

Risk Factors for Congenital Heart Defects: A case study







Admission Note

- BG XXX is the 3584 gram product of a 37 WBD singleton gestation to a 22 year old G2P1A1 Caucasian female via C-section 2° to late fetal decels and FTP.

Infant characteristics

- Sex ratio
 - Males > females
 - International HLHS OR=1.7 (95% CI:1.55-1.85)
- Weight
 - BWI SGA OR= 4.4 (95% CI: 2.9-6.8)
 - NBDPS SGA OR= 2.0-3.0
- Maternal ethnicity
 - BWI, Atlanta - no differences

Maternal History

- PMHx: No diabetes, HTN
- PSHx: 2001 MVA liver lac and small intestinal injury s/p SBR
- Meds: PNV began @ 1st prenatal visit
- PObHx: G1 - SAB

Diabetes and HLHS

- Baltimore Washington Infant Study
 - Cases (4/377):Controls (23/3572)
HLHS: OR = 1.7 (95% CI:0.6-4.8)
- National Birth Defects Prevention Study
 - Cases (3/192):Controls (21/4086)
 - HLHS: OR = 1.8 (95% CI: 0.4-7.8)

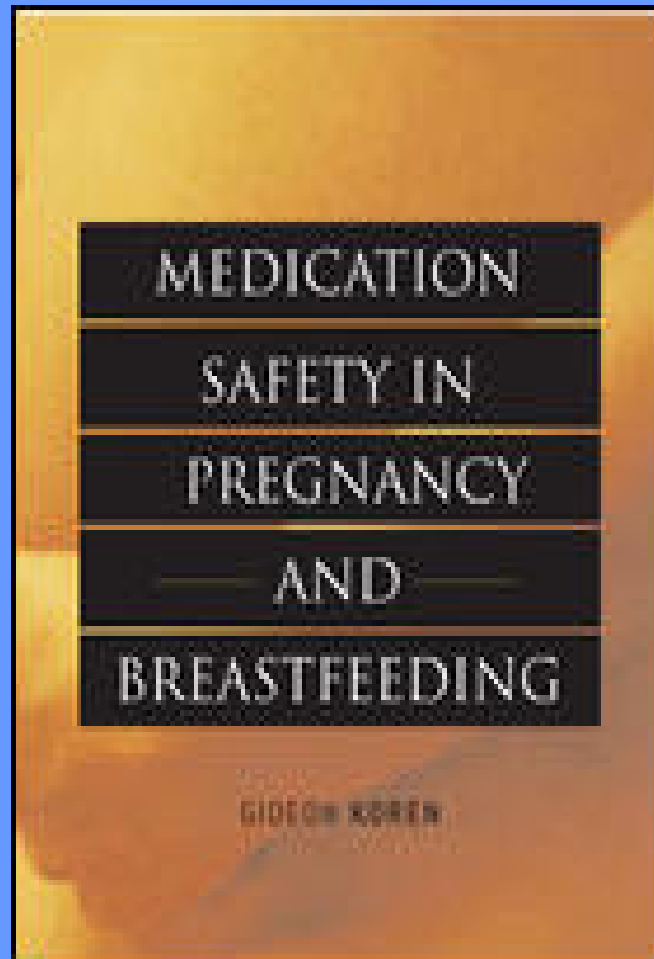
Diabetes and Other CHDs

- Hypertrophic cardiomyopathy
- Double outlet right ventricle
- Truncus arteriosus
- Transposition of the great arteries
- VSD

Mechanism

- Hyperglycemia - Oxidative Stress
- Hyperinsulinemia
- Hypoglycemia - Lactic Acidosis
- Modifiers of diabetic embryopathy
 - Antioxidants
 - Lipids
 - Arachidonic Acid
- Genetic Variants

Maternal Medications



FDA Pregnancy Categories

- A - Controlled studies in pregnancy (<1%)
- B - Animal studies show no risk or human data are reassuring
- C - Human data lacking; animal studies positive or not done (66%)
- D - Human data show risk; benefit may outweigh
- X - Animal or human data positive; no benefit

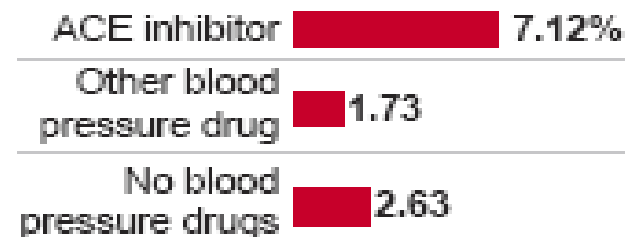
Maternal Hypertension

- Angiotensin-converting-enzyme (ACE) inhibitors
 - Tennessee Medicaid
 - 29,507 infants 1985-2000
 - OR = 3.7 (95% CI: 1.9 - 7.3)
- 1995 - 2002 use of ACE inhibitors increased from 2.4% to 4.4%

ACE inhibitors pose risk of birth defects

Mothers who used ACE inhibitors, a blood pressure treatment, were more than twice as likely to have babies with birth defects.

Percentage of birth defects



ACE inhibitor defects



SOURCE: New England
Journal of Medicine

AP

Multivitamins and Heart Defects

Conotruncal Heart Defects

Hungary '96 (RCT)
Atlanta 2000 (CC)

Outflow Tract Defects

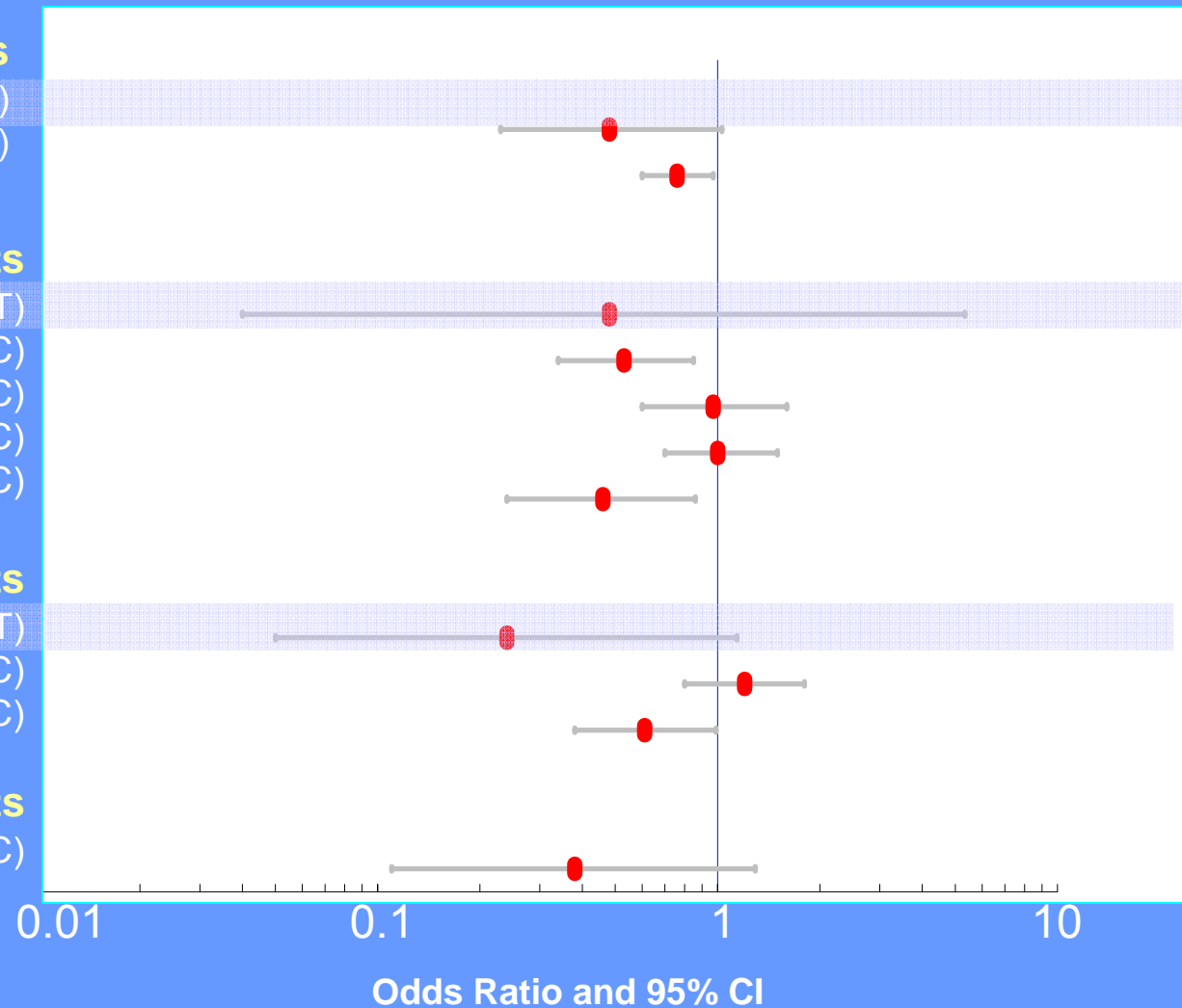
Hungary '96 (RCT)
California '95 (CC)
Baltimore-Washington '97 (CC)
U.S.- Canada '99 (CC)
Atlanta 2000 (CC)

Ventricular Septal Defects

Hungary '96 (RCT)
U.S.- Canada '99 (CC)
Atlanta 2000 (CC)

All Heart Defects

Atlanta 2000 (CC)

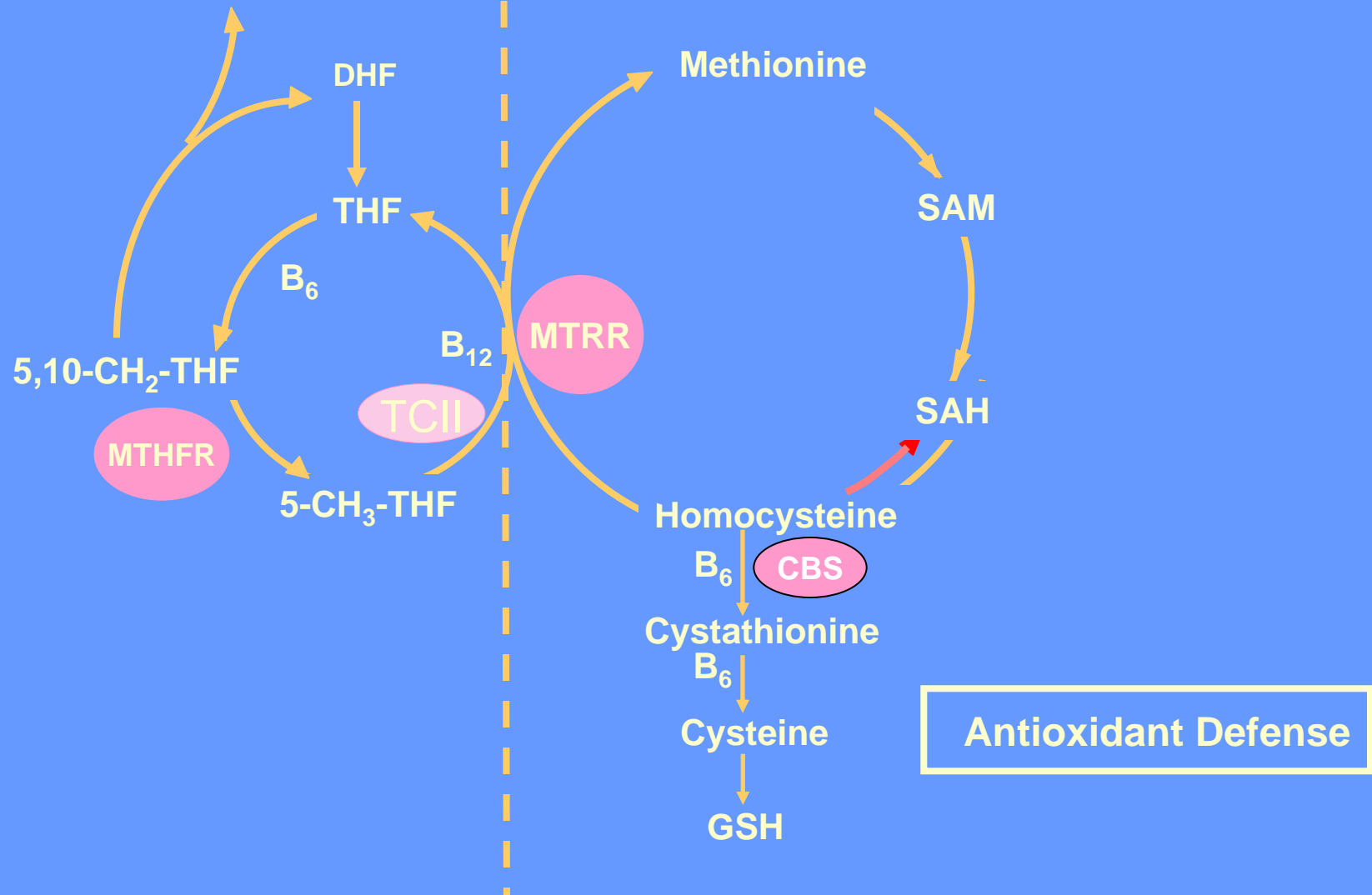


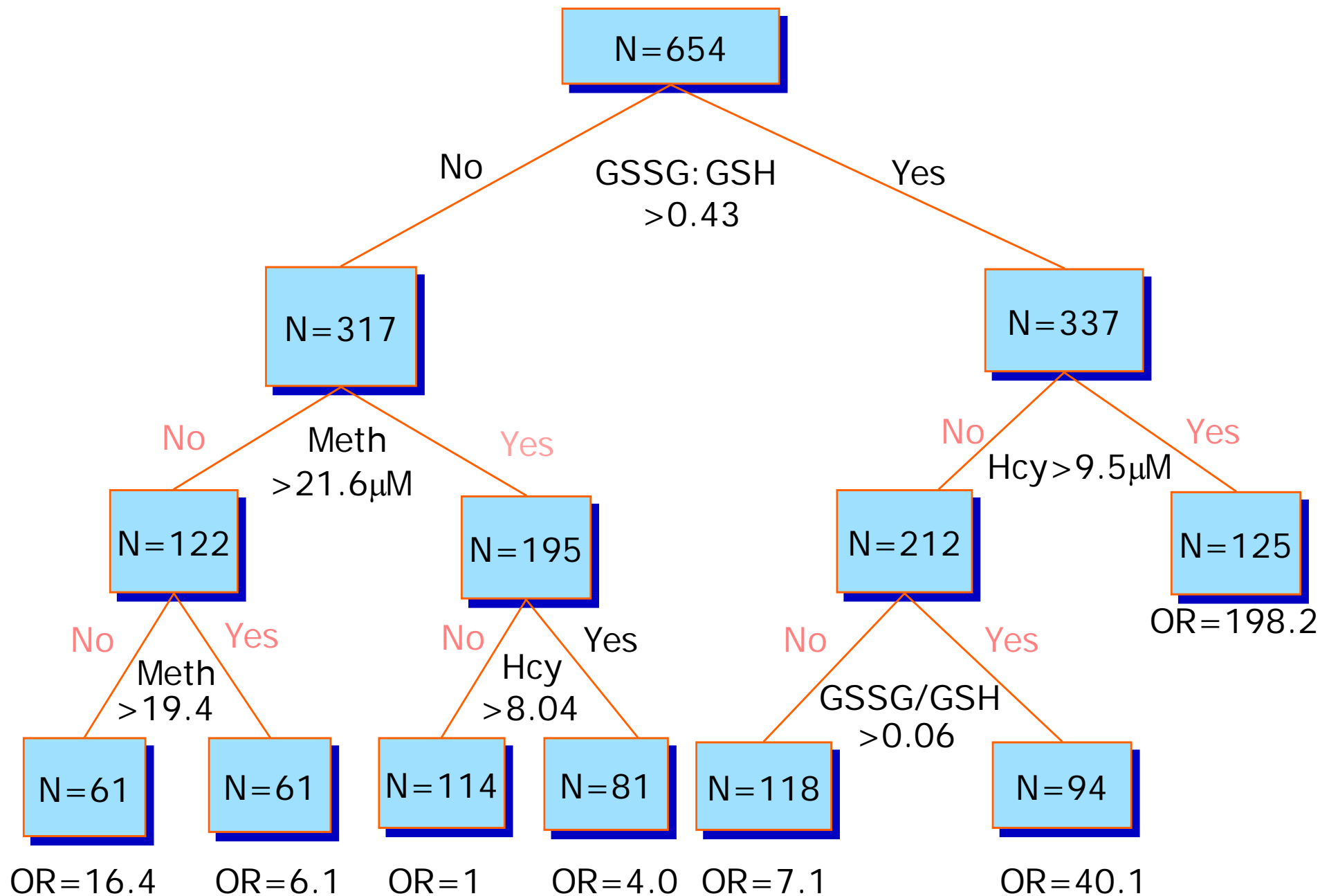
Botto LD, Mulinaire J, Erickson JD. Do multivitamins or folic acid supplements reduce the risk for congenital heart defects? Evidence and Gaps. Am J Med Genet 2003; 121A:95-101

Folic Acid Pathway

DNA Synthesis

DNA Methylation





Gaps identified by Botto AJMG 2003

- Do multivitamins reduce the risk?
- How much do they reduce the risk?
- What is the magnitude of effect?
- What components of multivitamins account for effect?
- What components of multivitamins account for effect?
- What dose is most effective?
- What is the mechanism?
- Do gene-environment interactions play a role?

Admission Note

- SocHx: Denies smoking, drug use
- Occassional alcohol use during 1st trimester
- Family Hx: noncontributory

Maternal smoking

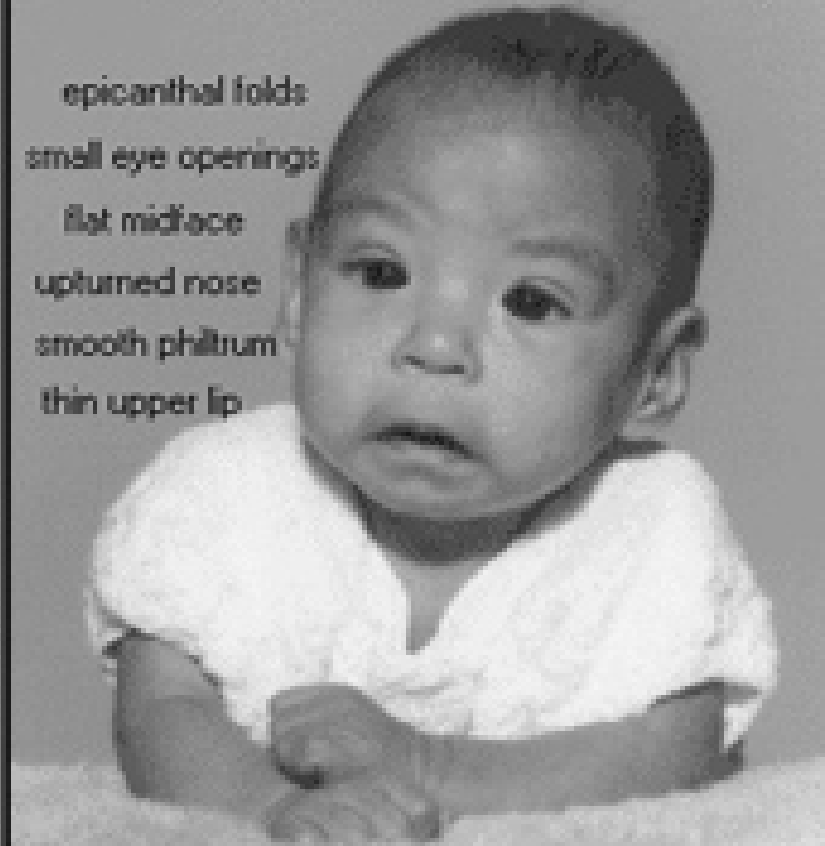
- BWI - nonsignificant OR
- NBDPS - nonsignificant OR

Alcohol Use

- 77.6% ever use alcohol
- 58.8% drink while pregnant
- Conotruncal heart defects
 - California Birth Defect Monitoring Program
 - $\leq 1X$ week OR = 1.3 (95% CI: 1.0, 1.9)
 - ≥ 1 week OR = 1.9 (95% CI: 1.0, 3.4)

FAS Facial Characteristics

epicanthal folds
small eye openings
flat midface
upturned nose
smooth philtrum
thin upper lip



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Family History

Use of Family History Information in Pediatric Primary Care and Public Health

CDC-Sponsored Workgroup Meeting

February 24–25, 2006

Doubletree Hotel Atlanta– Buckhead
1342 Peachtree Rd., NE
Atlanta, GA 30306



- BWI
 - OR = 4.8
 - 95% CI: 2.1 - 10.8

Maternal prenatal labs

- HIV/RPR/Hep B - negative
- Rubella - immune

Congenital Rubella Syndrome



Rubella Immune

- Rubella vaccination introduced in US 1969
- 91% of US women seropositive for rubella
- 75% of Sri Lankan women positive for rubella IgG

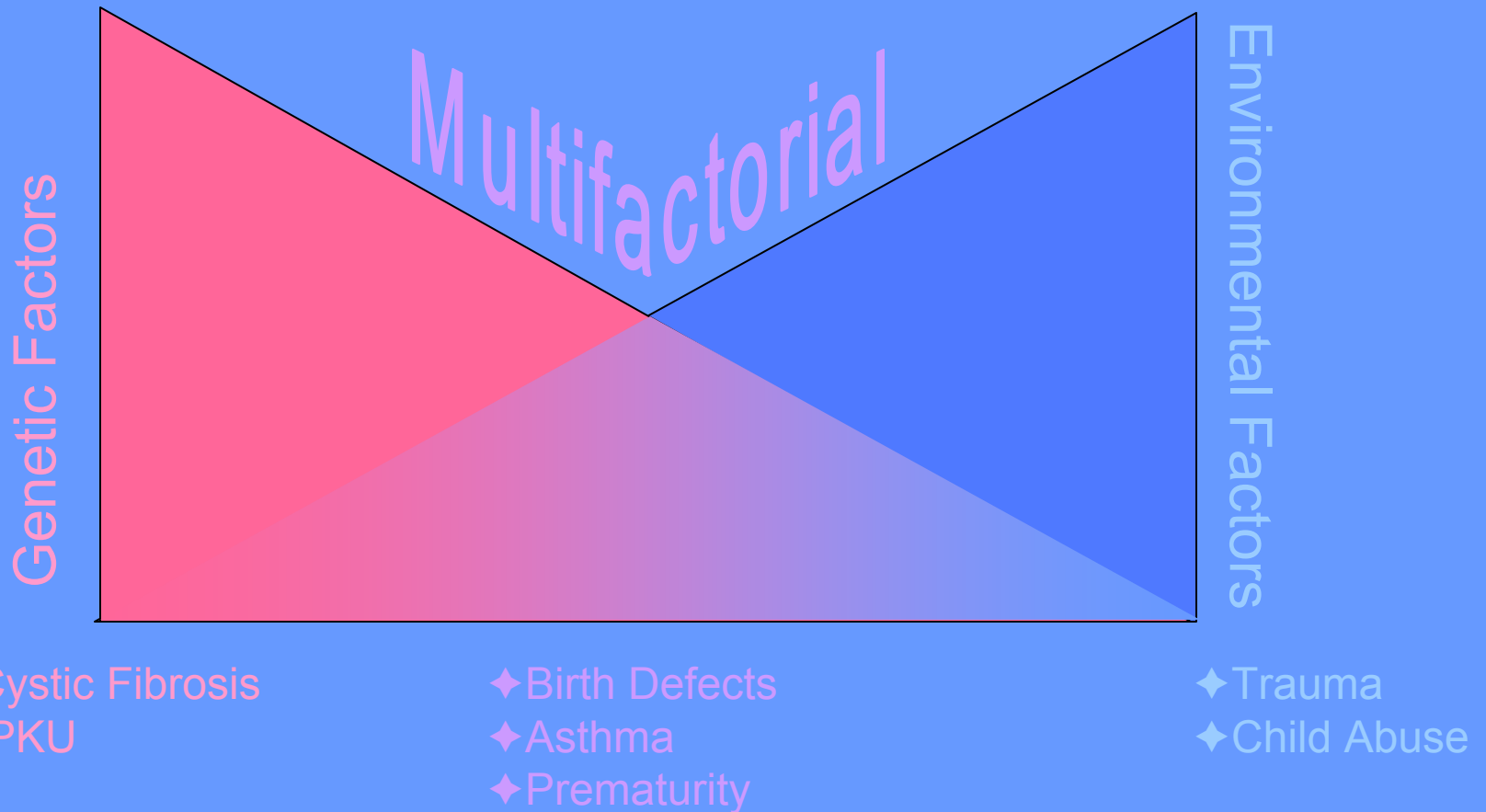
Admission Note

- PE: *General Appearance* - term newborn, mild respiratory distress, minimal central cyanosis initially, no obvious congenital malformations

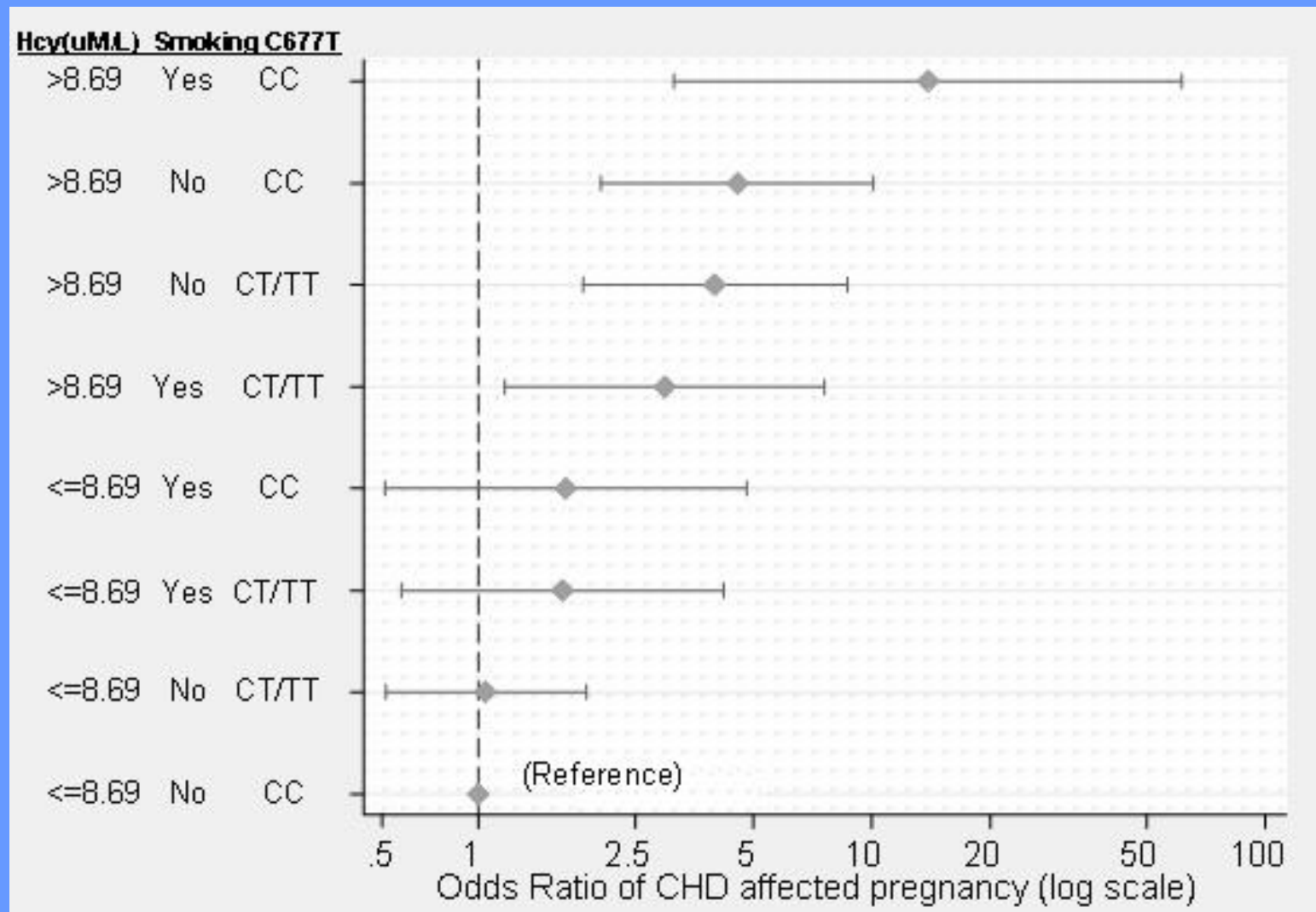
Down Syndrome

- Chromosome 21
- 50%
- Why??

Causes of Common Pediatric Conditions



Combined effect of homocysteine, smoking and MTHFR 677C>T genotype on CHD risk

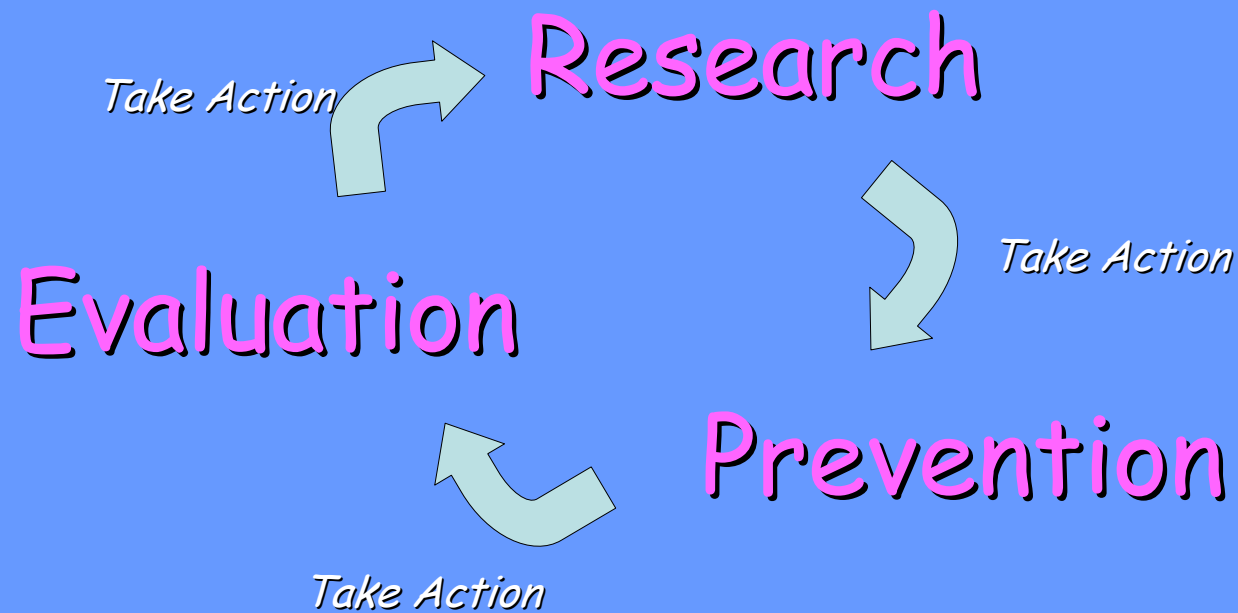


HapMap Project



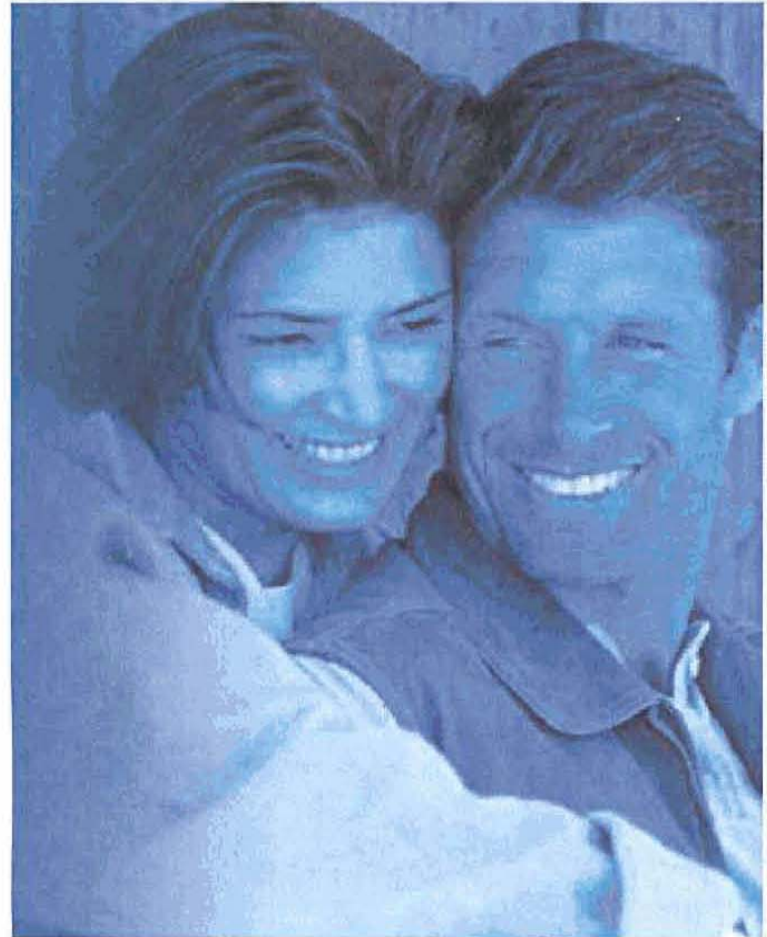
- International endeavor
 - Canada, China, Japan, Nigeria, United Kingdom and United States
 - Total of 270 individuals to be analyzed for 1 million SNPs
- Purpose
 - Provide a map of SNPs that will allow scientists to find and test susceptibility loci
 - Provide representative, genomewide haplotypes from different populations
 - Initial phase completed ahead of schedule
 - Publicly available data for 4 different populations

Birth Defects Research and Prevention





Why is Preconception Care a public health concern?



Preconception Care

- Risk assessment
- Health Promotion
- Intervention

Our Vision of Preconceptional Care

- Determine genetic susceptibilities: genome-wide association studies
- Establish genetic and metabolic high-risk profile
- Provide diagnostic tools for physicians
- Design targeted treatments
- The benefits will be widespread and many cannot even be predicted yet









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