PRETERM BIRTH AND ADULT OUTCOMES: Other Approaches and Methodologic Issues

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A BRIEF HISTORY OF THE FETAL ORIGINS HYPOTHESIS

- David Barker and colleagues published ecological studies in the 1980's linking infant health outcomes to CVD in the same regions of the UK decades later.
- This work was extended to examining associations between BW and CVD at the level of individual in the early 1990's.
- Later papers expanded into CVD risk factors, especially diabetes and hypertension, mainly in two cohorts born in Hertfordshire and Preston in the first half of the 20th century.
- Laboratory scientists enthusiastically adopted these ideas and studied them in animal models.
- Larger databases began to be used, including famine cohorts in Holland, Finland, Russia and China
- Recently, neonatologists have assessed whether premature and low birthweight babies are at higher CVD risk.

THE HYPOTHESIS EVOLVES

- Originally, birthweight was seen in exclusively nutritional terms
  - "The thesis of this book is that a baby's nourishment before birth and during infancy … influences the diseases it will develop in later life"

    Barker DJP: Mothers, babies and disease in later life. London. BMJ Publishing Group, 1994
- More recently, a broader range of factors determining birthweight have been included, and the fetal origins hypothesis is no longer seen as exclusively nutritional.

BROADENING BEYOND NUTRITION

Barker Hypothesis

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Fetal Origins of Adult Disease

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Developmental Origins of Health and Disease

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Life Course Research

SOME METHODOLOGIC PROBLEMS THAT HAVE ARISEN IN THE FETAL ORIGINS LITERATURE

1. Hypothesis is moving target, often involving multiple post-hoc comparisons.
2. Selective citation of the literature, including non-citation of contrary findings.
3. Follow-up based on a small fraction of the original cohort
4. Internally contradictory findings at times
5. What is the magnitude of the effect?
6. Inappropriate statistical adjustments.
7. Failure to address confounding (e.g. maternal smoking, genetic effects, familial CVD risk factors)

SOME OF THE CRITICAL PAPERS

- Elford J, Whincup P, Shaper AG: Int J Epidemiol 1991; 20:833-844 and J Epidemiol and Comm Health 1992; 46:1-8
- Susser M, Paneth N: BMJ 1995; 310:411-2
- Joseph KS, Kramer M: Epidemiol Reviews 1996;18(2):158-74.
- Paneth N, Ahmed F, Stein AD: J Hypertension 1996;14 (Suppl 5) S121-129
- Huxley R, Neil A, Collins R: Lancet 2002;360:659-665
- Huxley R, Owen CG, Whincup P et al: JAMA 2004; 292:2755-64
- Tu, Y-K, West R, Ellison GTH et al: Am J Epidemiol 2005; 161: 27-32.
- Huxley R: B J Nutrition 2006; 95: 441–442
- Huxley R, Owen C, Whincup PH et al: A J Clin Nutr 2007; 85: 1244-1250

EFFECT SIZES

- Most fetal growth effect sizes are very small. Typical correlation coefficients of BW and adult BP are about .01 to .02.
- Effects are often described as changes per kg of infant weight. Typical values for BP are 2-5 mm systolic per kg of birthweight
- One kg is more than two standard deviations in birthweight. At 40 weeks 1 kg is the difference between the 10th percentile and the 90th percentile. We know of nothing that can change BW by a kg.
- For both blood pressure and diabetes, measures of current weight and BMI exert far greater effects than birthweight

WRONG STATISTICAL ADJUSTMENTS

- A fairly consistent finding, especially for adult BP, is that the associations with BW are greatly magnified if adjustment is made for current (adult) weight. Often a 1-2 mm BP increase per kg decrease of BW, or even no difference, is converted into a 5-6 mm difference when adult weight is included in the model. In at least one study, the direction was reversed from positive to negative.
- The reason is that LBW babies are consistently smaller and thinner than higher weight babies. Thus the BP being modeled, with adjustment, is the BP they would be expected to have if they were as large as adults born with higher BW.
- But they are not as large, and thus do not have as large a BMI contribution to their BP.

KEY MODELING EXERCISE

- **Tu Y-K, West R, Ellison GTH, Gilthorpe MS: Why Evidence for the Fetal Origins of Adult Disease Might Be a Statistical Artifact: The "Reversal Paradox" for the Relation between Birth Weight and Blood Pressure in Later Life. Am J Epidemiology 2005; 161: 27-32**

ASSUMPTIONS OF THE MODELING EXERCISE

1. **No correlation between BW and adult BP**

2. **A positive correlation between BW and adult weight**

3. **A positive correlation between adult weight and BP**

RESULTS OF THE MODELING EXERCISE

A negative correlation between BW and BP emerges when adult weight is controlled in the analysis. The size of this correlation is a function of the magnitude of both the BW-adult weight correlation and the adult weight-BP correlation, both of which are positive whenever they have been examined.

For example, if both are 0.25:

- **One kg of BW will be associated with - 1.31 mm Hg of BP.**

If both are 0.35:

- **One kg of BW will be associated with – 2.74 mm Hg.**

Both findings are within the range found in the fetal origins literature

CONFOUNDING ISSUES

- Prematurity and low birthweight do not exist in a vacuum. Both are powerfully linked to measures of social class in the mother.
- Low birthweight is strongly linked to smoking and to maternal hypertension (and possibly even to higher BP in the normal range).
- Literature shows evidence that low birthweight and preterm birth may be prominent in families with higher incidences of heart disease.

EFFECT OF MATERNAL SMOKING ON BIRTHWEIGHT

SMOKING STATUS	BIRTHWEIGHT	BIRTHWEIGHT DIFFERENCE
NON-SMOKERS	3,357	
< 5 CIGARETTES/DAY	3,307	-50
5-14 CIGARETTES/DAY	3,169	-188
≥ 15 CIGARETTES/DAY	3,144	-213

From Rush D, Cassano P: Relationship of cigarette smoking and social class to birthweight and perinatal mortality among all births in Britain 5-11 April, 1970. J Epid Comm Health 1983;249-255

EFFECT OF OCCUPATIONAL SOCIAL CLASS ON BIRTHWEIGHT

SOCIAL CLASS STATUS	BIRTHWEIGHT	BIRTHWEIGHT DIFFERENCE
1 HIGH MANAGER OR PROFESSIONAL	3,300	
2 INTERMEDIATE MANAGER OR PROFESSIONAL	3,286	-14
3A SUPERVISORY CLERICAL	3,261	-39
3B SKILLED MANUAL	3,219	-81
4 SEMI OR UNSKILLED	3,169	-131
5 CASUAL WORKERS	3,139	-161

From Rush D, Cassano P: Relationship of cigarette smoking and social class to birthweight and perinatal mortality among all births in Britain 5-11 April, 1970. J Epid Comm Health 1983;249-255

GENETIC TRANSMISSION?

- Mothers, fathers and grandparents of low birthweight babies have been shown to have elevated cardiovascular risk, at times appearing before the birth of the index child.

- This suggests the possibility of shared genetic risk factors between mother and infant that are manifest in low birthweight

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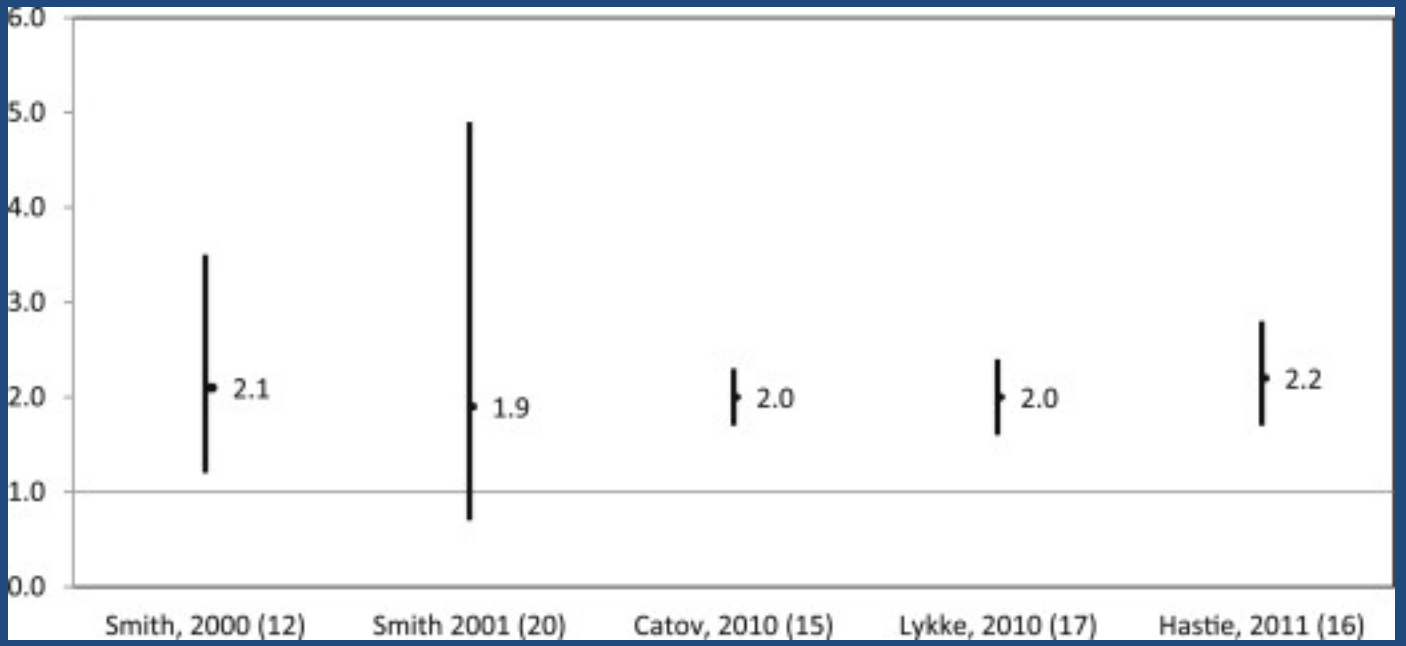
MOTHER, GRANDPARENTS OR BABY?

STUDY	POPULATION	OUTCOME	RELATIVE RISK OF CVD
Pell 2004	All births 1981-1985 in Scotland (N = 119,668 mothers)	Stroke in mothers 14-19 years post birth (N = 342)	**RR = 2.51** for delivering a baby < 2,500 g, compared to ≥ 3,500 g
Smith 2010	120,317 Scottish births, 1992-2006	Death or hospital admission for CHD in maternal grandparents	**RR = 0.82 for** grandparental risk of heart disease per kg increase of birthweight
Pariente 2014	47,585 Israeli deliveries; 653 women with abruption	51 CVD deaths 11-22 years post birth	**RR = 6.3** for women with abruption
Dietz 2013	4,820 interviewed parous NHANES women 20-64	CVD and risk factors	Birth < 2,500g **RR = 2.1** for CVD; **RR = 1.65** for having > 2 CVD risk factors

PRETERM BIRTH AND LATER MATERNAL DEATH FROM CORONARY HEART DISEASE IN FIVE STUDIES



Robbins CL et al: History of preterm birth and subsequent cardiovascular disease: a systematic review. AJOG 210:285-297

CASE CONTROL STUDIES

- This approach has been less used than cohort approaches in the fetal origins literature
- Useful for studying rarer outcomes
- Useful for studying much later outcomes
- Especially useful when archived biological material is available from pregnancy or early live, permitting assessment of inaccessible exposures or intermediary steps in causal pathways

PSYCHIATRIC DISORDERS			
REFERENCE	**COUNTRY**	**FINDINGS IN RELATION TO**	
		BIRTHWEIGHT	**GESTATIONAL AGE**
SCHIZOPHRENIA			
Nielson 2013	Denmark	RR of **1.23** for birthweight <10TH % of FGR	No association
Bersani 2003	Italy	OR= 1.01 per 100 g	No association
BIPOLAR DISORDER			
Ogendahl 2006	Denmark	No association	No association
DEPRESSION			
Preti 2000	Italy	Cases weighed **200 g** less at birth	No association
TOURETTE'S SYNDROME			
Burd 1999	USA	Cases weighed 100 g less	Cases 0.4 wks shorter

ADULT CANCERS			
REFERENCE	**COUNTRY**	**FINDINGS IN RELATION TO**	
		BIRTHWEIGHT	**GESTATIONAL AGE**
PROSTATE			
Ekbom 2000	Sweden	No association	OR **= 0.94** per wk increase in GA
BREAST CANCER			
Hubinette 2001	Sweden	Increased risk > 3kg Co-twin with BC heavier at birth	**Significant increase** risk in twins > 40 weeks GA
Innes 2000	USA	OR = **3.10** for BW > 4,500g	OR = **0.11** for < 33 wks
ESOPHAGEAL			
Akre 2006	Sweden	No association	OR = **0.4** for GA > 41 wks in adenocarcinoma of cardia only

CHILDHOOD CANCERS			
REFERENCE	**COUNTRY**	**FINDING IN RELATION TO**	
		BIRTHWEIGHT	**GESTATIONAL AGE**
TESTICULAR			
Richiardi 2003	Sweden	OR = 1.35 > 4kg vs 2500-3999g (NS)	OR = **0.64** post-term vs term
BRAIN TUMORS			
Schmidt 2010	Scandinavia	OR = **1.27** for BW > 4.5 kg. OR = **1.50** for BW < 2 kg OR = 1.28 for SGA. OR = **1.26** for LGA	OR = **1.58** per wk decrease in GA
Emerson 1991	USA	OR = **1.4** for BW > 4 kg	
LEUKEMIA			
Hjalgrim 2004	Scandinavia	ALL: OR = **1.26** per 1-kg increase in BW CML: higher risk < 1,500g	B-ALL:OR = **0.87** per 2 wk increase in GA
OSTEOGENIC SARCOMA			
Operstalski 1987	USA	OR = **2.1** for <25th percentile birth length	OR = **2.7** for GA "> one week early"
NEUROBLASTOMA			
Johnson 1985	USA	OR = **3.2** for term birth < 2,500g	OR = **0.29** for GA < 37 wks.

THE UTILITY OF NESTED CASE-CONTROL STUDIES WITH BIOLOGICAL SAMPLES IN PREGNANCY

- The Norwegian and Danish cohorts of 100,000 each have biological samples archived
- Finland has > 1 million serum specimens from pregnancy archived.
- Many US states have archives of newborn blood spots (Michigan > 4 million; California > 12 million).
- Serum from others in the NCPP (1959-1966) is still archived (N = about 50,000). That archive has been used to show that schizophrenic adults had mothers with Higher IL-8 in maternal 2^{nd}/3^{rd} trimester serum.

CONCLUSIONS

- Effect size should be described in realistic terms. The effect of 100 grams change in BW is more useful than the effect of a kg.
- We must avoid statistical adjustments that have been shown to produce artefact such as controlling for an intermediate that is linked to exposure and outcome
- We must examine potential confounders, including especially
  - familial CVD (especially maternal hypertension)
  - maternal smoking
  - socio-economic status at the birth of the child.
- Use of archived collections from the perinatal period (especially maternal serum and newborn blood spot) linking to later disorders in nested case-control studies, could be a valuable approach