# ADULT OUTCOMES OF VERY PRETERM BIRTH

Nigel Paneth MD MPH

Grand Rounds
Department of Pediatrics
Yale University
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# Thanks for inviting me!

The New Yorker,

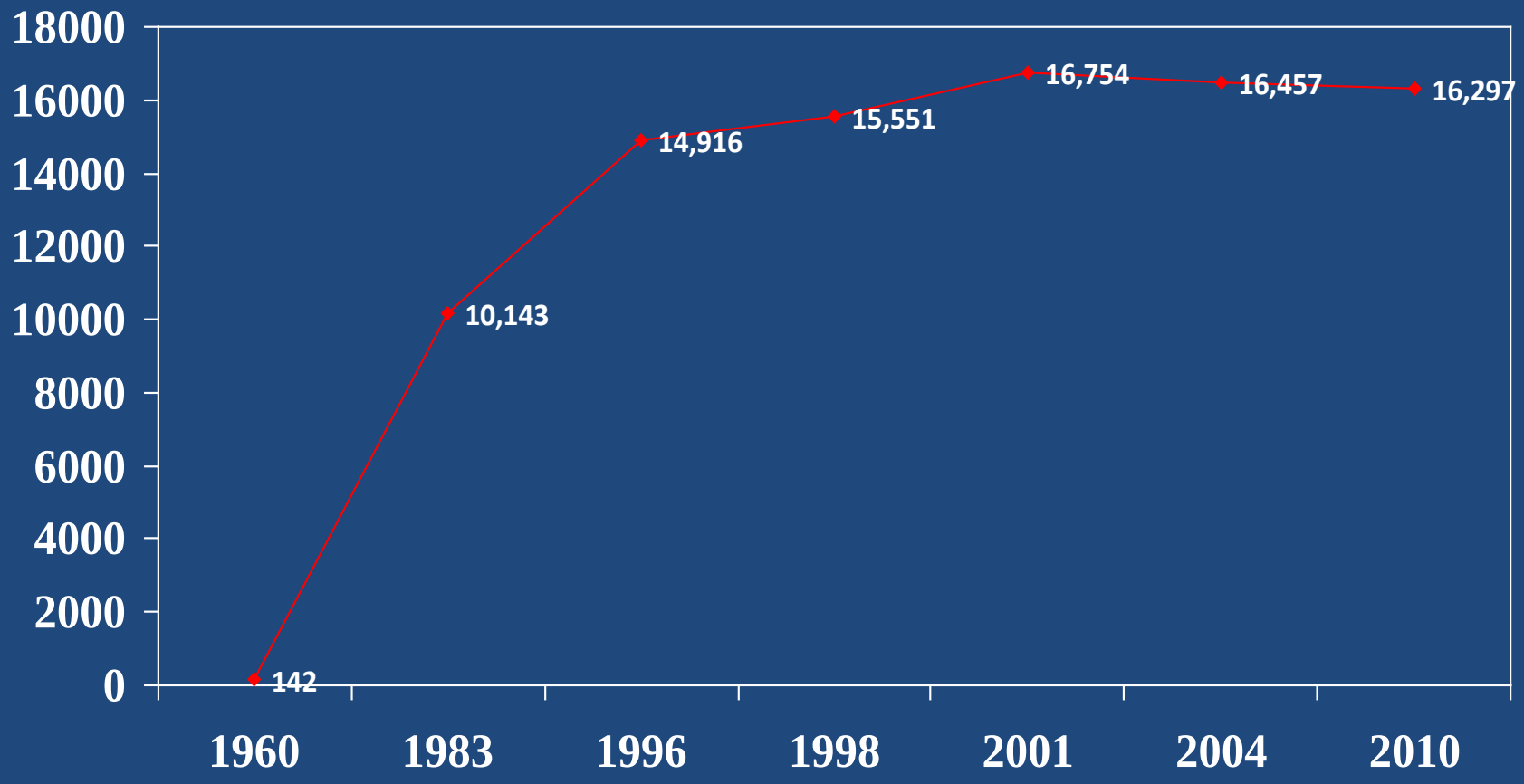
November 2001

*"And it was so typically brilliant of you to have invited an epidemiologist."*

Richard Ehrenkranz (1946-2018)

Jack C. Sinclair
(1933-2014)

# NUMBER OF CHILDREN < 1,000 G SURVIVING TO AGE ONE IN THE US 1960-2010




Data for 1960 based on white population only

# TOPICS I WILL ADDRESS

- NEURO-DEVELOPMENT
- PULMONARY OUTCOMES
- CARDIOVASCULAR RISK FACTORS AND DISEASE
- BEHAVIOR AND PSYCHOPATHOLOGY
- WELL-BEING
  - SOCIAL FUNCTIONING
  - SOCIO-ECONOMIC STATUS
  - CRIMINAL ACTIVITY
  - HEALTH (covered above)

# SOME SOURCES

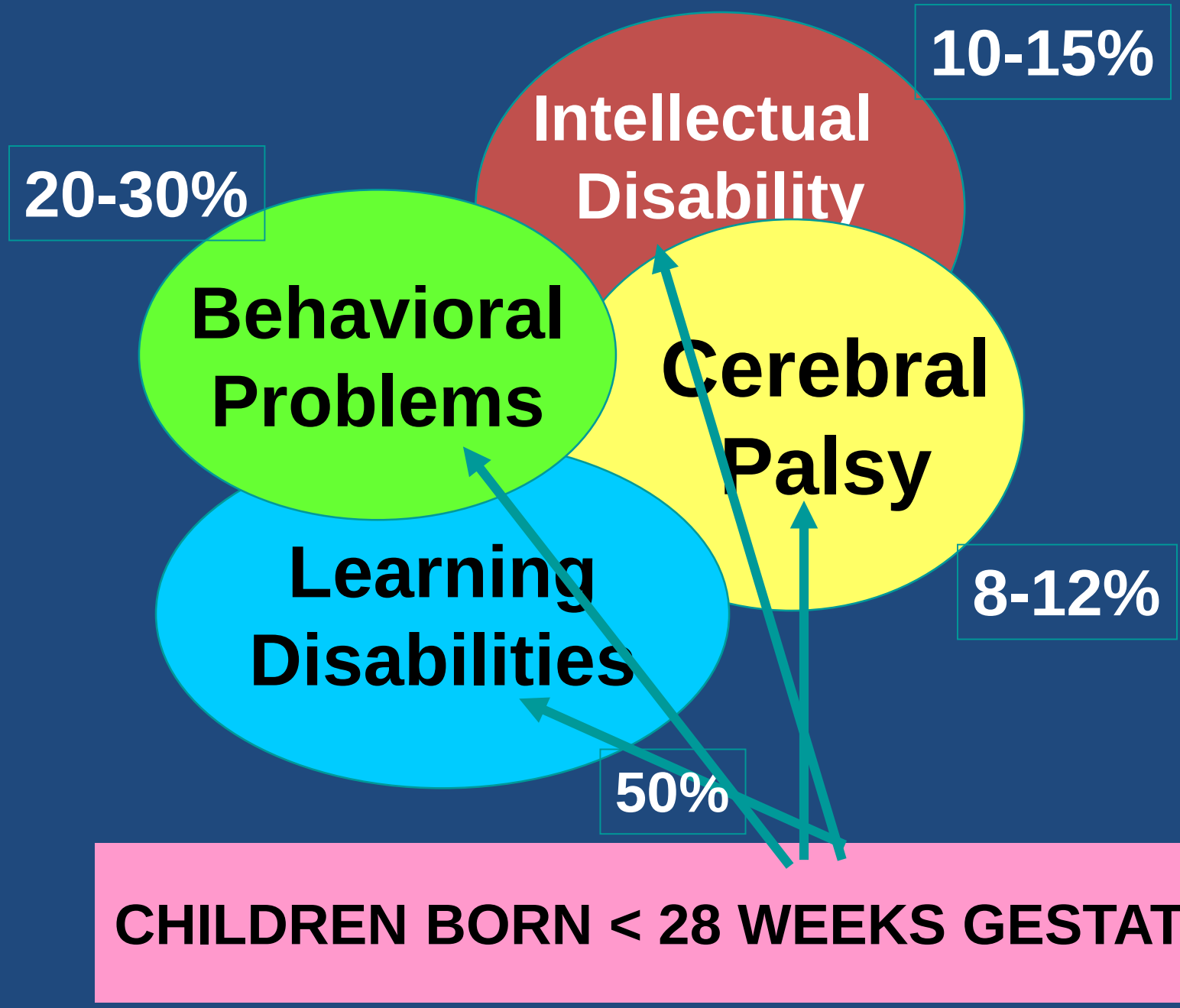
- August 2015 NIH Conference on *Adults Born Preterm: Epidemiology and Biological Basis for Outcomes.* which I co-chaired with Tonse Raju.
  - Raju T, Pemberton V, Buist S, Blaisdell C, Moxy-Mims M, Saigal S and Adults Born Preterm Conference Speakers and Discussants. *J Pediatrics* 2017 Feb; 181: 309-18.
  - Raju TNK, Buist AS, Blaisdell CJ, Moxey-Mims M, Saigal S: *Acta Paediatrica* 2017 Sep;106:1409-1437.
- The Adults Born Preterm International Collaboration (APIC) – eleven cohorts in Europe, Australia and North America
  - http://www.apic-preterm.org/
- Several large Scandinavian birth cohorts with record linkages

# 11 PREMATURE COHORTS FOLLOWED TO ADULTHOOD

| Cohort | Birth years | Current age | Sample size |
|---|---|---|---|
| Cleveland, Ohio | 1977-79 | 40-42 | 213 |
| Hamilton, Ontario | 1977-1982 | 37-42 | 130 |
| Melbourne, Australia | 1977-1983 | 36-42 | 155 |
| Helsinki, Finland | 1978-1985 | 34-41 | 164 |
| Belfast, Northern Ireland | 1979-1993 | 26-40 | 68 |
| Vancouver, BC | 1981-1986 | 33-38 | 51 |
| Netherlands | 1983 | 36 | 458 |
| Northern Finland (Oulu, Lapland) | 1985-1989 | 30-34 | 134 |
| Bavaria, Germany | 1985-1986 | 33-34 | 203 |
| Trondheim, Norway | 1986-1988 | 32-34 | 41 |
| Providence, RI | 1989-1992 | 27-30 | 295 |

# NEURODEVELOPMENTAL DISORDERS

| TABLE 1: ESTIMATES OF THE PREVALENCE OF NEURODEVELOPMENTAL DISABILITIES IN THE US | |
|---|---|
| **DISABILITY** | **PREVALENCE** |
| CEREBRAL PALSY | 1.5 – 4 per 1,000 live births |
| EPILEPSY | 1% by age 20 |
| HEARING LOSS | 0.5% |
| VISION LOSS | 0.5% - 1% |
| SEVERE INTELLECTUAL DISABILITY | 3 - 5 per 1,000 live births |
| MILD INTELLECTUAL DISABILITY | 1 - 1.7% of the child population |
| AUTISM SPECTRUM DISORDER | Between 1% and 1.5% of US children now carry the diagnostic label of ASD |
| LEARNING DISABILITIES | 9-10% |
| ATTENTION DEFICIT/HYPERACTIVITY DISORDER | 5-7% |
| TOTAL (allowing for overlap among disabilities) | 16% - 21% |


10-15%
Intellectual Disability
20-30%
Behavioral Problems
Cerebral Palsy
Learning Disabilities
8-12%
50%
CHILDREN BORN < 28 WEEKS GESTATION

# AUTISM

Two studies that have used ADOS/ADIR to diagnose ASD in preterm births

- Pinto-Martin J et al: Pediatrics. 2011. Nov; 128(5):883-91.
  - An estimated prevalence of 5% in early adulthood with birthweight < 2kg.
- Joseph RM et al Autism Research 2017 Feb; 10(2):224-232.
  - Prevalence estimates by GA at age 10
    - Entire ELGAN cohort (23 – 28 weeks) = 7.1%
      - 23-24 weeks = 15.0%
      - 25-26 weeks = 6.5%
      - 27 weeks = 3.4%

## PROPORTION OF 8-11 YEAR OLD CHILDREN < 1 KG WITH COGNITION AND SCHOOL ACHIEVEMENT SCORES IN THE NORMAL RANGE (SCORES > 85).

## DATA FROM POPULATION-BASED COHORTS IN THE US, CANADA, GERMANY, THE NETHERLANDS

| | |
|---|---|
| IQ | 44% - 62% |
| READING | 46% – 81% |
| ARITHMETIC | 31% – 76% |
| SPELLING | 39% – 65% |
| HELD BACK/SPECIAL EDUCATION | More than 50% in all cohorts combined |

Saigal et al Pediatrics 2003; 112: 943

# PULMONARY OUTCOMES

# ASTHMA

Consistent finding of an excess of asthma

**Notable papers:**

- Harju M, Keski-Nisula L, Georgiadis L: J Pediatr 2014 Feb;164(2):295-9.e1. National case-control study from Finland. 2,661 asthma cases and 41,551 controls.

  Risk of asthma inversely proportional to GA. Children (up to age 13) born < 32 weeks had RR of 3.9 for asthma diagnosis

- Broström EB, Akre O, Katz-Salamon M et al: Eur J Epidemiol 2013 Jan;28(1):79-85. 6,425 <35 weeks/< 2.0 kg (F) or 2.1 kg (M) and matched term controls from 4 Swedish hospitals 1925-1949 assessed at age 60-80.

  Risk of asthma elevated only in women. RR = 5.7 <32 weeks

# PULMONARY FUNCTION

Consistent findings of a mild decrease in pulmonary function in prematures overall, and a moderate decrease in children who had BPD

- Notable paper: Kotecha SJ., Edwards MO, Watkins WJ et al: *Thorax* 2013 Aug;68(8):760-6. Meta-analysis of %FEV1 in 59 studies.
  - Prematures without BPD: **-** 7.2%
  - Prematures with $O_2$ dependency at 28 days: **-** 16.2%
  - Prematures with $O_2$ dependency at 36 weeks PMA: **-** 18.9%
- Other studies show mild reductions in:
  - airway resistance
  - exercise tolerance
  - CO diffusion capacity

# CARDIOVASCULAR RISK FACTORS AND CARDIOVASCULAR DISEASE

# TWO METHODOLOGICAL CAUTIONS IN RELATION TO CARDIOVASCULAR OUTCOMES IN PREMATURES

1. Confounding by shared risk factors for preterm birth
2. Inappropriate statistical adjustments

# IF LOW BIRTHWEIGHT/PRETERM BIRTH IS ASSOCIATED WITH LATER CARDIOVASCULAR DISEASE, IS IT THE CAUSE?

- 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 or environmental risk factors between mother and infant that are manifest in low birthweight

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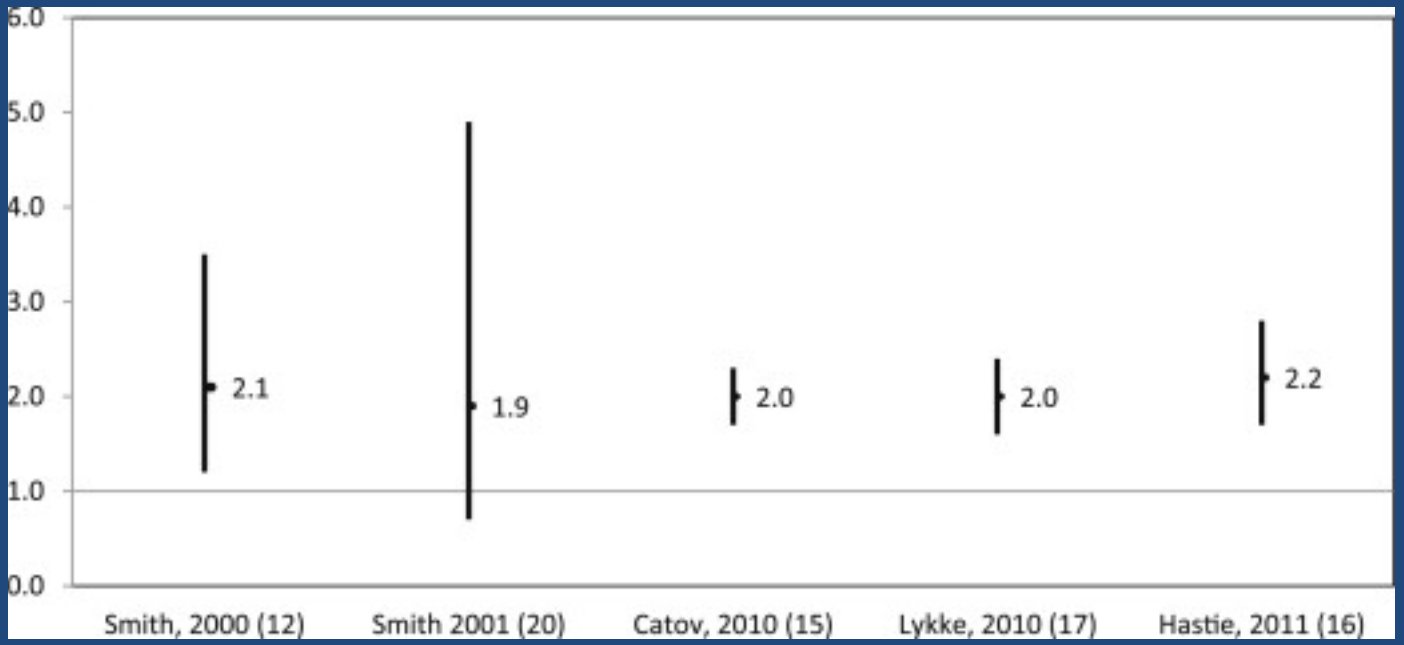
# PRETERM BIRTH AND LATER MATERNAL DEATH FROM CORONARY HEART DISEASE IN FIVE STUDIES




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

# 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.

# GESTATIONAL AGE AND ISCHEMIC HEART DISEASE

| STUDY | COUNTRY | N of BIRTHS | BIRTH YEARS | FINDING |
|---|---|---|---|---|
| Zoller 2015 | Sweden | 2 million | 1973-1992 | No effect |
| Kajantie 2015 | Finland | 19,000 | 1924-1944 | No effect |
| Ueda 2014 | Sweden | 1.3 million | 1983-1995 | No effect |
| Lawlor 2005 | Scotland | 11,000 | 1950-56 | No effect |

# ISCHEMIC HEART DISEASE AND FETAL GROWTH IMPAIRMENT

Zoller 2015 (Sweden):

- For adults between 1-2 SD below the mean of BW for GA, hazard ratio (HR) was 2.5 for MI and 1.5 for all ischemic heart disease.
- For adults > 2 SD below mean, HR was for MI 2.4, 1.9 for IHD.

Lawlor 2005 (Scotland):

- HR for each 1 kg increase in BW = 0.62 for CHD (adjusted for GA).

# GESTATIONAL AGE AND FETAL GROWTH IMPAIRMENT IN STROKE

- Lawlor 2005 (Scotland):
  - Inverse association of GA with risk (HR for each added week of gestation = 0.79 per week)
  - FGR effect on stroke also found. (HR for each 1 kg increase in BW = 0.48 ,adjusted for GA)
- Ueda 2014 (Sweden):
  - Adults born < 32 weeks had a HR for cerebrovascular disease of 1.9.

# BLOOD PRESSURE IN VLBW/EP YOUNG ADULTS

Fairly consistent small elevations in systolic and diastolic pressure in in later life with suggestion of stronger effect in females

- **Notable paper**: Hovi P, Vohr B, Ment LR: *Hypertension* 2016 Oct;68(4):880-7. Summary of 9 cohorts; n = 1,571 VLBW and 777 term-born controls
  - Males + 1.8 mm SBP, females + 4.7mm SBP as young adults
  - OR for hypertension: 2.3 in women, 1.1 in men
  - Maternal pre-eclampsia linked to raised BP, but SGA to lower BP.

# INSULIN RESISTANCE

Higher levels of insulin resistance not found in all prematures, but small differences are found in infants < 1.500g

- Parkinson et al (comparing < 37 weeks to term controls) found no differences in fasting glucose, insulin.
- Hovi P, Andersson S, Eriksson HG: NEJM 2007 May 17;356(20):2053-63 and Kajantie E, Strang-Karlsson S, Hovi P et al: J Clin Endocrinol Metab 2015 Jan;100(1):244-50) found slightly higher insulin resistance in a sample of young Helsinki adults <1,500g.

# DIABETES

The one large nationwide study of risk of diabetes suggested a small excess for births < 37 weeks

- Crump C, Winkleby MA, Sundquist K et al: 2011 May;34(5):1109-13.

630,090 Swedish births 1973-1979 (including 27,953 GA <37 weeks), followed to age 25-37 for diabetes medication prescription in 2005-2009. Data from all outpatient/inpatient pharmacies in Sweden.

- Any diabetes prescription: 1.5% in prematures; 1.2% in controls; risk 13% higher
- Insulin prescription: 1.0% in prematures; 0.8% in controls; risk 22% higher

# OTHER METABOLIC ISSUES

- Parkinson et al found no differences in BMI, waist-hip ratio, percentage fat mass, flow-mediated dilatation, intima-media thickness
- They found slightly elevated LDL, but no other lipid differences
- Morrison et al (Pediatrics 2016;138:e2016515) also found no lipid differences, but did find lower muscle mass, higher percent body fat.
- Tendency to more abdominal fat, in spite of lower BMI than controls, found in several studies.

# BEHAVIOR AND PSYCHOPATHOLOGY

# MAJOR PSYCHIATRIC DISORDERS

| REFERENCE | COUNTRY | FINDINGS IN RELATION TO | |
|---|---|---|---|
| | | BIRTHWEIGHT | GESTATIONAL AGE |
| **SCHIZOPHRENIA** | | | |
| Nielson 2013 | Denmark | RR of **1.23** for birthweight <10$^{TH}$ % 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 |

# LESS SEVERE PSYCHIATRIC OUTCOMES

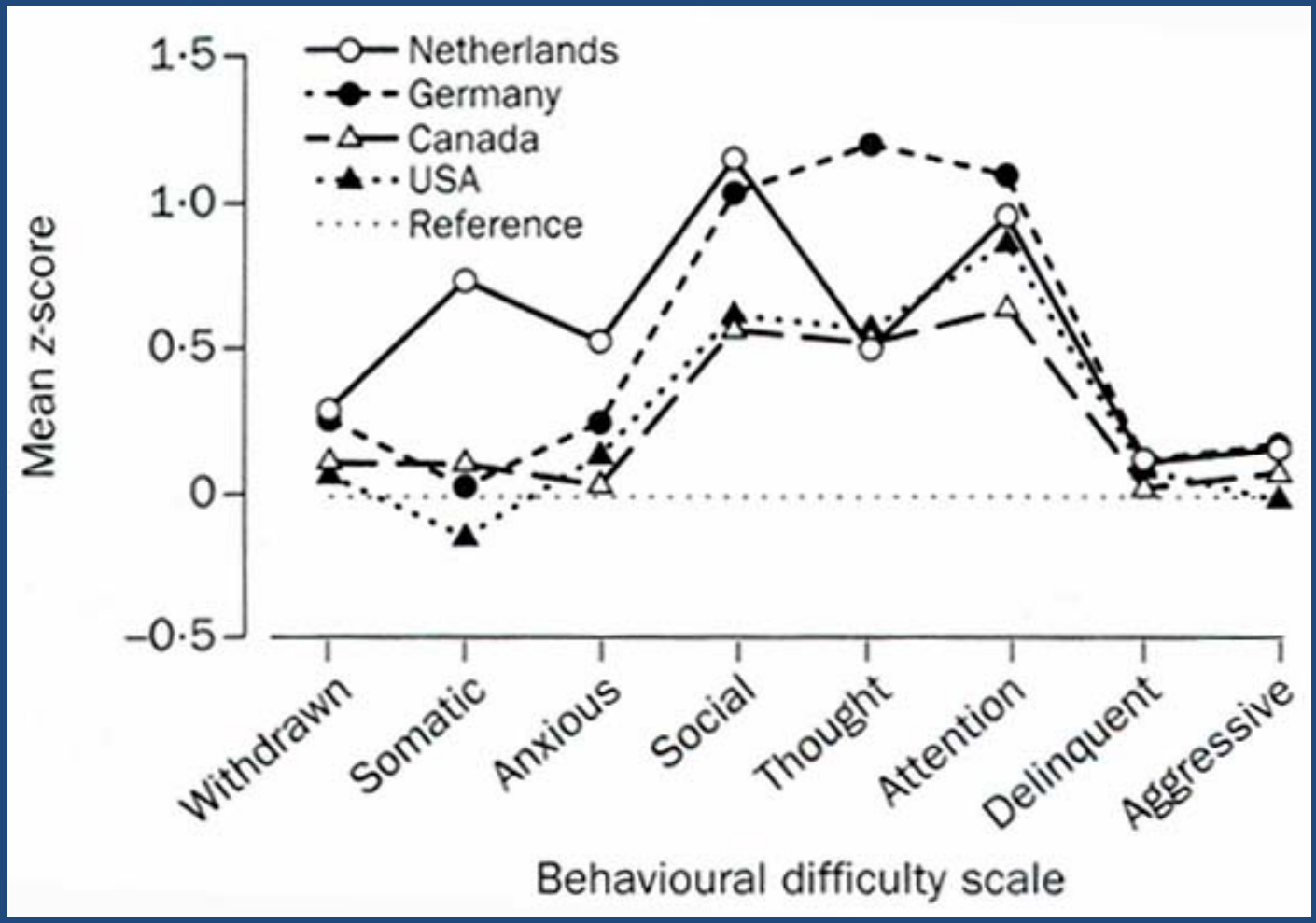
Consistent findings of higher levels of

- Anxiety problems
- Depressive symptoms
- Avoidant personality

These symptoms may be especially noted in children exposed to steroids in utero.

- Health related quality of life also lower, even in adults without neurodevelopmental disabilities

# BEHAVIOR IN SCHOOL-AGE CHILDREN BORN < I KG IN FOUR COUNTRIES



# WELL-BEING

# WELL BEING

- *Social functioning*
  - romantic relationships
  - number of children
  - current family functioning
  - Loneliness
  - social support
  - self-esteem.
- *Socio-economic status*
  - Education
  - Employment
  - income.
- *Criminal activity*
- *Health*

# SELF REPORT OF SOCIAL FUNCTIONING IN < 1KG SURVIVORS

- Romantic relationships
  - More likely to remain single, less likely to have children
- Current family functioning
  - Not different from normal weight controls
- Loneliness
  - Greater shyness, more social isolation and more loneliness
- Social support
  - Slightly , not significantly lower
- Self-esteem
  - Similar in adolescence, but lower than term controls in adulthood

# SOCIO-ECONOMIC STATUS

- Education – not dissimilar from term controls
- Employment – not dissimilar from term controls
- Income and wealth – considerably lower incomes than term controls

# CRIMINAL BEHAVIOR

- Less use of drugs, alcohol, tobacco; in general less likely to engage in risky behaviors
- Less contact with police
- Fewer convictions for crimes

# THE TWO SIDES OF PERSONALITY IN VERY PRETERM ADULTS

- Studies assessing personality characteristics suggest a specific “preterm personality” characterized by risk aversion, shyness and cautiousness in social relationships. Accordingly, adults born preterm start family later and in population studies are less likely to have children than those born at term.
- Some studies have also suggested higher average levels of conscientiousness. Conscientiousness is strongly associated with healthy lifestyle and good health.

# IMPLICATIONS FOR CLINICAL PRACTICE 1

- Premature and very low birthweight survivors, especially those with FGR, may be slightly more susceptible to hypertension, diabetes, and abdominal fat deposition. Some risks seem to be more pronounced in women. But very premature survivors are thinner and less likely to smoke.
- Seems sensible to alert families to the slightly increased risk of CVD and allied disorders, and to emphasize the standard approaches to primary CVD prevention via exercise, dietary prudence and not smoking. No special screening seems necessary.

# IMPLICATIONS FOR CLINICAL PRACTICE 2

- Very premature survivors are more susceptible than most other adults to a range of behavioral problems that impair their quality of life. These include especially shyness, social isolation and anxiety.
- These conditions occur even without developmental disabilities, but are exacerbated by lower cognitive, motor and verbal skills

# IMPLICATIONS FOR CLINICAL PRACTICE 3

Two modifiable features of childhood seem especially related to adult behavioral problems. Both over-protective parenting and peer-victimization more than doubled the risk of anxiety disorders in adult life.

Day KL et al: J Child Fam Studies 2018 Mar;27(3):907-915.

Advice in these areas to parents and schools may be useful .

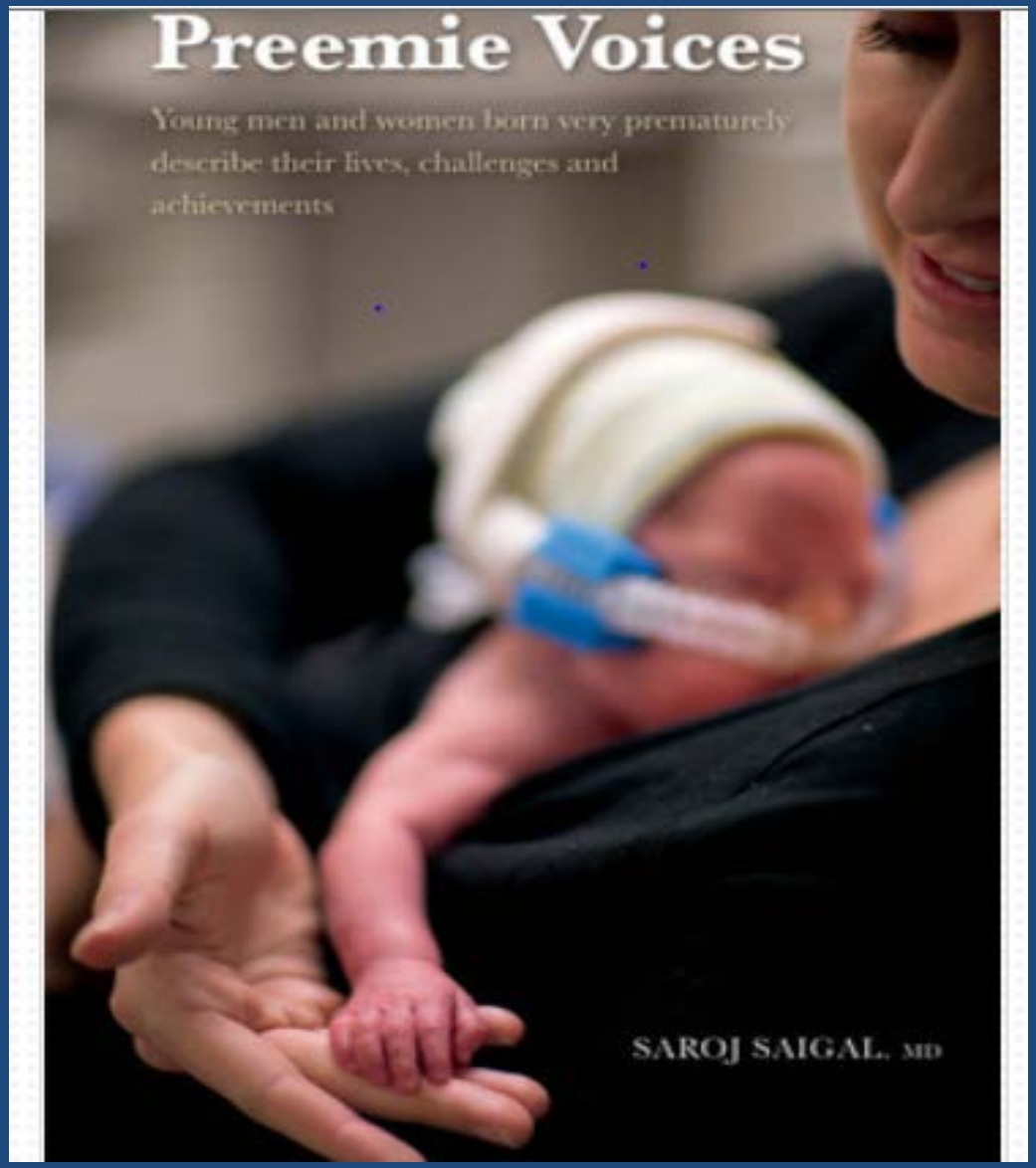
# FAMOUS PEOPLE BORN PREMATURELY

- Charles Darwin
- Victor Hugo
- Napoleon Bonaparte
- Isaac Newton
- Winston Churchill*
- Auguste Renoir
- Mark Twain
- Voltaire
- Stevie Wonder
- Michael J Fox

* Since WC was born 32 weeks and 5 days after his parents wedding, some have claimed that the shortness of his gestation might have been invented to solve a social problem.

www.saigalpreemievoices.com

Young people who were born weighing less than two pounds, three ounces provide candid and personal stories about their lives, challenges and accomplishments.



# THANK YOU

HAPPY TO TAKE QUESTIONS

This presentation can be downloaded from
http://www.epi.msu.edu/faculty/paneth/

# ADDITIONAL SLIDES

# CANCER

Two important childhood cancers – leukemia and brain tumors – have consistently been associated with higher birthweights; the association is may be a feature only of children in the upper quartile of weight for gestational age.

Prematurity/low birthweight has been associated with reduced risk of some cancers.

- Innes et al (Am J Epid 2000; 152(12):1121-8) found that women born at GA <33 weeks had an adjusted OR of 0.11 of having breast cancer before age 37
- Few studies of gestational age effects, but several studies since the above (largely on pre-menopausal BC) have found modestly decreased risks for low birthweight women

# HEPATOBLASTOMA RISK < 1,500 G

| STUDY | COUNTRY | ODDS RATIO |
|---|---|---|
| Spector LG et al: Pediatrics. 2009 Jul; 124(1): 96–104 | USA | 17.1 |
| De Fine Licht S et al Int J Cancer . 2012 Aug 15;131(4):E555-61 | NORWAY, SWEDEN, DENMARK, FINLAND | 9.5 |
| Heck JE et al Cancer Epidemiology. 2013 Aug;37(4):390-5. OR = 15.4 | USA | 15.4 |
| Ikeda H J Pediatr Surg 2015 Sep;50(9):1506-12. | JAPAN | 16% of cases |
| Pu CL et al: Zhonghua Gan Zang Bing Za Zi. 2009 Jun;17(6):459-6 | CHINA | 26.0 (< 1 kg) |

# BLOOD PRESSURE IN ALL PREMATURES

Moderate elevation of blood pressure usually found, again more pronounced in females. Hints of excess risk of hypertension, and effects on BP more notable in prematures who were also SGA

**Notable papers in adults born < 37 weeks:**

- Juonala M, Cheung MM, Sabin MA et al: J *Hypertension* 2015 Aug;33(8):1542-8. 1,756 participants in Finnish cardiovascular cohort.
  - 7.3 mm elevation in SBP at age 41, but *only* if also SGA. No elevation in BP if premature/AGA.
- Parkinson JR, Hyde MJ, Gale C et al: *Pediatrics* 2013 Apr;131(4):e1240-63. 27 studies of 17,030 preterm (<37 weeks) and 295,262 term adults (≥ 18 years)
  - SBP 2.4 mm higher in males, 4.9 mm higher in females