Diabetes and Birth Defects

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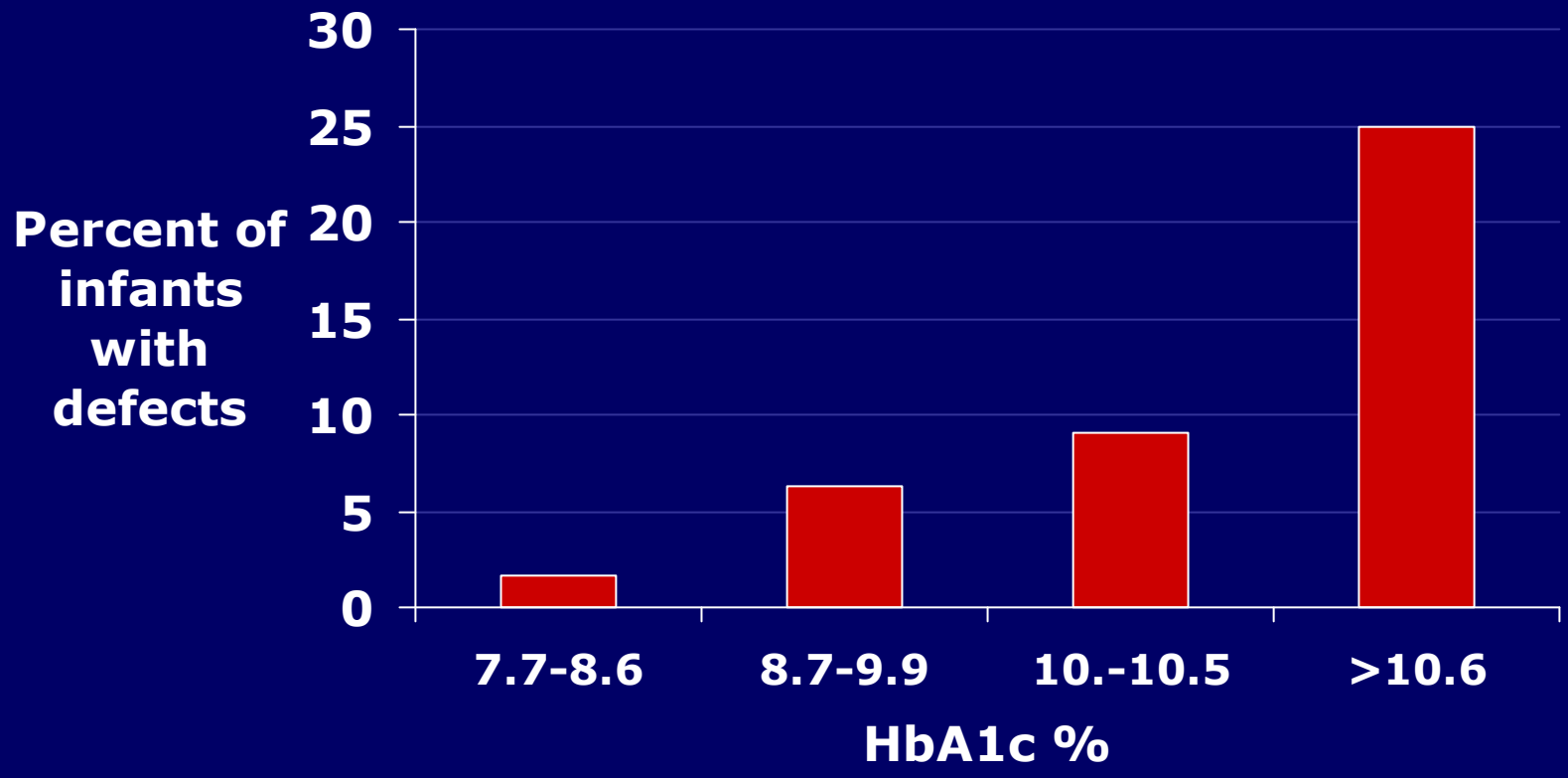
Outline

- Associations of diabetes with birth defects
- Preconception care and the prevention of birth defects
- Challenges and opportunities for prevention of birth defects

Birth defects associated with pregestational diabetes

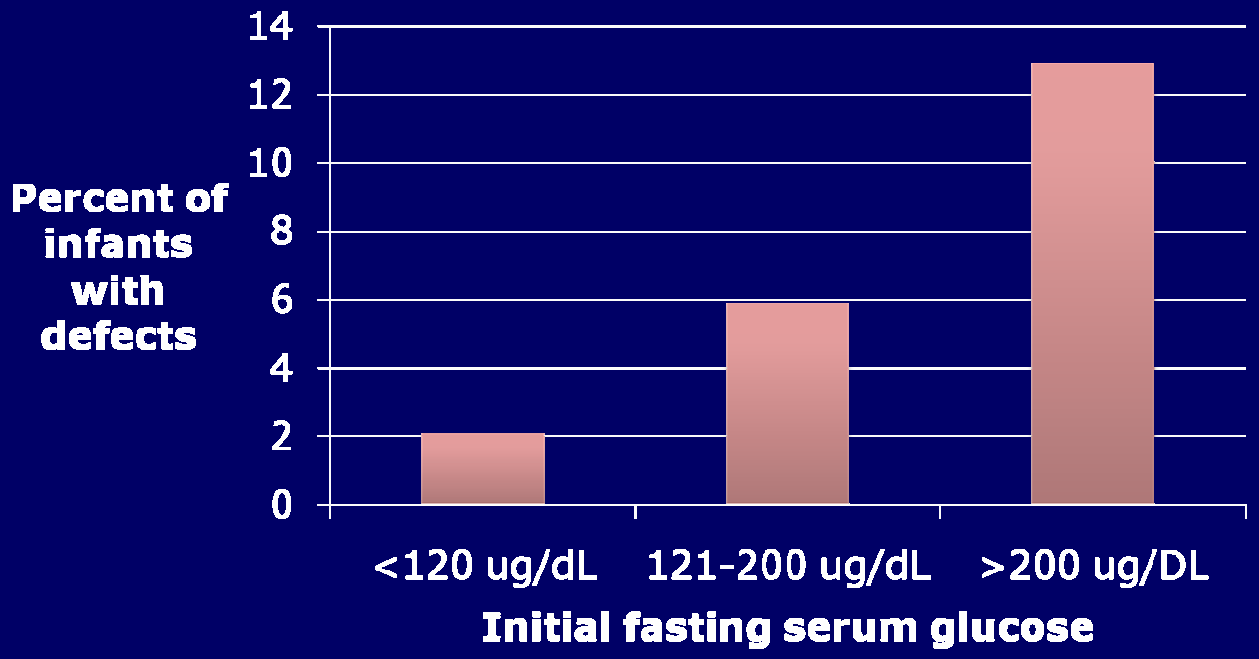
- Pregestational diabetes (PGDM) (type 1 or type 2) is a well known teratogen
  - Across animal species
  - Several organ systems susceptible
    - Some more susceptible than others
      - Musculoskeletal
        - e.g., sacral agenesis
      - CVM
        - e.g., conotruncal defects
      - CNS
        - e.g., anencephaly

Rates of major defects by HbA1c at 1st prenatal visit among women with type 1 diabetes



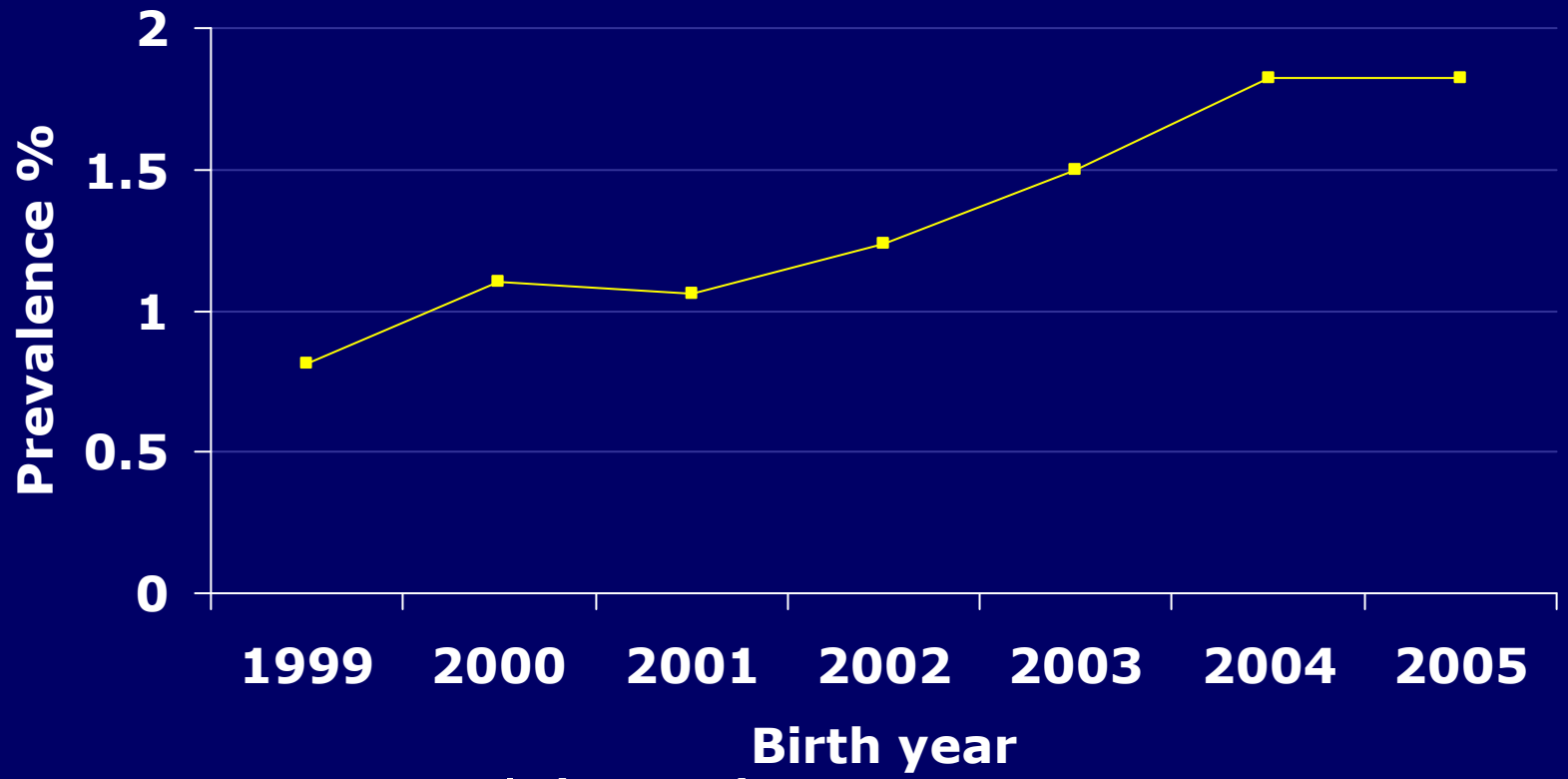
Kitzmiller et al (1991)

Rates of major defects by initial fasting serum glucose among women with type 2 and gestational diabetes



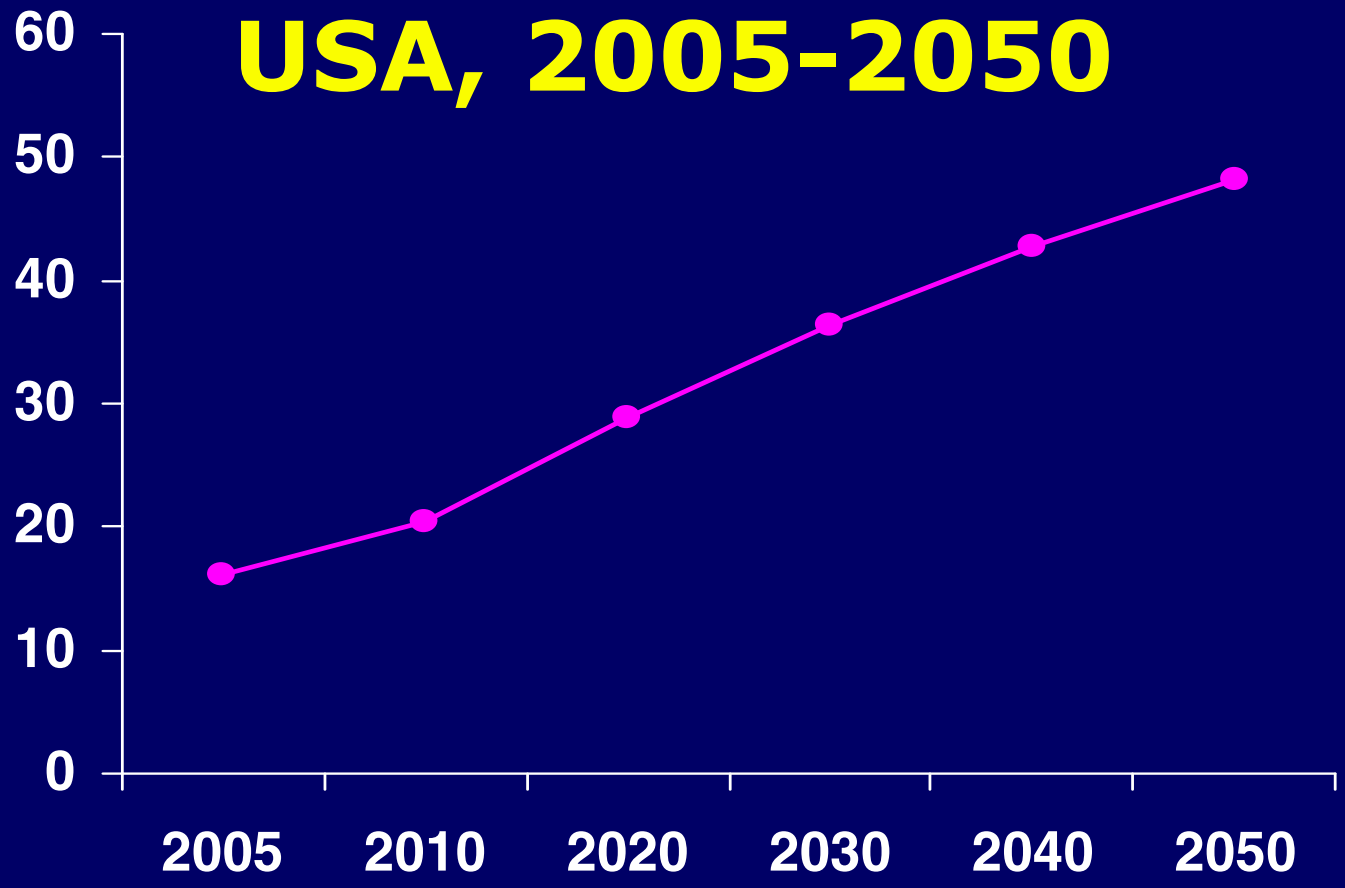
Schaefer-Graf et al AJOG (2000)

Prevalence of preexisting diabetes per 100 births, age- and race/ethnicity adjusted, by year, Kaiser Permanente Southern California

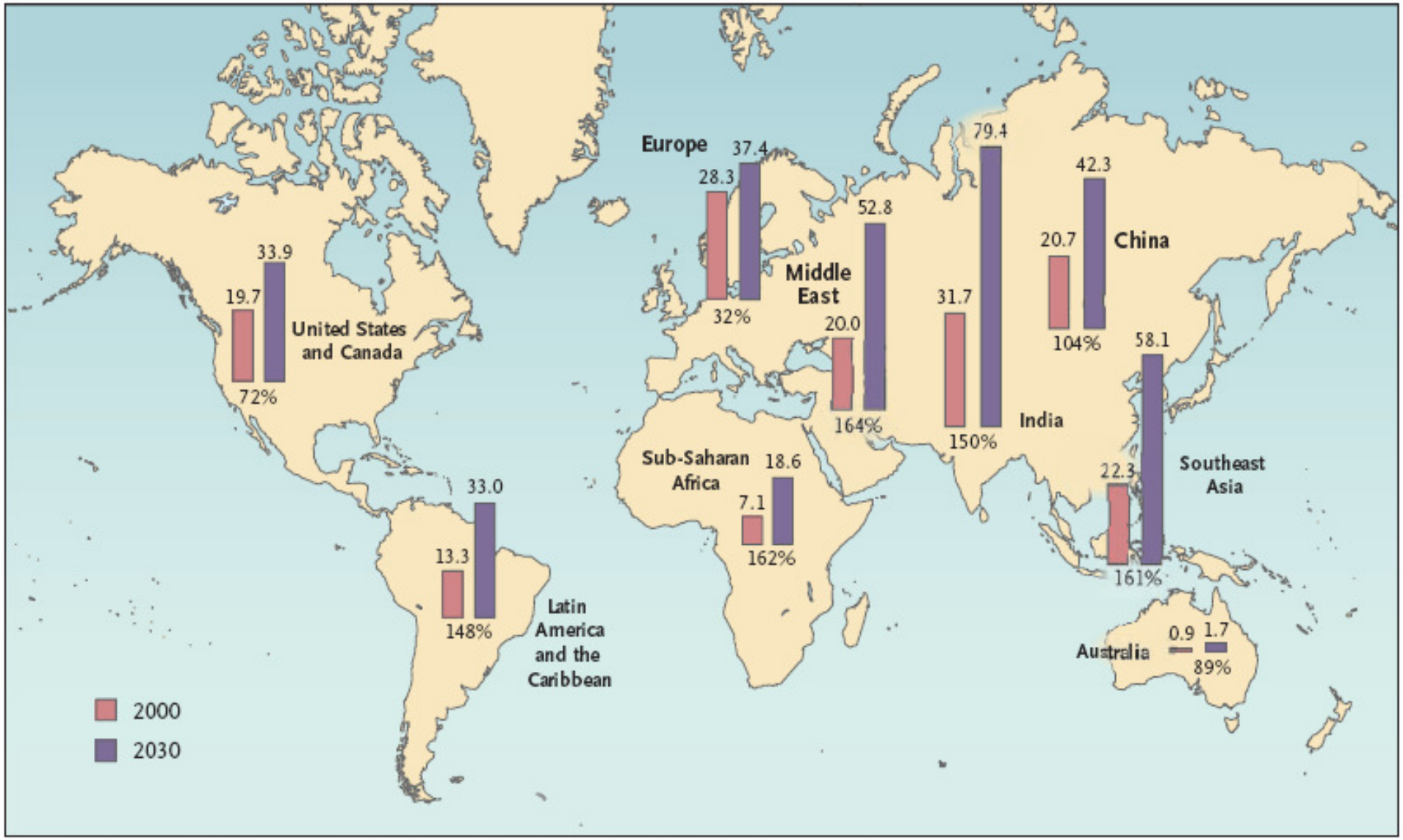


Lawrence et al (2008)

Projected increase in numbers (millions) with diagnosed diabetes, USA, 2005-2050



Narayan KM et al. *Diabetes Care*, 2006



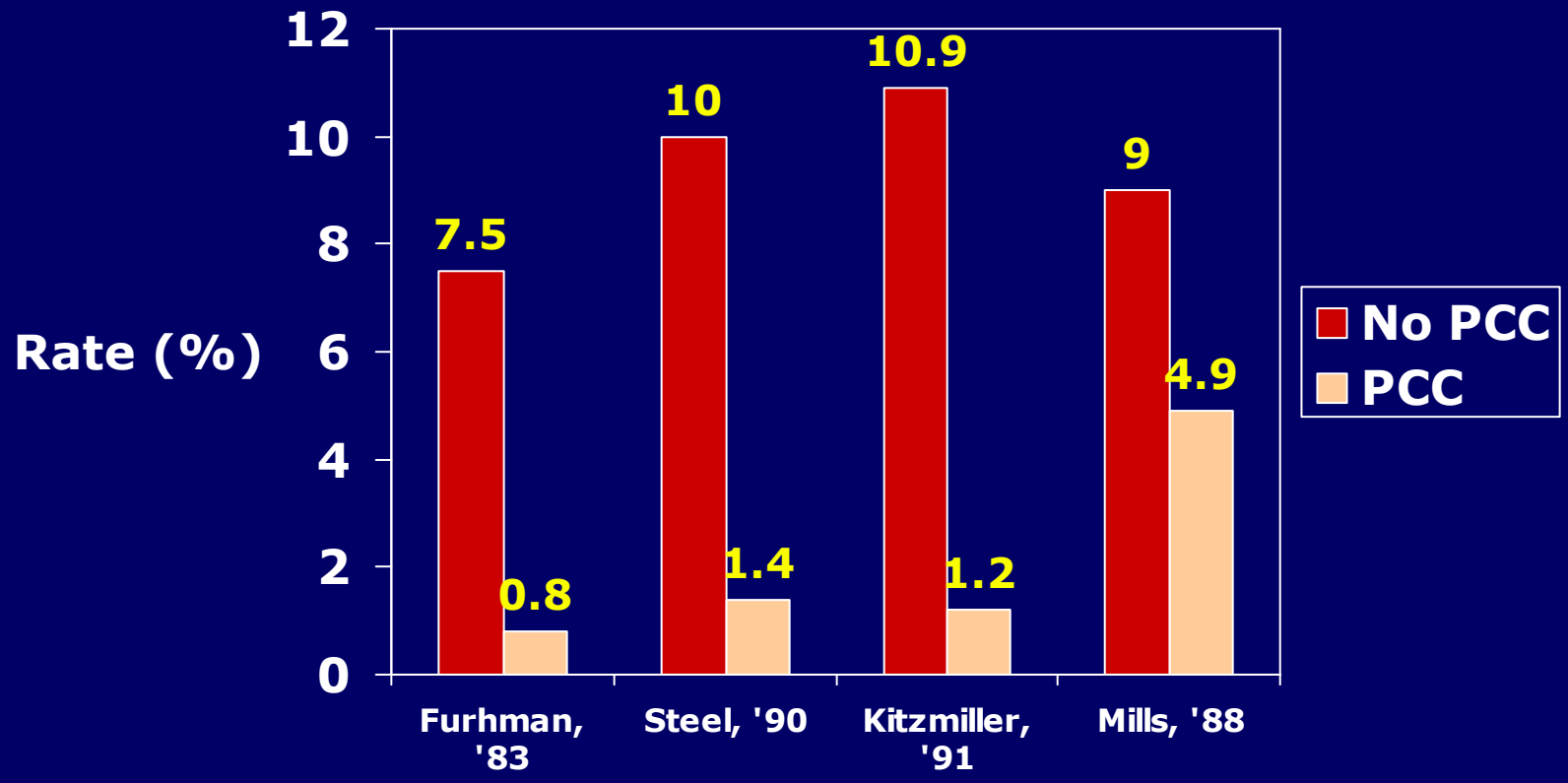
Millions of Cases of Diabetes in 2000 and Projections for 2030, with Projected Percent Changes.

Data are from Wild et al.[3]

Hossain et al. N Engl J Med 2007; 356:213-215

Can preconception care reduce the risk for birth defects associated with diabetes?

Rates of birth defects among offspring to women with PGDM by participation in preconception care



Preconception care for diabetes and risk of major defects

- Pooled analysis, 14 studies (Ray, 2001) of pregnancies to women with type 1 diabetes
  - 1459 offspring without preconception care – 6.5% major defects
  - 1192 offspring with preconception care – 2.1% major defects
- Dutch study (Evers et al. 2004) of 323 pregnancies to women with type 1 diabetes
  - Unplanned pregnancies – 12.1% defects
  - Planned pregnancies – 4.2% defects

Glycemic control and risk for birth defects

- West Midlands study, 182 women with type 2 diabetes receiving early prenatal care, 1990-2002 (Dunne et al., 2003)
  - Rate of birth defects by first HbA1c
    - Normal (33%) 3.3%
    - Moderately elevated (38%) 7.2%
    - Extremely elevated (29%) 20.7%
- Diabetes Complications Control Trial (DCCT) of 1441 adults with type 1 diabetes randomly assigned to conventional or intensive therapy (Loeken, 2005)
  - 180 women became pregnant
    - 1 birth defect in intensive therapy group
    - 8 birth defects in conventional therapy group

Efficacy vs. effectiveness

- **Efficacy**
  - the extent to which a specific intervention or service produces a beneficial result under ideal circumstances (i.e., controlled settings)
- **Effectiveness**
  - the extent to which a specific intervention or service does what it is intended to do

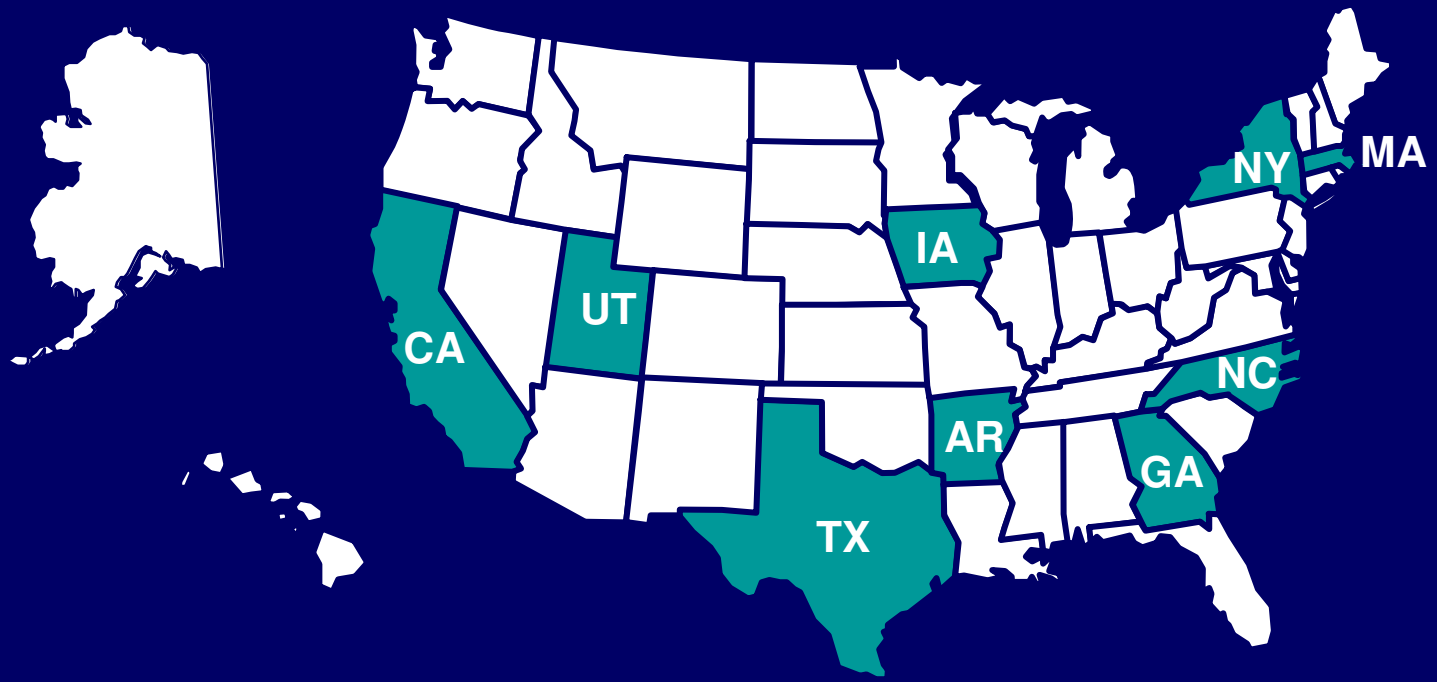
To what extent is preconception care reaching women with diabetes?

- Is diabetes continuing to be associated with birth defects today?

The National Birth Defects Prevention Study (NDBPS)

- Case-control study of major birth defects
- Study subjects born Oct 1,1997-Dec 31, 2002
- Cases identified from 9 study centers with population-based surveillance systems
  - AR, CA, GA, IA, MA, NC, NY, TX, UT

Centers Participating in the National Birth Defects Prevention Study



The National Birth Defects Prevention Study (NDBPS)

- **Controls**
  - **Liveborn infants without major birth defects randomly selected from birth cohorts from same region**
    - **From birth certificates: GA, IA, MA**
    - **From birth hospitals: AR, CA, GA, NC, NY, TX, UT**
- **Telephone interviews in English or Spanish between 6 weeks and 2 years post-delivery**
- **Participation rate**
  - **70.5 percent (cases)**
  - **67.2 percent (controls)**

Birth defects

- Neural tube defects
  - Anencephaly
  - Spina bifida
- Hydrocephalus
- Cataract
- Anotia/microtia
- Cardiac defects
- Oral clefts
  - Cleft palate
  - Cleft lip w/wo cleft palate
- Esophageal atresia
- Intestinal atresias
  - Ileal, Jejunal, Multiple
  - Duodenal
- Biliary atresia
- Anorectal atresia
- Hypospadias
- Limb reduction defects
- Craniosynostosis
- Diaphragmatic hernia
- Omphalocele
- Gastroschisis
- Sacral agenesis

- Cardiac defects
  - Heterotaxia
  - Conotruncal defects
    - Tetralogy of Fallot
    - D-Transposition of the great arteries
  - Atrioventricular septal defect
  - Total anomalous pulmonary venous return
  - Left ventricular outflow tract obstructions
    - Hypoplastic left heart syndrome
    - Coarctation of the aorta
    - Aortic stenosis
    - LVOTO associations
      - Coarctation + ASD
      - Coarctation + VSD
      - Coarctation + ASD + VSD
  - Right ventricular outflow tract obstructions
    - Pulmonary atresia
    - Pulmonic valve stenosis
    - RVOTO associations
      - Pulmonic valve stenosis + VSD
      - Pulmonic valve stenosis + ASD
  - Septal defects
    - Ventricular septal defect, perimembranous
    - Ventricular septal defect, muscular
    - Atrial septal defect, secundum
    - Atrial septal defect, OS/NOS
    - Septal associations
      - ASD + VSD

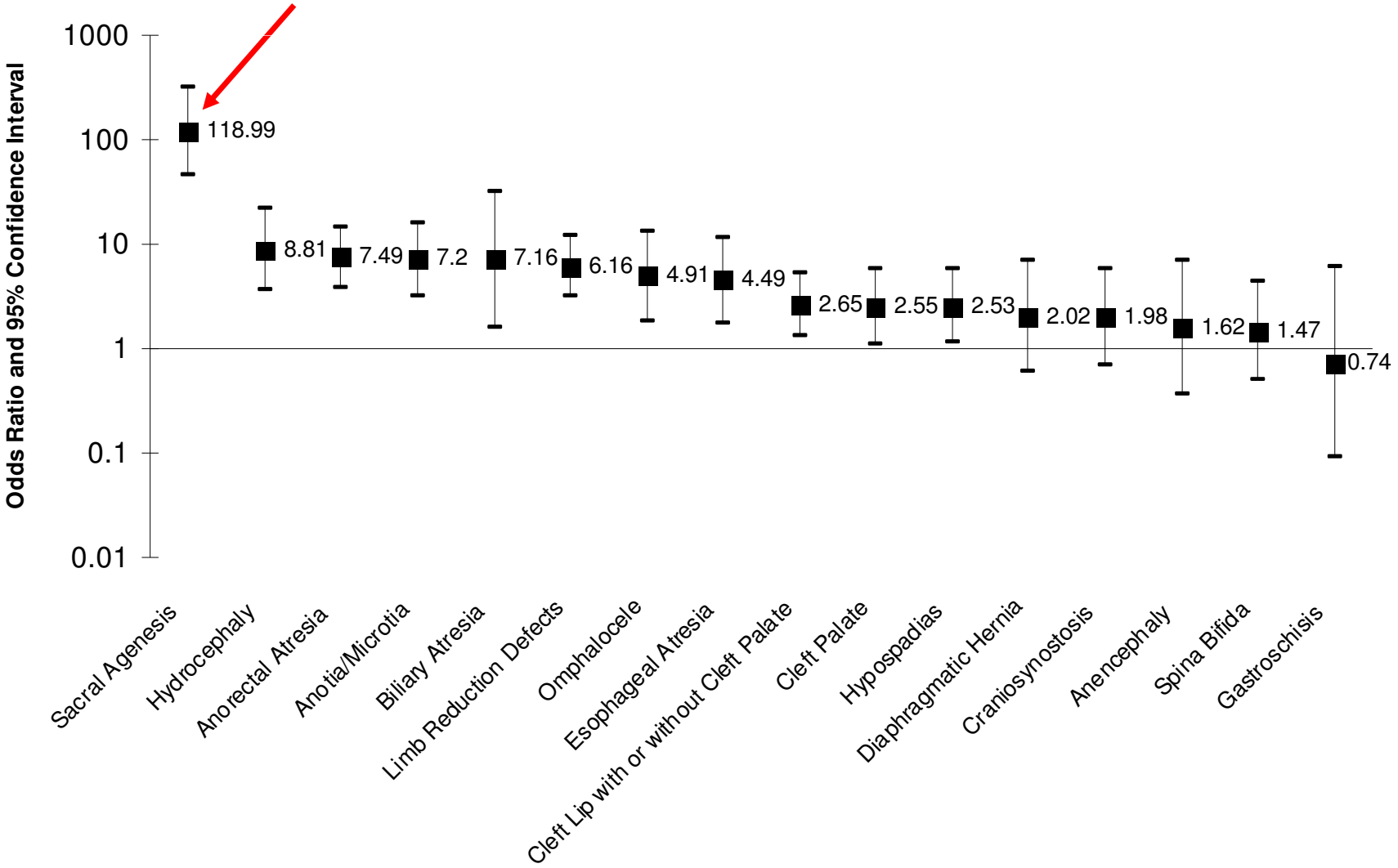
Diabetes definition

- **Responses to two questions:**
  - **1: Were you ever told by a doctor that you had diabetes (including gestational diabetes), sometimes called sugar diabetes or diabetes mellitus?**
  - **2: What type of diabetes did you have? Was it:**
    - **Gestational, that is during pregnancy only**
    - **Insulin-dependent diabetes, also called Type 1 or Juvenile**
    - **Non-insulin dependent diabetes, also called Type 2 or Adult-onset**
    - **DK**
- **Analytic variables for pregestational diabetes (combination of Type 1 and Type 2) and gestational diabetes**

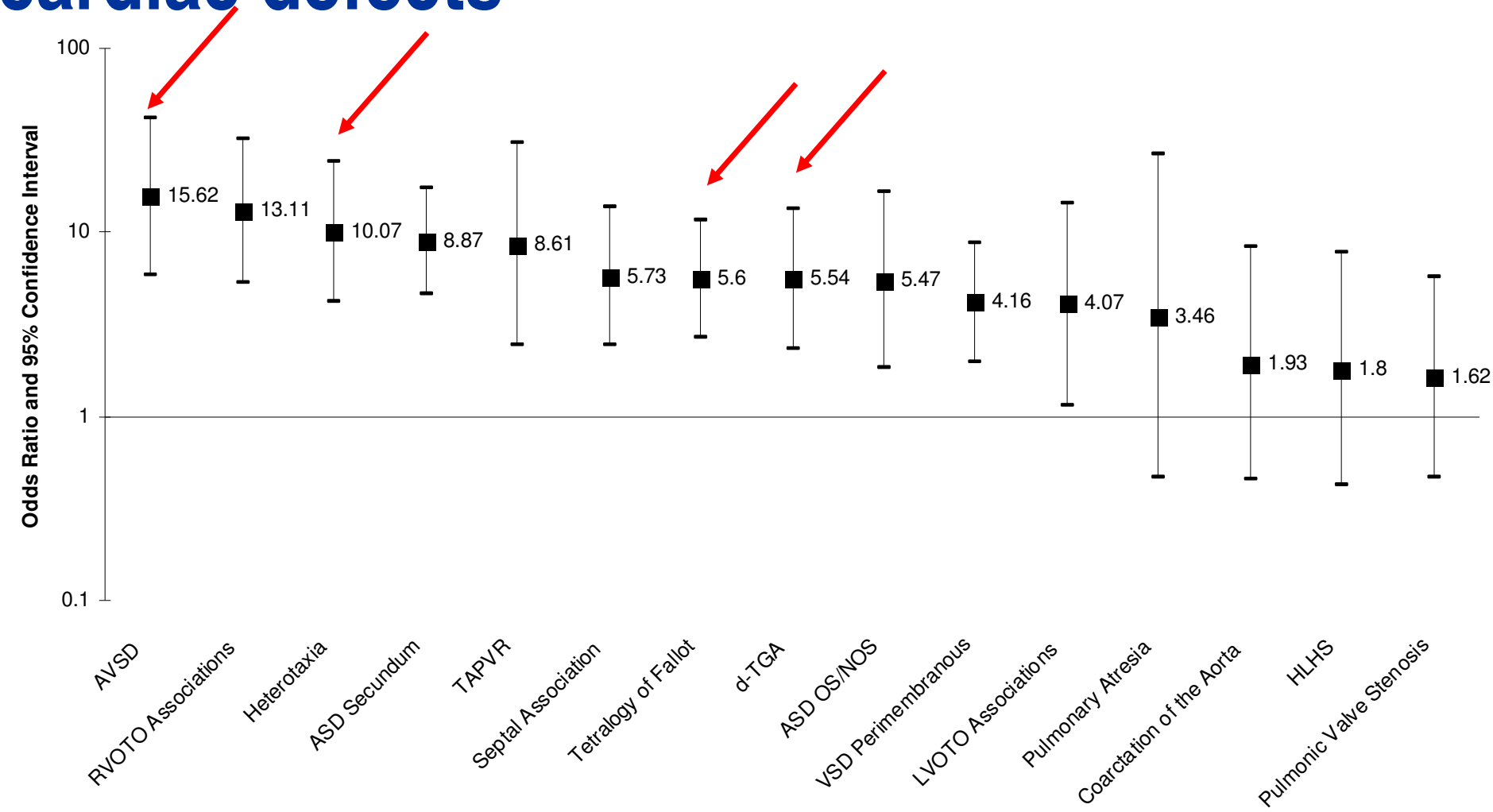
Number exposed and crude odds ratios, by type of diabetes

	Controls (n=4086)	All cases (n=9929)	All isolated cases (n=8491)	All multiple cases (n=1346)
No diabetes	3835	8994	7732	1177
Pregestational	21	209	141	65
	ref	4.24 (2.70-6.64)	3.33 (2.10-5.27)	10.09 (6.14-16.57)
Type 1	9	106	71	34
	ref	5.02 (2.54-9.93)	3.91 (1.95-7.83)	12.31 (5.89-25.74)
Type 2	12	103	70	31
	ref	3.66 (2.01-6.66)	2.89 (1.57-5.34)	8.42 (4.31-16.44)
Gestational	230	726	618	104
	ref	1.35 (1.15-1.57)	1.33 (1.14-1.56)	1.47 (1.16-1.87)

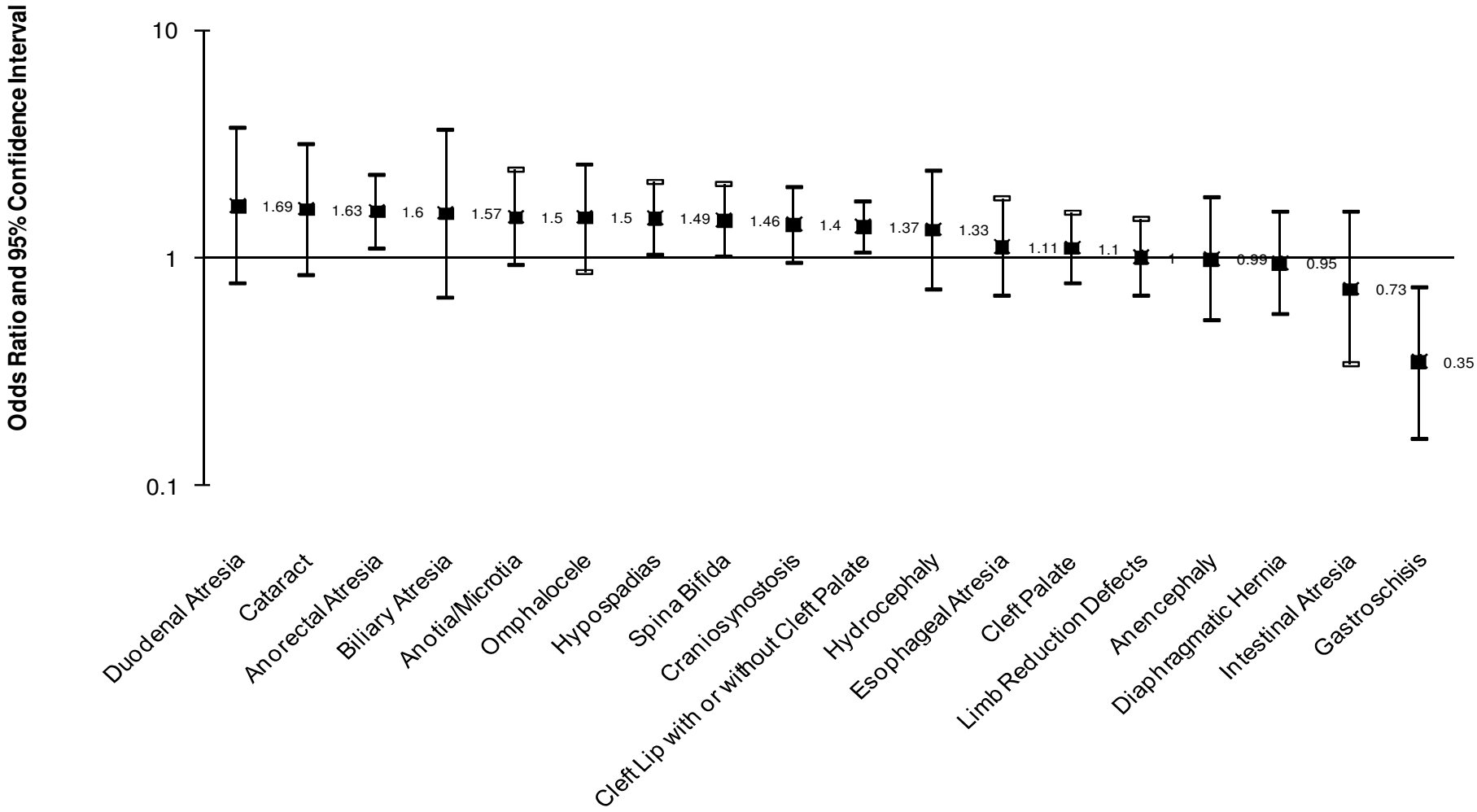
Odds ratios for pregestational diabetes and non-cardiac defects



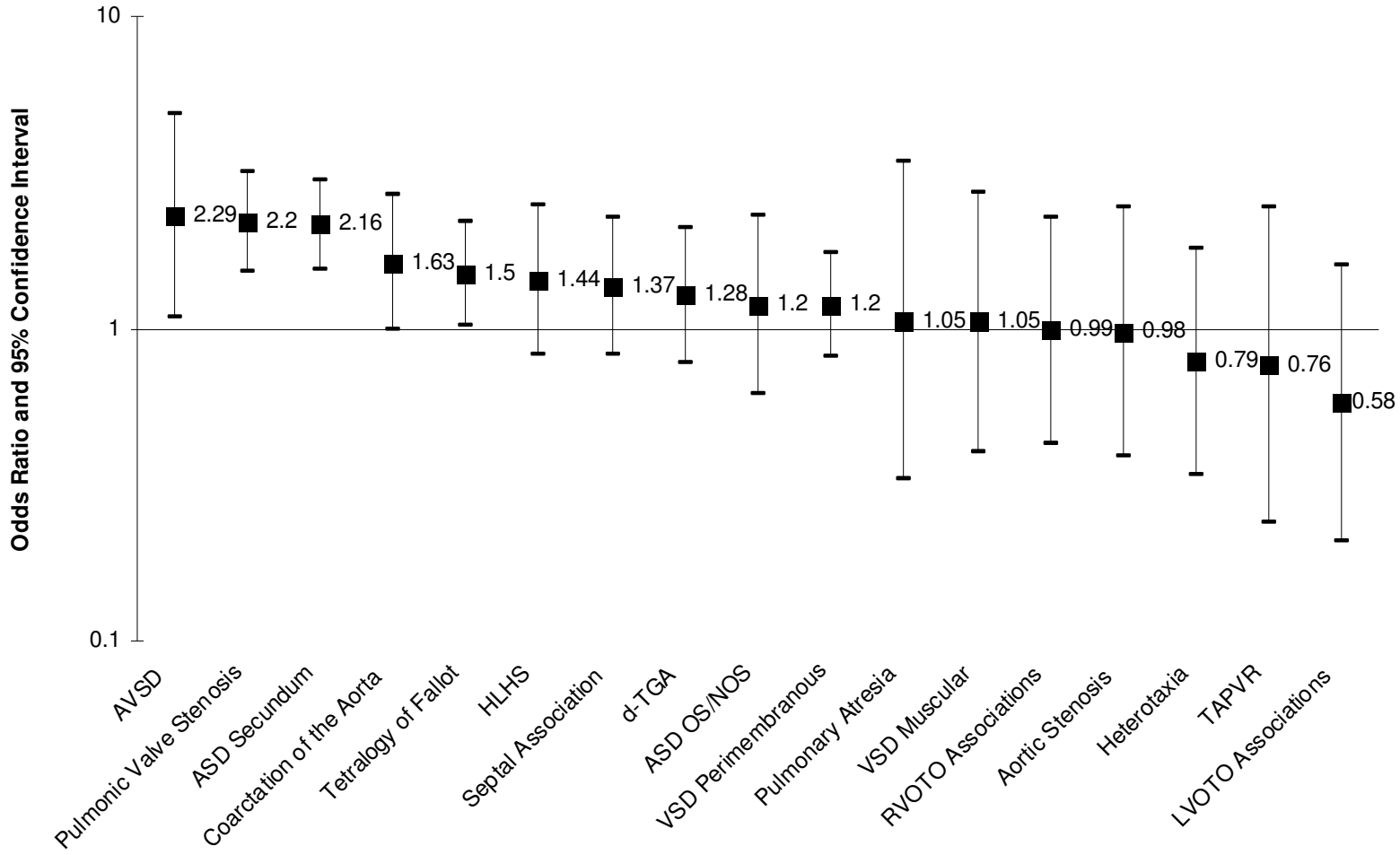
Odds ratios for pregestational diabetes and cardiac defects



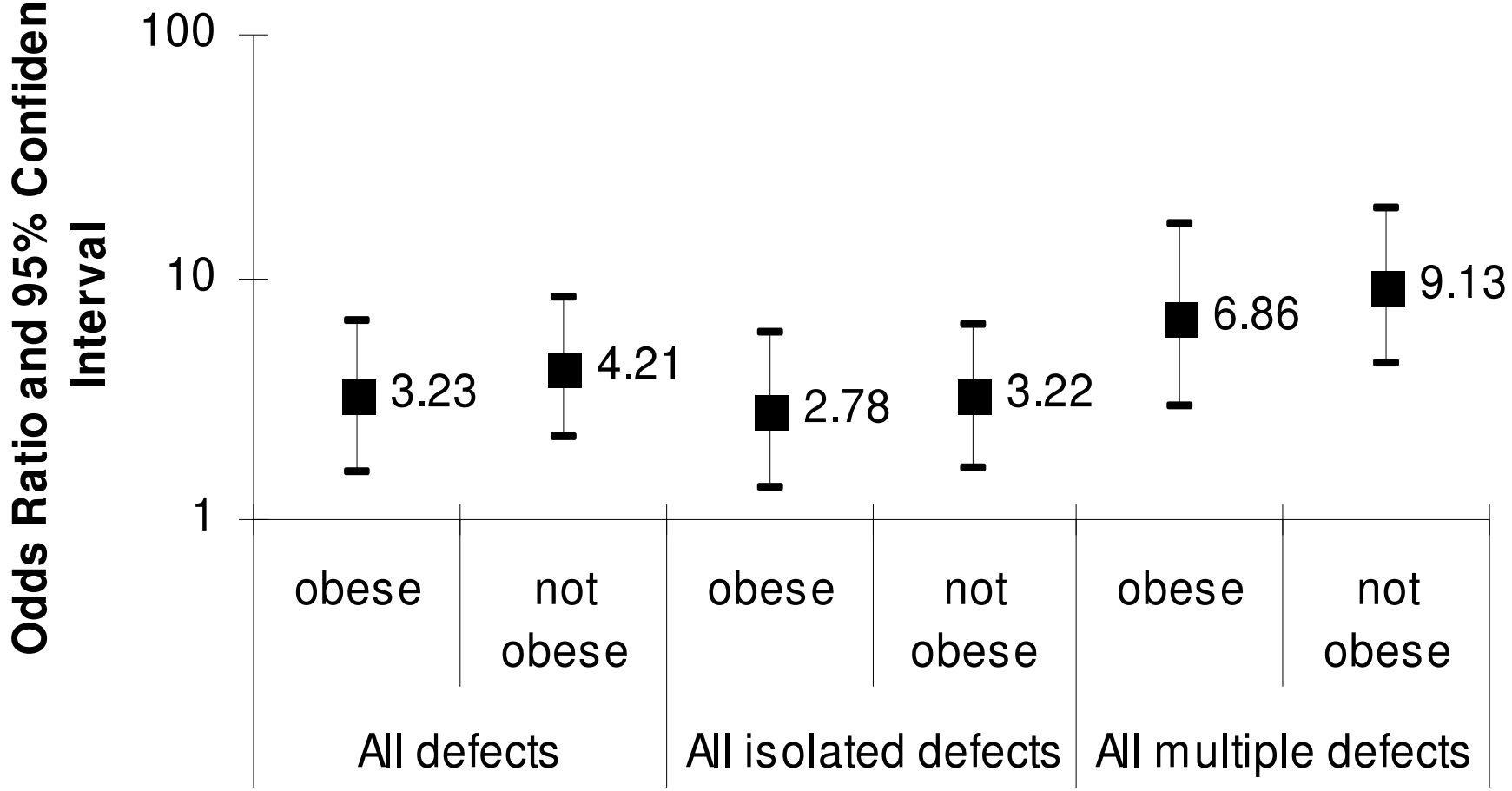
Odds ratios for gestational diabetes and non-cardiac defects



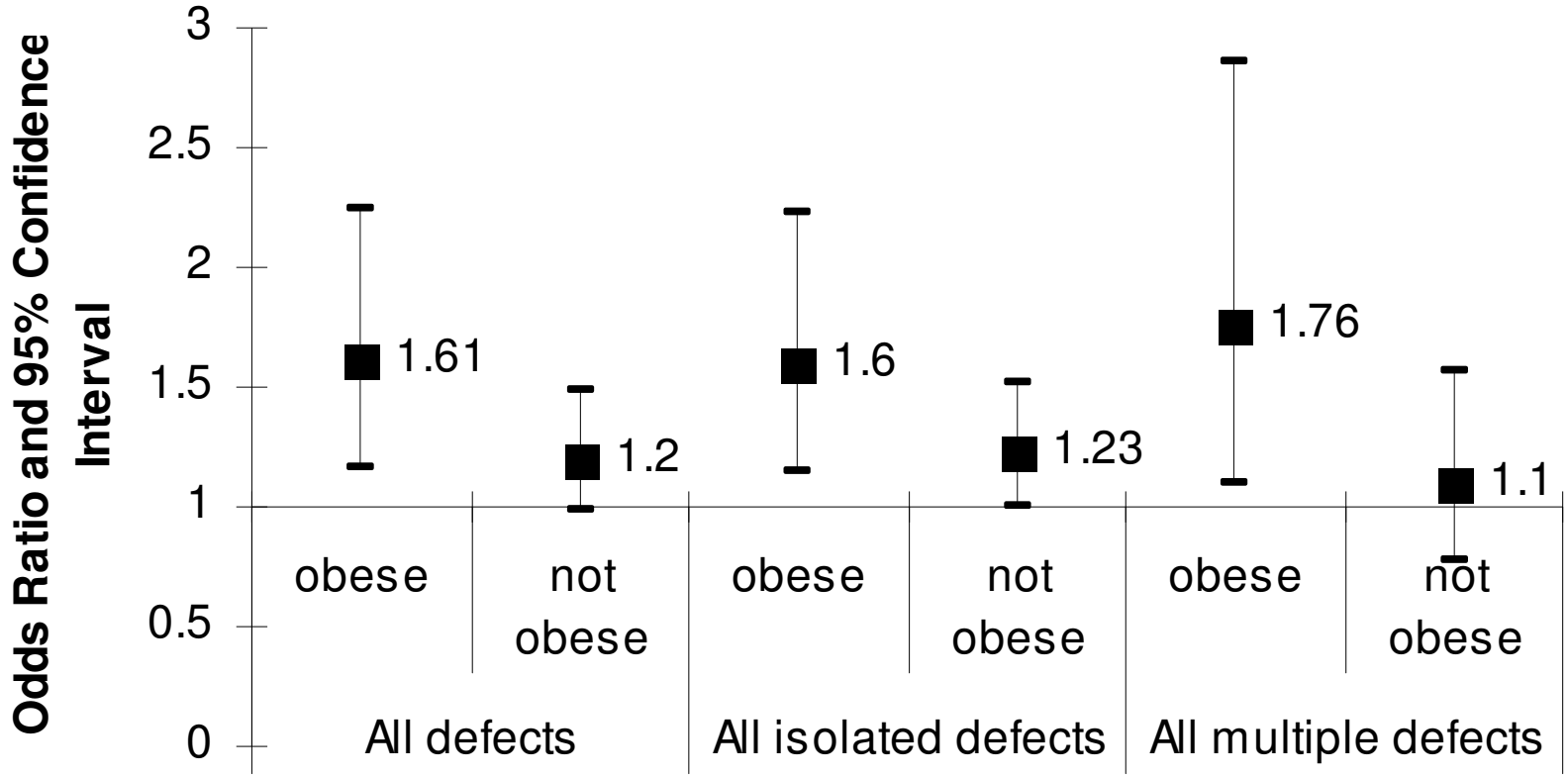
Odds ratios for gestational diabetes and cardiac defects



Odds ratios for pregestational diabetes and birth defects, by pregravid obesity



Odds ratios for gestational diabetes and birth defects, by pre-gravid obesity



Summary: Pregestational diabetes

- Associated with an increased risk for a wider range of defects than previously reported
  - Associations moderate to strong
  - Associations stronger for multiple than for isolated defects
- Effect not modified by maternal pre-gravid obesity

Summary: Gestational diabetes

- Relatively fewer and weaker associations
  - No variation in effect between isolated and multiple defects
- Associations limited to offspring of mothers with pre-gravid obesity
  - suggesting associations might be with undiagnosed type 2 diabetes

What are the challenges and opportunities for prevention of birth defects associated with diabetes?

- Among women with known pre-gestational diabetes
  - > 50% do not plan their pregnancies
  - Many lack access to preconception care and educational services
  - Even in managed care settings, preconception counseling for diabetic women is inadequate (Kim et al, 2005)
- Among women with gestational diabetes
  - post-partum screening for diabetes can be infrequent (Almario et al., 2007)
- Among women with undiagnosed diabetes
  - How to identify them?

Possible strategies for women with a history of pregestational diabetes

- Offer preconception care with a multidisciplinary team to
  - Optimize general health and glycemic control
    - Counsel re family planning
    - Healthy lifestyle (weight loss/control, exercise)
  - Review risks for birth defects
  - Promote use of folic acid
  - Define and maintain target glucose levels before and during pregnancy
    - Guidelines by ADA (Diabetes Care, 2008), ACOG (Obstet Gynecol, 2005)
- Monitor pregnancy for birth defects

Possible strategies for women with a history of gestational diabetes

- Conduct post-partum evaluations to determine baseline glycemic status
  - If type 2 diabetes, offer preconception counseling
  - If normal,
    - Counsel re family planning, healthy lifestyle
    - Screen for GDM in subsequent pregnancies
  - If prediabetes or overweight,

Possible strategies for women with prediabetes or who are overweight

- **Promote/enroll/offer preconception care**
  - **Counsel re family planning**
  - **Promote healthy lifestyle (weight loss/control, exercise)**
  - **Monitor glycemic status**

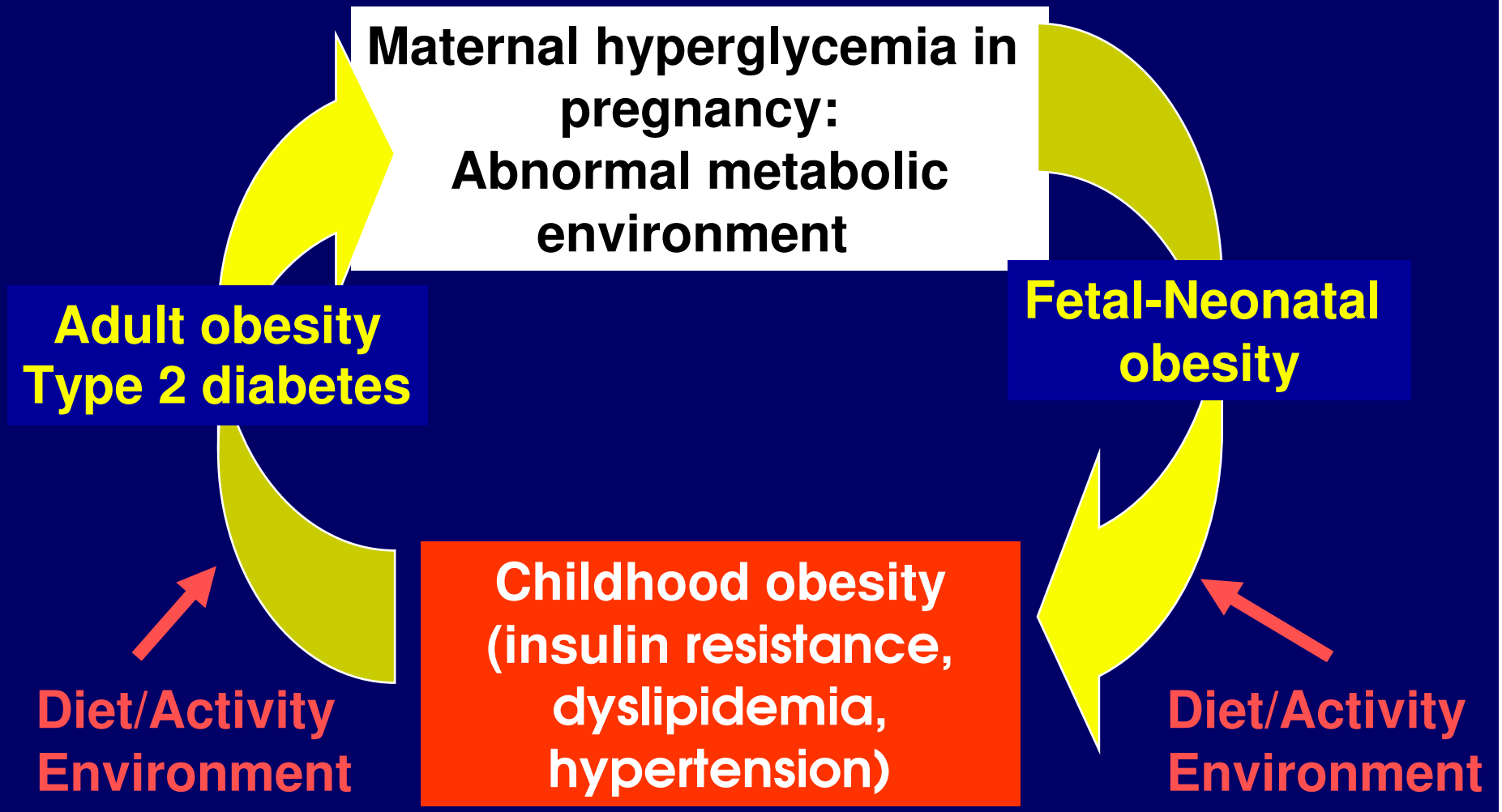
Conclusions

- Pregestational diabetes is a teratogen of public health importance today
  - potency, range of effects, increasing prevalence, and potential for prevention
- Although preconception care has the potential of preventing birth defects associated with diabetes,
  - many offspring to women with pregestational diabetes continue to be at increased risk for birth defects

Conclusions

- **Most likely reason**
  - **Many women with pregestational diabetes have no access to quality preconception care**
- **What is needed**
  - **A concerted effort to eliminate barriers to access to quality preconception care for women with pregestational diabetes**

Maternal hyperglycemia in pregnancy: Long-term implications



Potential benefits of efforts of preventing preconception and prenatal hyperglycemia

- Go beyond prevention of birth defects
  - obstetric complications
  - fetal and neonetal complications
  - childhood obesity and type 2 diabetes among the offspring
  - Maternal risks for gestational and type 2 diabetes and complications

Dr.,

I just read the article about your study. My son was born in 2000 with several heart defects. He had surgery to correct them in 2002, and didn't make it. His mother was diagnosed with diabetes while pregnant with him. A year later, my daughter was born with truncus arteriosus. She had surgery exactly one year after her brother to the day. She's doing fine today. Your article and study helped me understand a little better what I have gone through. Anyway, I just wanted to thank you for releasing this info, and helping me understand a little more. Keep up the good work.

Thanks,

Epistemologist

"the Stone Age did not end for lack of stone."