57. low Vitamin D levels, 58. low socioeconomic status, 59. market economy, 60. marrying in later life 61. maternal employment, 62. maternal obesity, 63. maternal over-nutrition during pregnancy, 64. maternal smoking, 65. meat consumption, 66. menopause, 67. mental disabilities, 68. no or short term breastfeeding, 69. non-parental childcare 70. outdoor advertising, 71. overeating, 72. participation in Supplemental Nutrition Assistance Program (formerly Food Stamp Program) 73. perceived weight discrimination, 74. perception of neighborhood safety, 75. physical disabilities, 76. prenatal maternal exposure to natural disasters, 77. poor emotional coping 78. sleep deficits, 79. skipping breakfast, 80. snacking, 81. smoking cessation, 82. spanking children, 83. stair design 84. stress, artificial lighting, air conditioning, 85. sugar-sweetened beverages, 86. taste for fat 87. trans fats, 88. transportation by car, 89. television set in bedrooms 90. television viewing, 91. thyroid dysfunction 92. vending machines, 93. virus, 94. weight gain inducing drugs, 95. working long hours,

96. NEW too much homework, 97. NEW insufficient body heat, 98. NEW imagining the smell of food, 99. NEW dust components, 100. NEW living with grandparents in China, 101. NEW estrogens, 102. NEW thermogenic adipocytes, 103. NEW prenatal exposure to cigarette smoke, 104. NEW starting college.

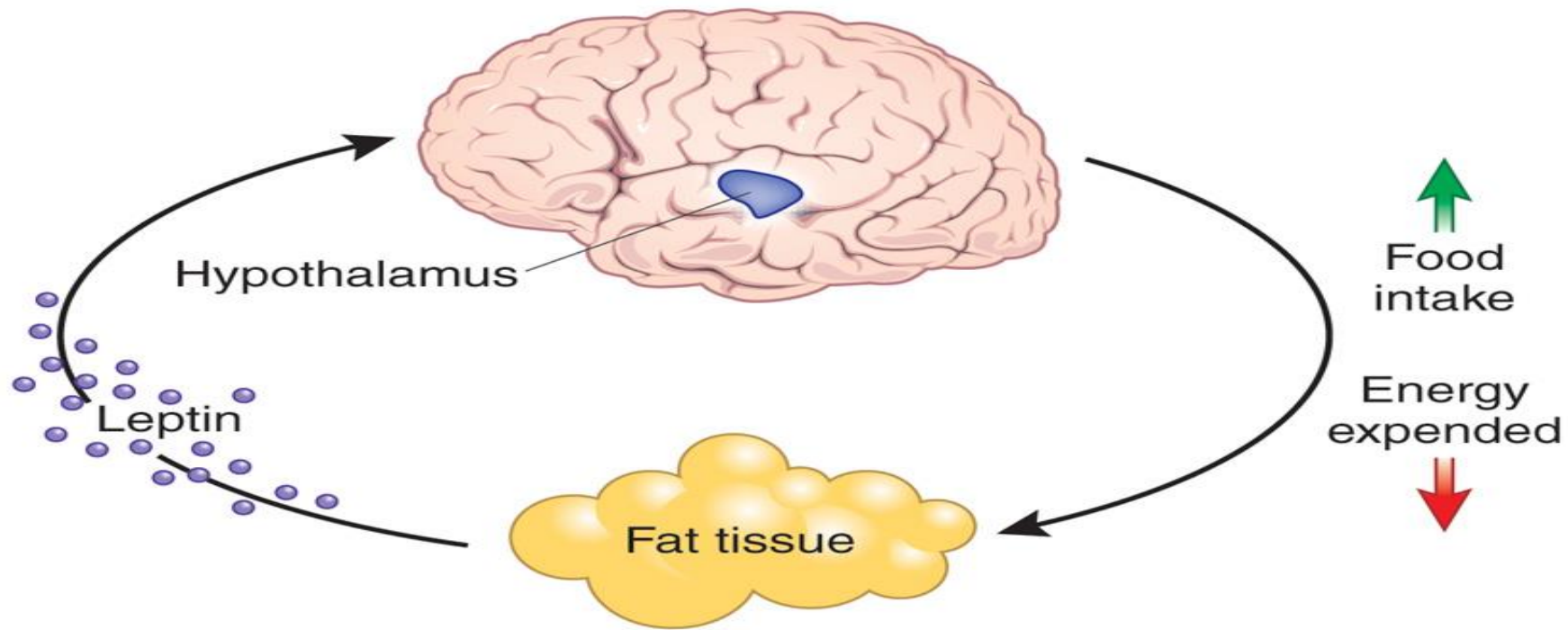
Every essential for a functional life must be carefully regulated

Temperature
Oxygen saturation
Blood pressure
Blood glucose
Fuel stores



The regulation of energy stores is still working when a obese patient has lost weight following bariatric surgery

The brain is key to the control of energy balance

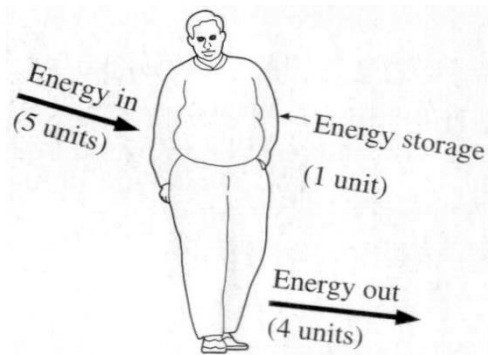


Oh, if it were as simple as energy in energy out and will power!

First law of thermodynamics – Conservation of energy **True**

This notion is fundamentally flawed, for one simple reason: it assumes that **weight is the “dependent”** variable in this equation.

Indeed, everything we know about human physiology points to the fact that it is as much (if not more) **body weight itself that determines energy intake and output as vice versa.**



$$\text{Energy Intake} = \text{weight (REE)} + \text{NREE}$$

Biological systems are regulated

ENERGY BALANCE

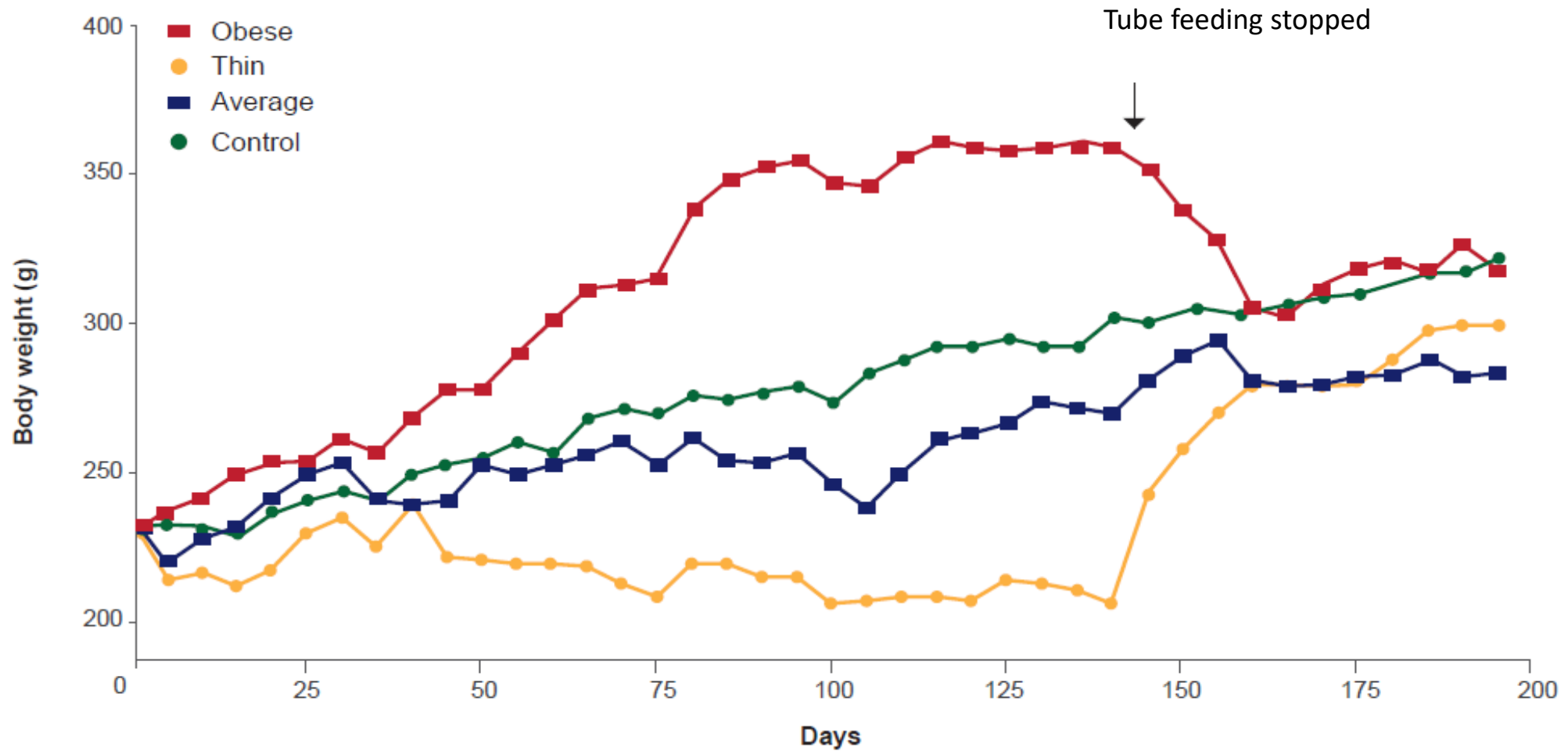


Controversies in Obesity

Haslam, David W., Sharma, Arya M., le Roux, Carel W. (Eds.)

Effect of different feeding regimens on body weight in rats

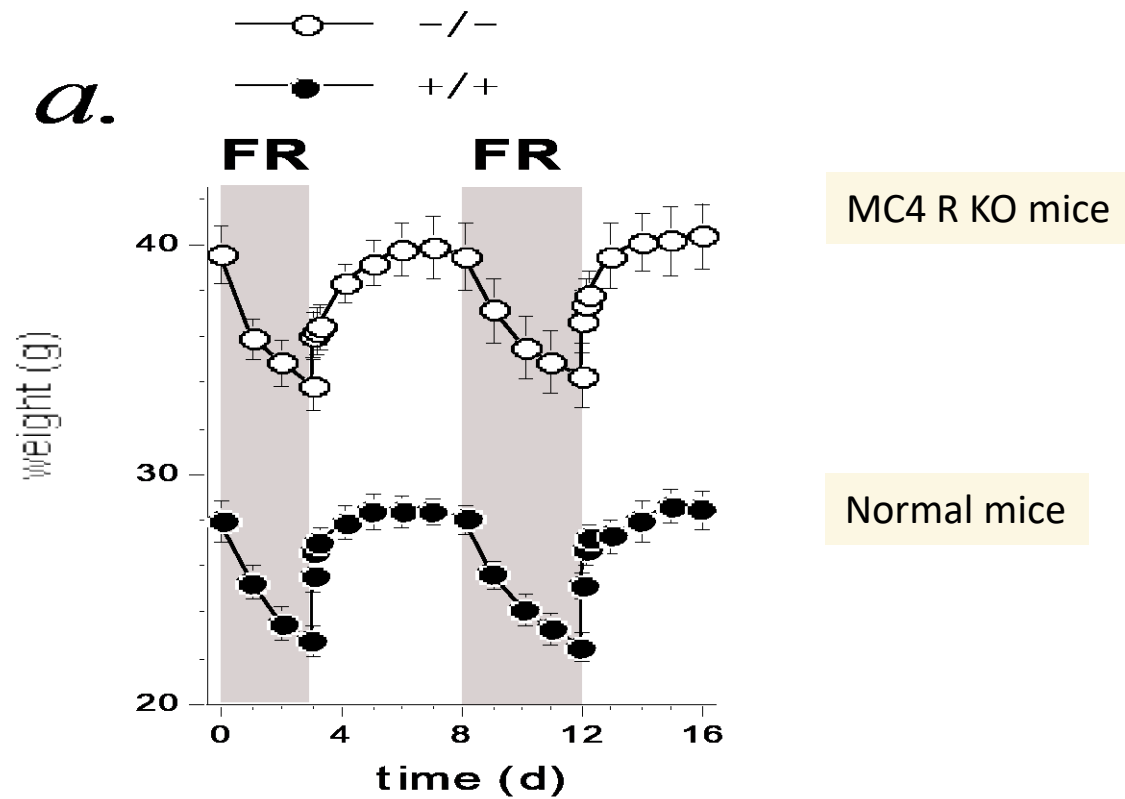
Weight trajectories are set early in life and are difficult to change



Effect of tube feeding 50% excess (obese) and 20% deficit (thin) calories compared with pair-fed (average) and free feeding (control) animals on body weight.

Evidence for a set-point

Food Restriction



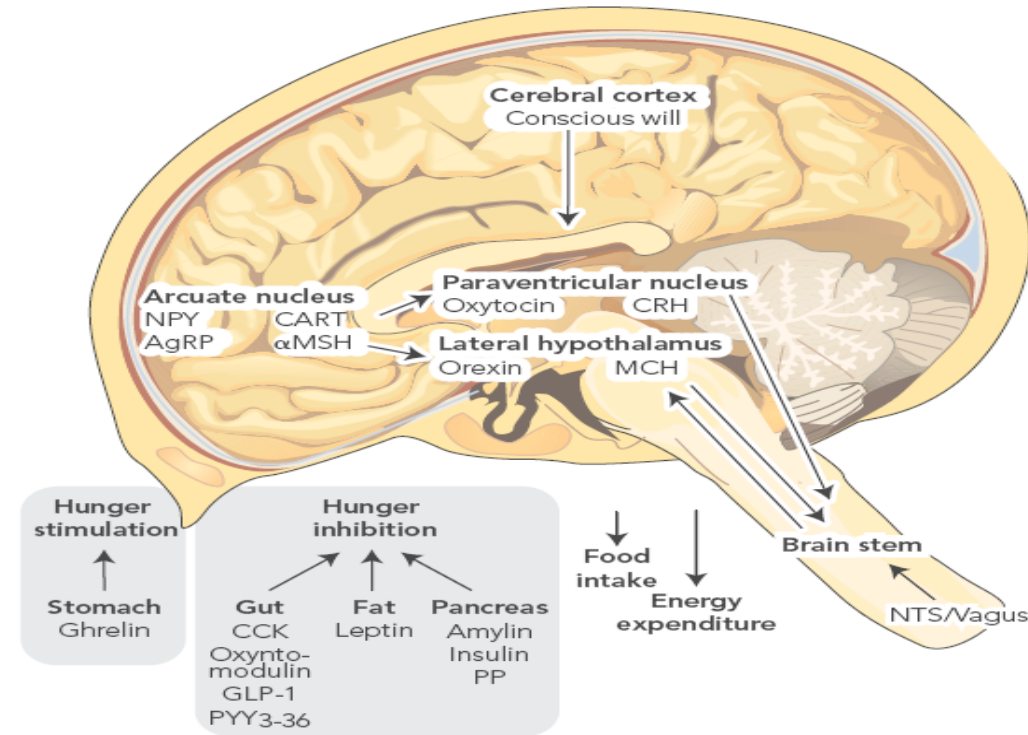
From Cowley M. Monash University, Melbourne

The balance between anabolic and catabolic pathways!

Both pathways can be altered to respond to over and under feeding, but the bias is to actively respond to weight loss

This response is physiologically essential and of course supports survival

“We have 9 hormones to switch off hunger
And just one to turn it on”



AgRP = agouti-related peptide. CART = cocaine and amphetamine-regulated transcript. CCK = cholecystokinin. CRH = corticotropin-releasing hormone. GLP-1 = glucagon-like peptide. MCH = melanin-concentrating hormone. αMSH = alpha melanocyte-stimulating hormone. NPY = neuropeptide Y. NTS = nucleus of the tractus solitarius. PP = pancreatic polypeptide. PYY = peptide YY.

Proietto, J. (2011). "Why is treating obesity so difficult? Justification for the role of bariatric surgery." Med J Aust **195**(3): 144-146

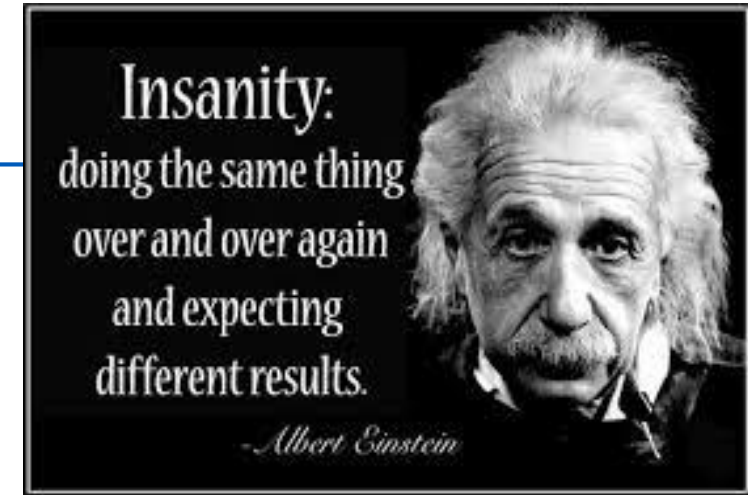
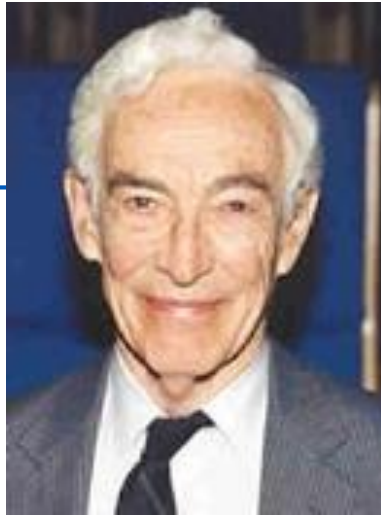
Early life events load the gun and pull the trigger on a lifetime of obesity

We must respect that personal responsibility, lifestyle choice and willpower play a very limited role in obesity as we see it in adolescents and adults.

Our understanding of this chronic disease must respect these determinants of obesity and its complications.

The language **WE** use, the example **WE** provide, and the education **WE** deliver needs to reflect reality.

Respect, dignity, compassion, and professionalism – **No Blame**



“He surveyed obesity treatment studies in the late '50s and found that the nation's diet programs could claim only a 2 percent success rate. He was an early advocate for the use of bariatric surgery to induce weight loss. He also published the first modern account of binge eating in obese individuals.”

**Our philosophy is simple and straightforward -
overweight individuals should be treated
compassionately and professionally.**

Albert J. Stunkard Weight Management Program