DOHaD Risks for Cardiovascular Disease

Developmental Origins of Health and Disease: Risks for Cardiovascular Disease

Current Understanding and Potential for Further Investigation

Objectives:

1. Understand the risk factors for cardiovascular disease.
2. Understand the effect of low birth weight on coronary artery disease as well as the impact low birth weight on the traditional cardiovascular disease risk factors.
3. Understand the effects of “catch up” growth and obesity on heart disease and stroke.

Cardiovascular Disease Risk Factors

Major Risk Factors

- High Blood Pressure
- High Blood Cholesterol/Fatty Acids
- Diabetes
- Tobacco Use
- Overweight and Obesity
- Physical Inactivity
- Gender (men present earlier)
- Heredity

Contributing Risk Factors

- Stress
- Sex hormones
- Birth control pills
- Excess alcohol

Barker and Colleagues Initial Discovery

Two Landmark Studies:

Hertfordshire Study

"close geographical relations between current mortality rates for ischaemic heart disease and past infant mortality"

Barker DJ, Osmond C. Infant mortality, childhood nutrition and ischemic heart disease in England and Wales. *Lancet.* 1986;1:1077–1081.

Helsinki University Hospital Study

"weight at one year of age predicted death from ischemic heart disease"

Barker DJ, Winter PD, Osmond C, Margetts B, Simmonds SJ. Weight in infancy and death from ischemic heart disease. *Lancet.* 1989;2:577–580.

Hypothesis: Fetal Origins of Coronary Heart Disease

The Fetal Origins Hypothesis:

states that fetal undernutrition in middle to late gestation, which leads to disproportionate fetal growth, programs later coronary heart disease.

Barker DJP. Fetal Origins of Coronary Heart Disease.
BMJ 1995;311:171-4.

Coronary Heart Disease

Coronary Artery Disease

- Caused by atherosclerotic plaque buildup in arteries suppling blood to the heart, coronary arteries
- Plaque is made up of lipids, cholesterol, fibrous elements, and inflammatory molecules
- Plaque causes narrowed arteries reducing myocardial blood flow resulting cardiac chest pain, angina
- Ulcerated plaque can initiate platelet aggregation and thrombus formation blocking blood flow causing a heart attack, myocardial infarction

Why is this Important?

- Coronary artery disease and associated CV disease is the leading cause of morbidity and mortality in the developed world
- Undeveloped world catching up and may surpass
- Substantial social and economic impact
- Long term effect
- Fetal programming effects span generations

The Initial Discovery and Challenges that Followed

The initial findings clearly challenged traditional wisdom

- The debate: can this be true?
- Were the initial observations independent of the "traditional" risk factors?
- The work that followed

With Improved Care Are Things Better?

- Barker's original studies: 1921-1925 & 1911-1930 when infant mortality rates were high
- Infant mortality rates improved
- Is the association lost?

Findings the same:

- Singleton births between 1950 and 1956
- Birth weight is inversely associated with CHD
- Plus birth weight inversely associated with stroke

Debbie A. Lawlor et al. Birth Weight Is Inversely Associated with Incident Coronary Heart Disease and Stroke Among Individuals Born in the 1950s Findings from the Aberdeen Children of the 1950s Prospective Cohort Study. Circulation. 2005; 112:1414-1418.

DOHaD Risks for Cardiovascular Disease

- Initial epidemiological studies controlled at least in part for then established cardiovascular risk factors
- Over time it became clear that “Fetal Origins of Adult Disease” were not separate from the traditional risk factors
- Fetal Origins research has provided new insight into CV risk factors
- Fetal Origins research has substantially added our understanding of CV risk

Fetal Origins and Insulin Resistance

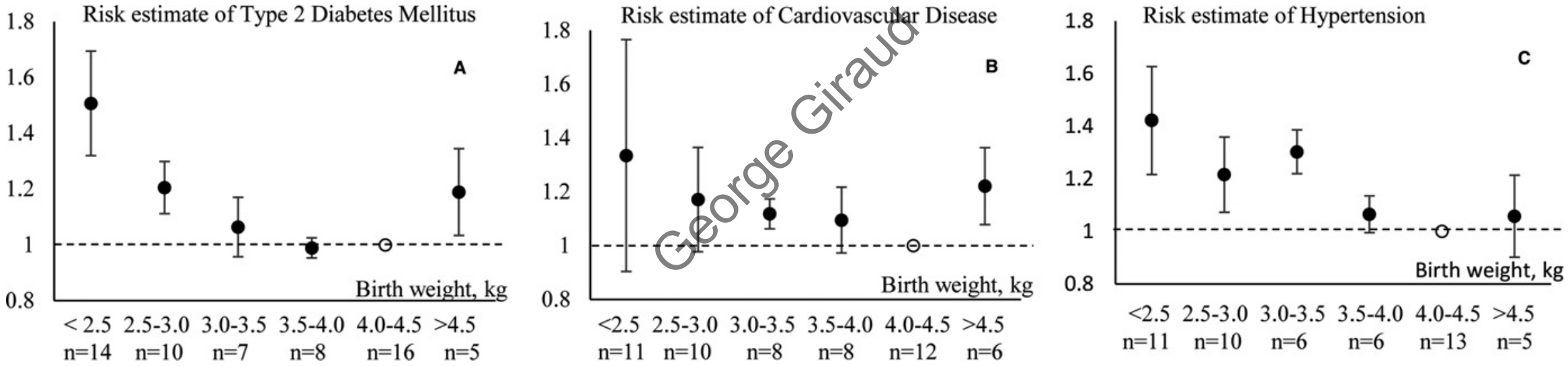
More from the Helsinki Cohort

Persons who have coronary events as adults:

- tend to have been small at birth and thin at two years of age
- after which they tended to increase their BMI rapidly
- this pattern of growth is also related to insulin resistance in later life

David J.P. Barker, Clive Osmond, Tom J. Forsén, Eero Kajantie, Johan G. Eriksson. Trajectories of Growth among Children Who Have Coronary Events as Adults. N Engl J Med 2005;353:1802-9.

Impact of Birth Weight on Diabetes & Hypertension



Ravn Knop M, et al. Birth Weight and Risk of Type 2 Diabetes Mellitus, Cardiovascular Disease, and Hypertension in Adults: A Meta-Analysis of 7 646 267 Participants From 135 Studies. J Am Heart Assoc. 2018;7:e008870.

Fetal Origins and Diabetes

Lausanne, Switzerland Study

- Cross-sectional population-based study on 1458 women and 1088 men aged 35–75
- Adjusted for age
  - smoking status
  - physical activity
  - fat mass
- Compared to normal birth weight adults, low birth weight adults had higher prevalence of diabetes and obesity

Jornayvaz FR et al. Low birth weight leads to obesity, diabetes and increased leptin levels in adults: the CoLaus study. Cardiovasc Diabetol (2016) 15:73.

Fetal Origins: Vascular Endothelial Dysfunction

- Studied endothelial responses of the brachial artery in adults 20-28 years of age
- Vascular measures were related to classic risk factors: smoking history, lipid profile, blood pressure, fasting insulin, exercise capacity, body mass index, combined risk score and birth weight
- Low birth weight was associated with reduced flow-mediated dilation
- Conclusion: Low birth weight is associated with endothelial dysfunction in young adults

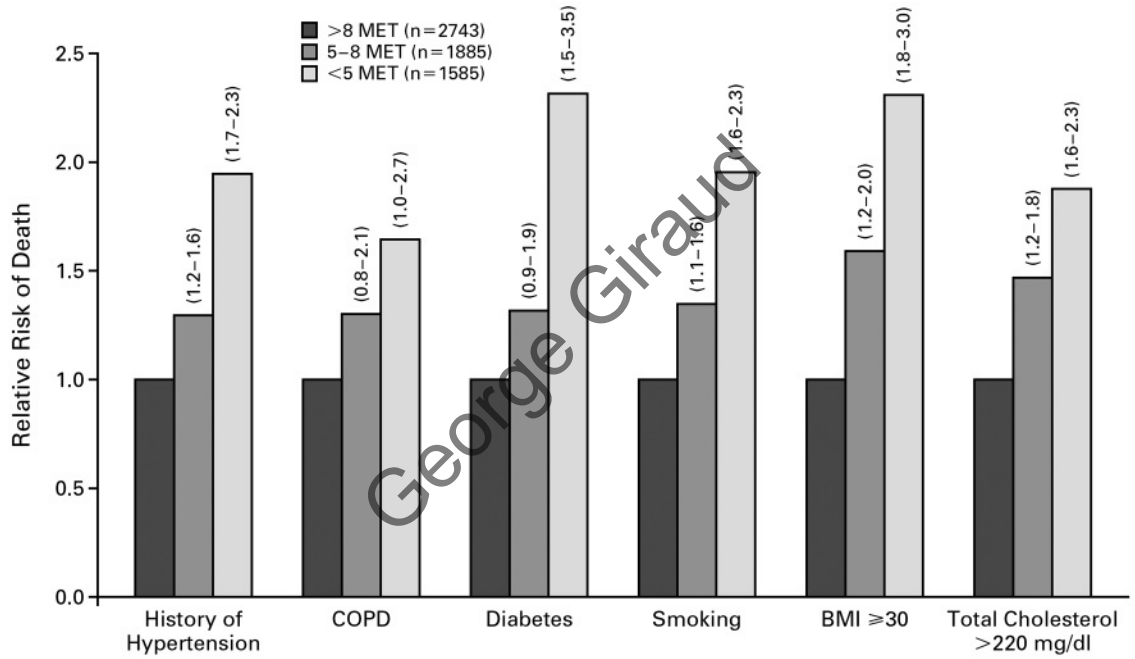
Leeson CPM, Kattenhorn M, Morley R, Lucas A, Deanfield JE.
Impact of Low Birth Weight and Cardiovascular Risk Factors on Endothelial Function in Early Adult Life.
Circulation. 2001;103:1264-1268.

Exercise Capacity in Young Adults Born Small for Gestational Age

- 81 adults born SGA, median age 34 years
- 77 control normal birth weight, median age 34 years
- Compared to controls, adults born SGA had:
  - lower maximal exercise workload
  - lower oxygen consumption
  - exercise capacity correlated with left ventricular mass
- Conclusion: Young adults born SGA have markedly reduced exercise capacity

Crispi F, et al. Exercise Capacity in Young Adults Born Small for Gestational Age
JAMA Cardiology published on line July 21, 2021

Exercise, Risk Factors and Risk of Death



Relative risk of mortality from any cause among subjects with various risk factors and exercise capacities (95% confidence intervals for the relative risks in parentheses). BMI: Body Mass Index, COPD: Chronic Obstructive Pulmonary Disease; modified from Myers and Colleagues.

Fetal Origins: Can This Be True?

With increasing evidence, the debate faded

- Extensive epidemiological work supports the Barker hypothesis
- Developmental programming plays a central role in CV disease
- Palinski and Napoli suggested research should focus on mechanistic studies and intervention

Palinski W, Napoli C. Impaired Fetal Growth, Cardiovascular Disease, and the Need to Move on. Circulation. 2008;117:341-343

Developmental Programing and the Heart

- Myocardial infarction causes left ventricular dysfunction which accelerates pump failure and death.
- No matter the initial cardiac insult, the cardiomyocytes bear the hemodynamic burden.
- It is generally agreed the cardiomyocyte number is set during prenatal life.
- Fewer cardiomyocytes at birth disadvantage the heart for life.

Fetal Origins & Cardiomyocytes

- Many factors modulate fetal cardiac growth increasing or decreasing cardiomyocyte number to advantage or disadvantage
- Some examples:
  - fetal hypertension
  - ventricular wall stress
  - growth factors: angiotensin II, cortisol, IGF1, ANP, T3, cortisol, etc.
  - undernutrition
  - IUGR
  - Placental insufficiency

Thornburg K, Jonker S, O'Tierney P, Chattergoon N, Louey S, Faber J, Giraud G.
Regulation of the cardiomyocyte population in the developing heart.
Prog Biophys Mol Biol. 2011 Jul;106(1):289-99.

Placental Insufficiency & Cardiomyocyte Number

- Determined the effects of placental insufficiency on cardiomyocyte size, maturation and proliferation
  - substantially depressed growth of the heart
  - reduced cell cycle activity in both ventricles by ~70%
  - the proportion of binucleated myocytes was also lower c/w impaired maturation
  - suppressed cardiomyocyte proliferation
  - suppressed cardiomyocyte maturation

Samantha Louey S, Jonker SS, Giraud GD, Thornburg KL. Placental insufficiency decreases cell cycle activity and terminal maturation in fetal sheep cardiomyocytes. J Physiol 580.2 (2007) pp 639–648.

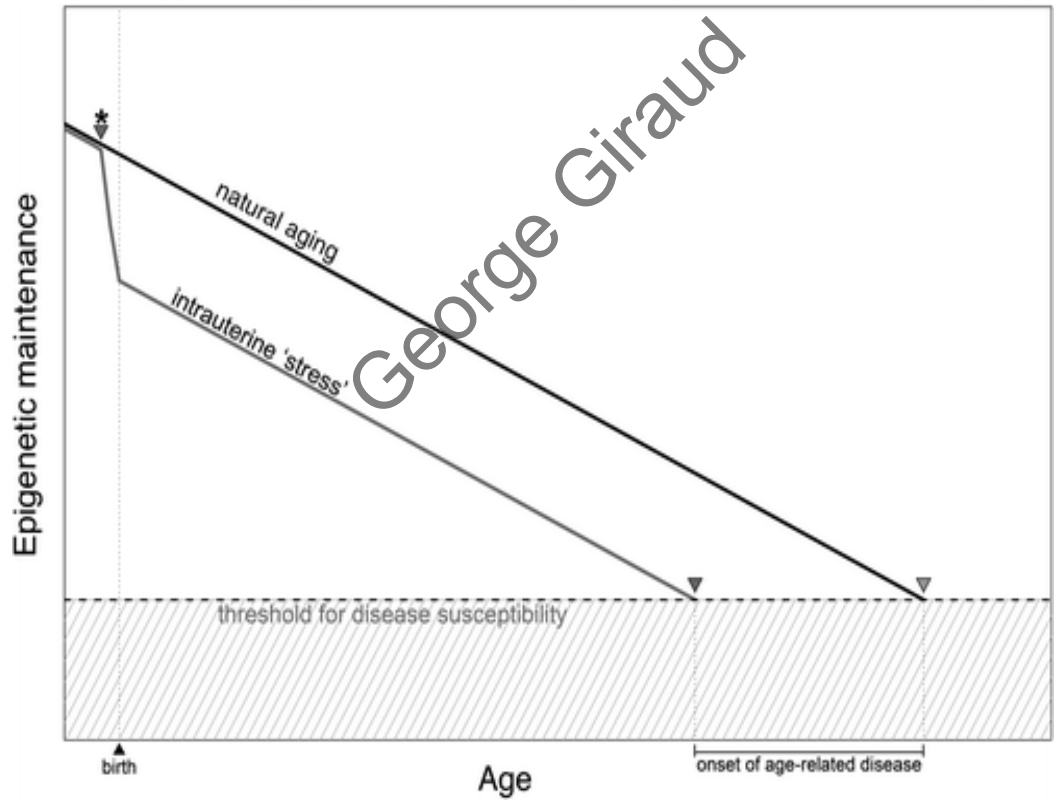
Avenues of Further Investigation

It is clear that:

- Intrauterine challenges have major effects on predisposition to disease
- Fetal Origins play a central role in the genesis of CV disease
- Exact mechanisms not established
- Great opportunity for further basic and clinical investigation
- Changes in gene expression likely play a central role

Conceptualizing Fetal Programming

Thompson and Einstein have provided a clear conceptualization of how fetal programming may alter disease predisposition resulting in earlier clinical presentation of disease.



Thompson RF, Einstein FH. Epigenetic Basis for Fetal Origins of Age-Related Disease. Journal of Woman's Health 19 No 3, 210 Published Online:25 Mar10 https://doi.org/10.1089/jwh.2009.1408

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Exploration of Fetal Origins:

- Has shown us what we didn't know
- There remains an immense knowledge gap
- The underlying mechanisms are not understood
- Great opportunity for further investigation no matter the discipline
- Substantial opportunity to improve overall health
- Incredible potential to improve health world-wide