Maternal Vitamin Intake and Autism Spectrum Disorders

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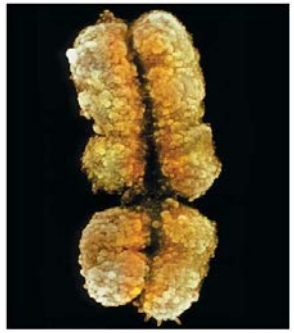
Autism Spectrum Disorder (ASD)

- Neurodevelopmental Disorder
  - Impairments in Social Reciprocity
  - Language / Communication Deficits
  - Repetitive Behaviors / Restricted Interests

- Prevalence in U.S.:
- Sex ratio 4:1
- Highly Heritable



Study Design

CHARGE Case-Control Study

*CH*ildhood *A*utism *R*isks from *G*enetics and *E*nvironment

PI: Irva Hertz-Picciotto

3 Diagnostic Groups

California DDS

1. Autism
2. Developmental Delay

AU, ASD

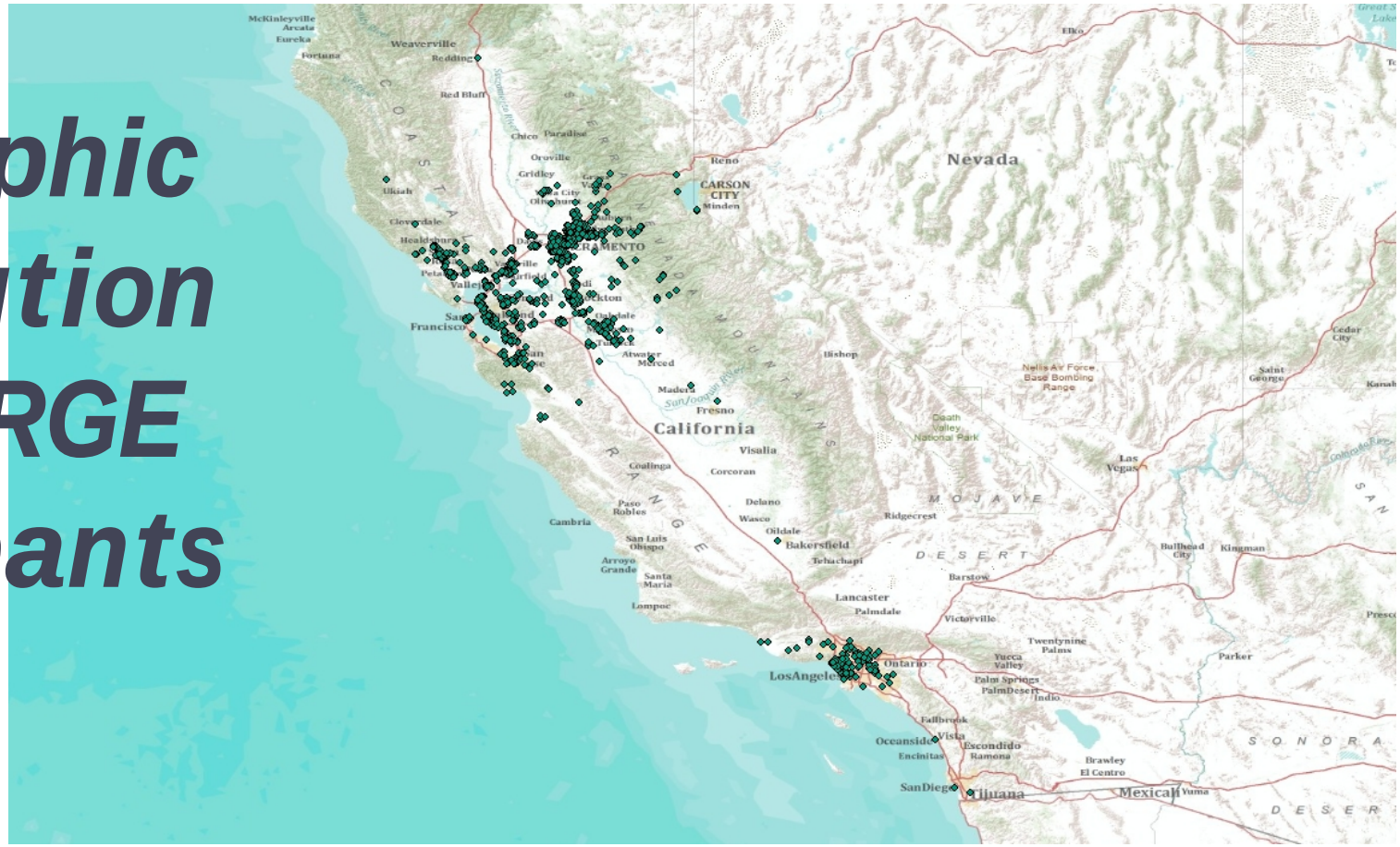
DD

California Birth files

3. General Population Frequency matched to projected distributions in cases of: age, gender & geography

TD

Geographic Distribution of CHARGE Participants



Vitamin Questions

The next questions are about prenatal vitamins and other supplements you may have taken.

40. a. During the index time [and through the end of breast feeding], did you take any….					b. What was the brand name you took?
Prenatal vitamins	Y	N	RF	DK	
Multivitamins	Y	N	RF	DK	
Vitamin A	Y	N	RF	DK	
Vitamin B6	Y	N	RF	DK	
Vitamin B12	Y	N	RF	DK	
Folic acid	Y	N	RF	DK	
Vitamin C	Y	N	RF	DK	
Vitamin D	Y	N	RF	DK	
Vitamin E	Y	N	RF	DK	
Iron	Y	N	RF	DK	
Calcium	Y	N	RF	DK	
Zinc	Y	N	RF	DK	
Cereals	Y	N	RF	DK	
Other supplements e.g. Slim Fast, Instant Breakfast, protein powder, brewer's yeast	Y	N	RF	DK	
ST John's worts	Y	N	RF	DK	
Ginseng	Y	N	RF	DK	

Vitamin Questions

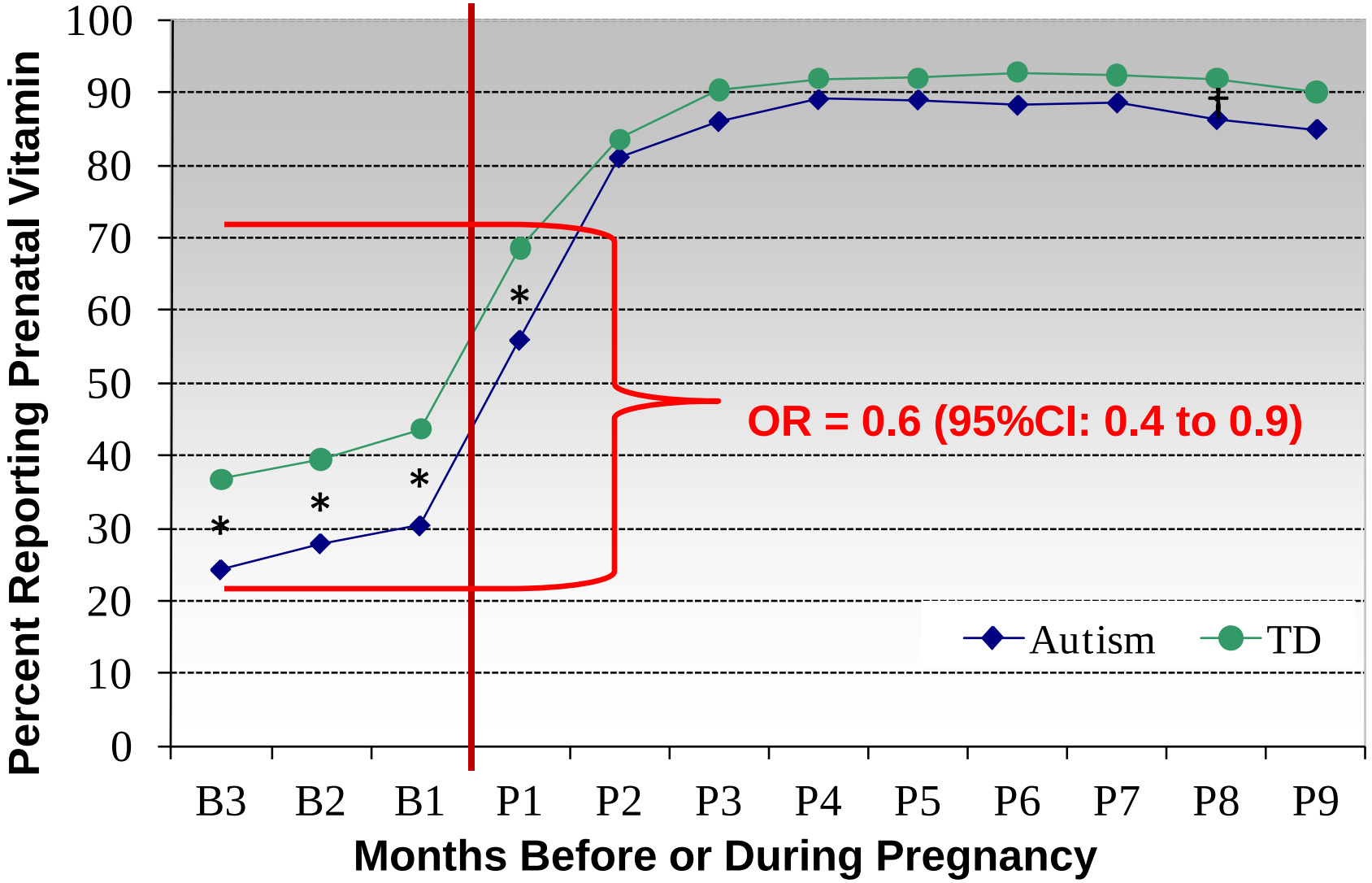
For each 'yes' response in 40:

41. During which months [including breastfeeding] did you take (VITAMIN/ SUPPLEMENT NAME)?
    _____**-3 -2 -1 1 2 3 4 5 6 7 8 9 BF RF DK**

42. How many pills/servings per day of (VITAMIN/ SUPPLEMENT NAME) did you take? And, what was the frequency for each dose/serving?

NAME	**#PILLS/SERVINGS**	**FREQUENCY**
_____	_____ RF DK	_____ RF DK

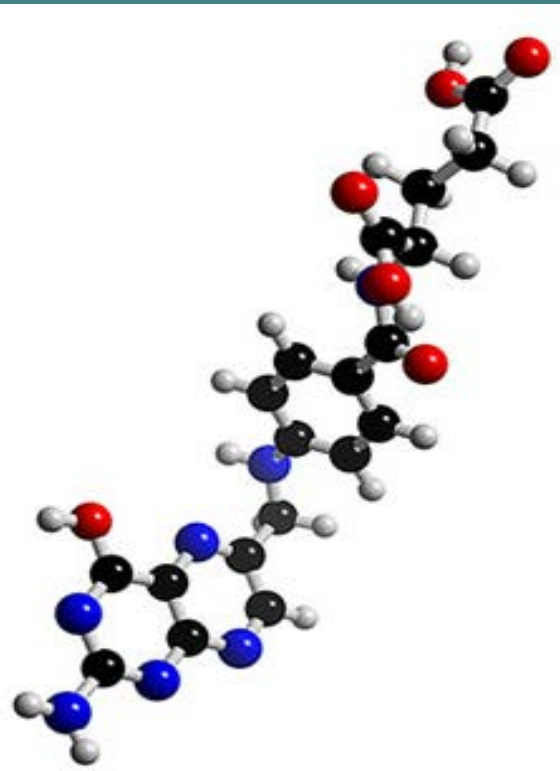
Prenatal Vitamin Use by Perinatal Month



Schmidt et al, 2011

Folic Acid

- Synthetic form of folate, essential water-soluble vitamin B9
- Folic acid supplementation prevents 50-70 percent of neural tube defects
- Mechanism remains unknown

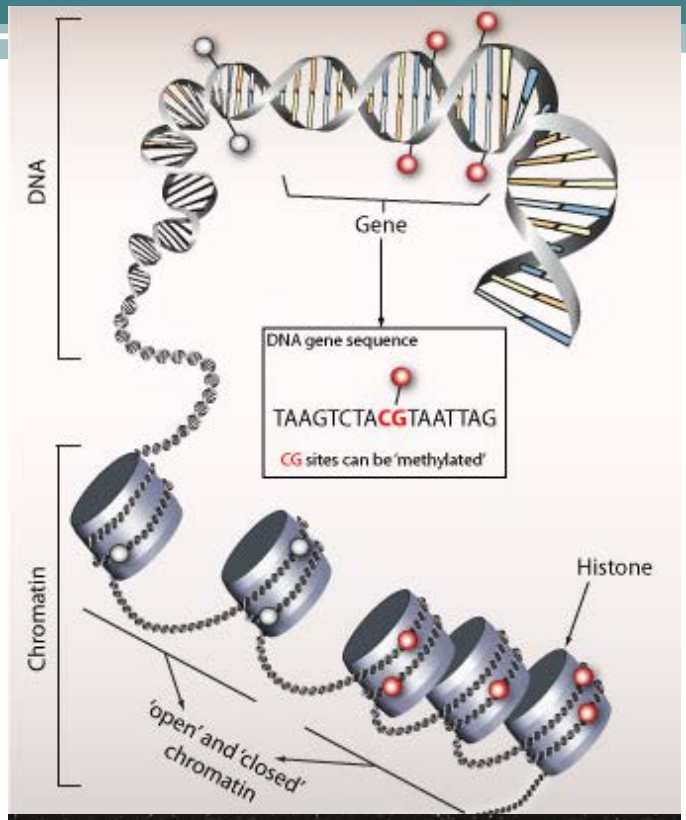


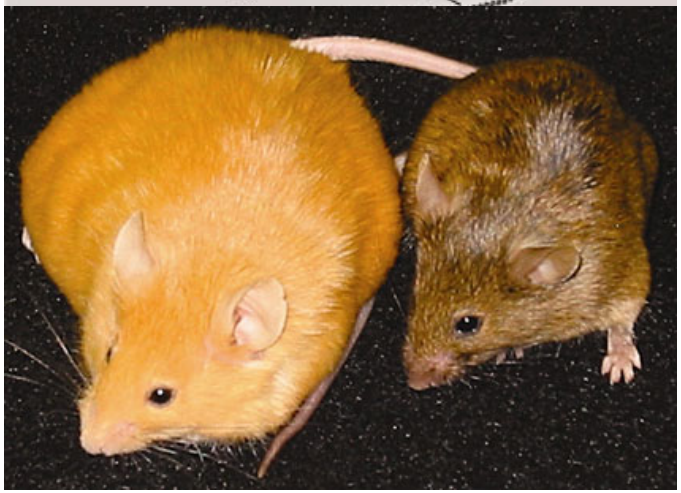
B-Complex Vitamins Needed for Methylation

Methyl Donors	Cofactors
Folate	Vitamin B12
Betaine/Choline	Vitamin B6
Methionine	

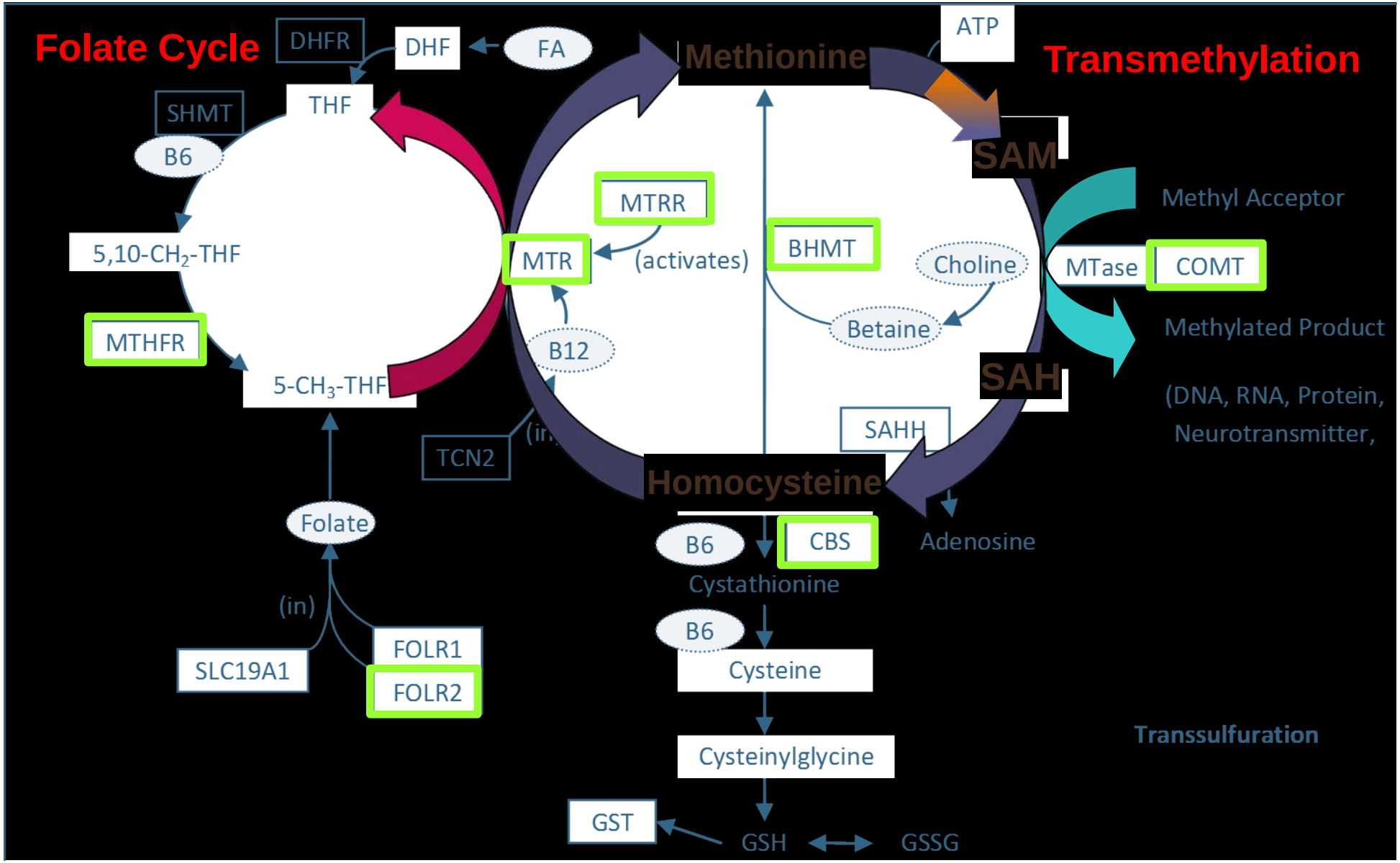
Maternal Dietary Methyl Donors Influence Child's:

- DNA Methylation
- Gene expression
- Health outcomes





Folate, Methionine, and Transmethylation Pathways



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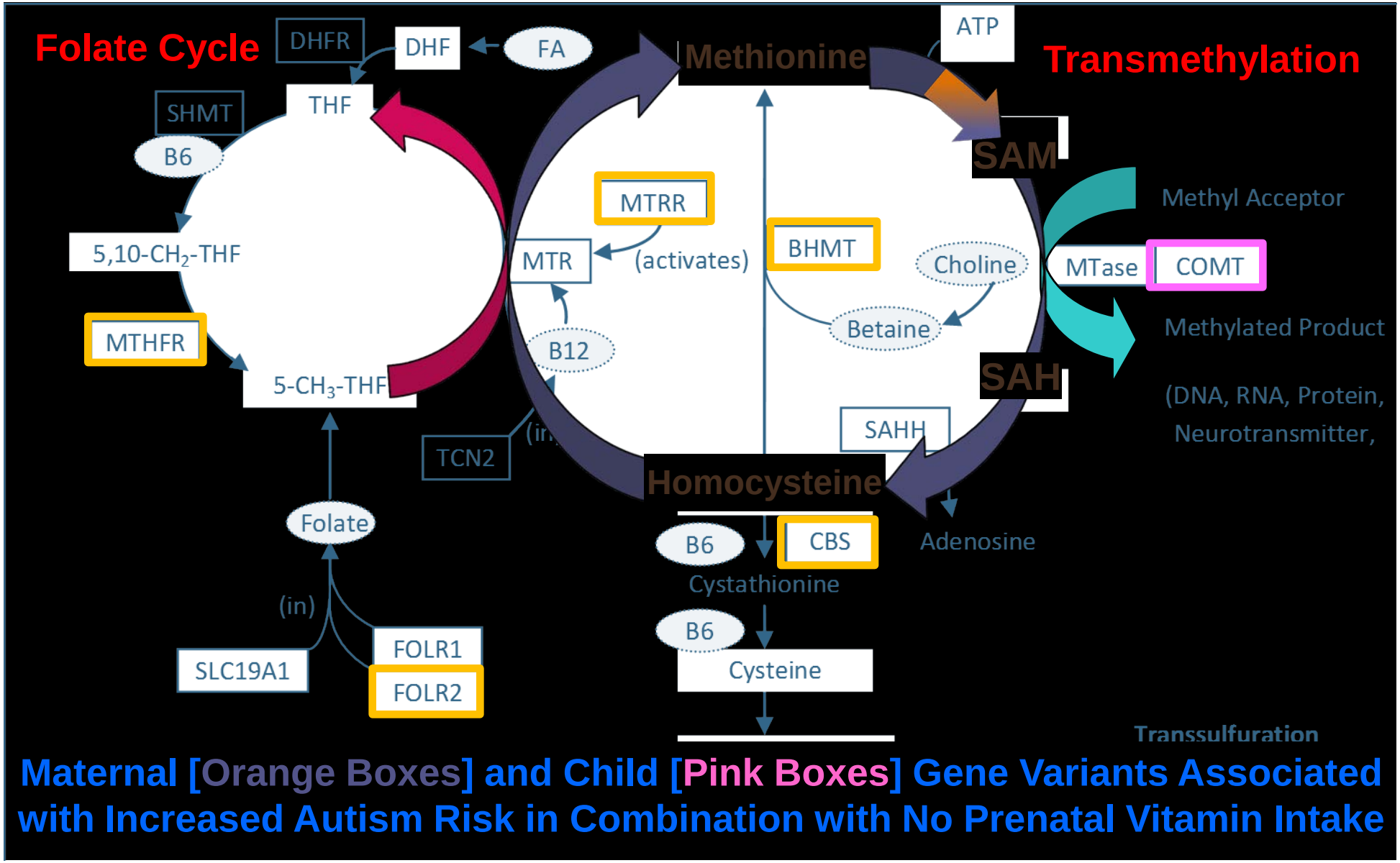
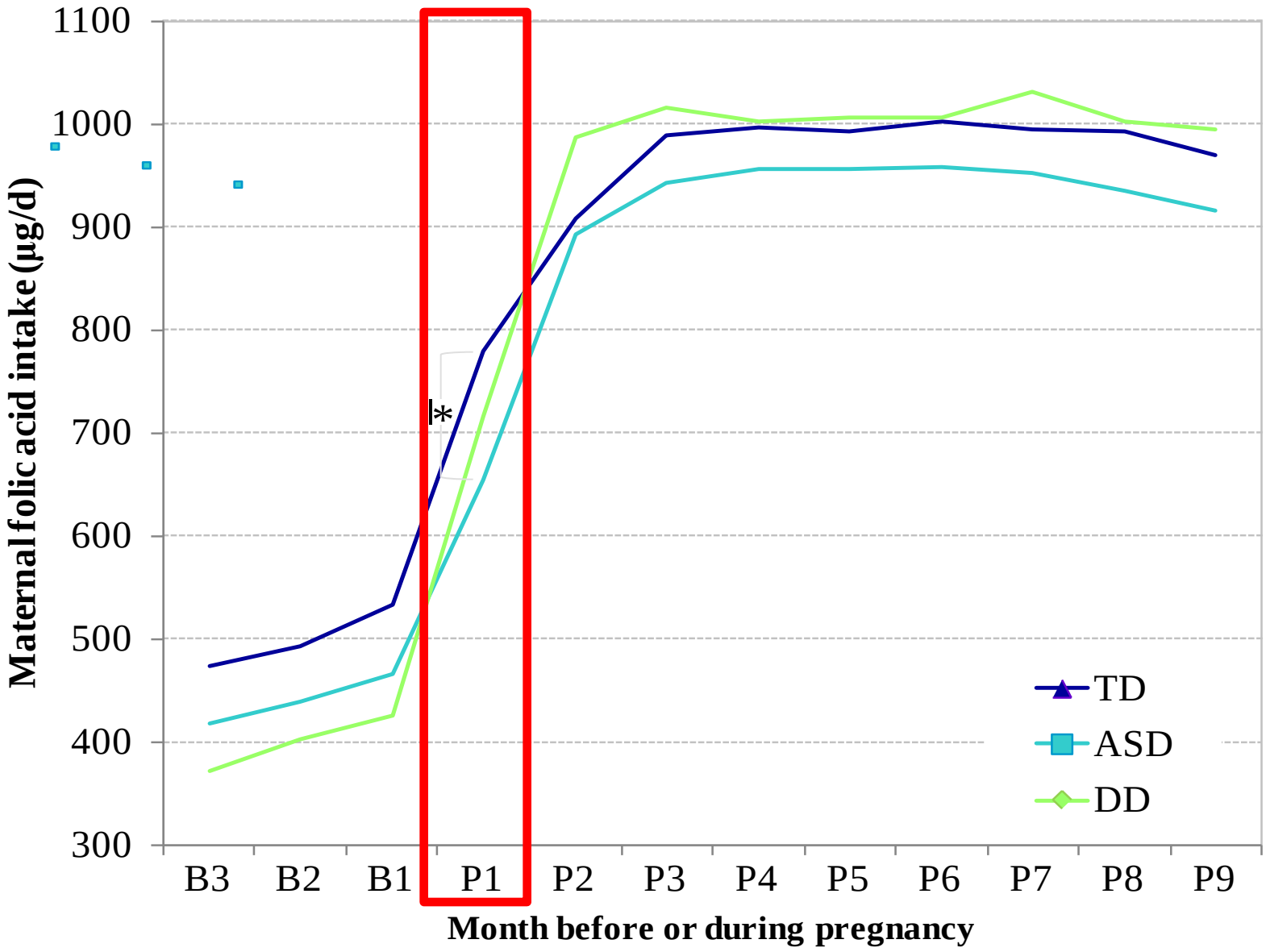


Mean (SE) Maternal Folic Acid Intake By Pregnancy Month



Folic Acid (P1) and ASD

Increased Folic Acid → Decreased Risk for ASD

Folic Acid Intake (µg/d)	OR (95% CI)	P
0	Reference	
< 500	0.73 (0.31, 1.69)	0.46
500 – 800	0.64 (0.24, 1.71)	0.38
800 – 1000	0.57 (0.24, 1.35)	0.20
1000+	0.41 (0.17, 0.96)	0.04

P_{trend}=0.001

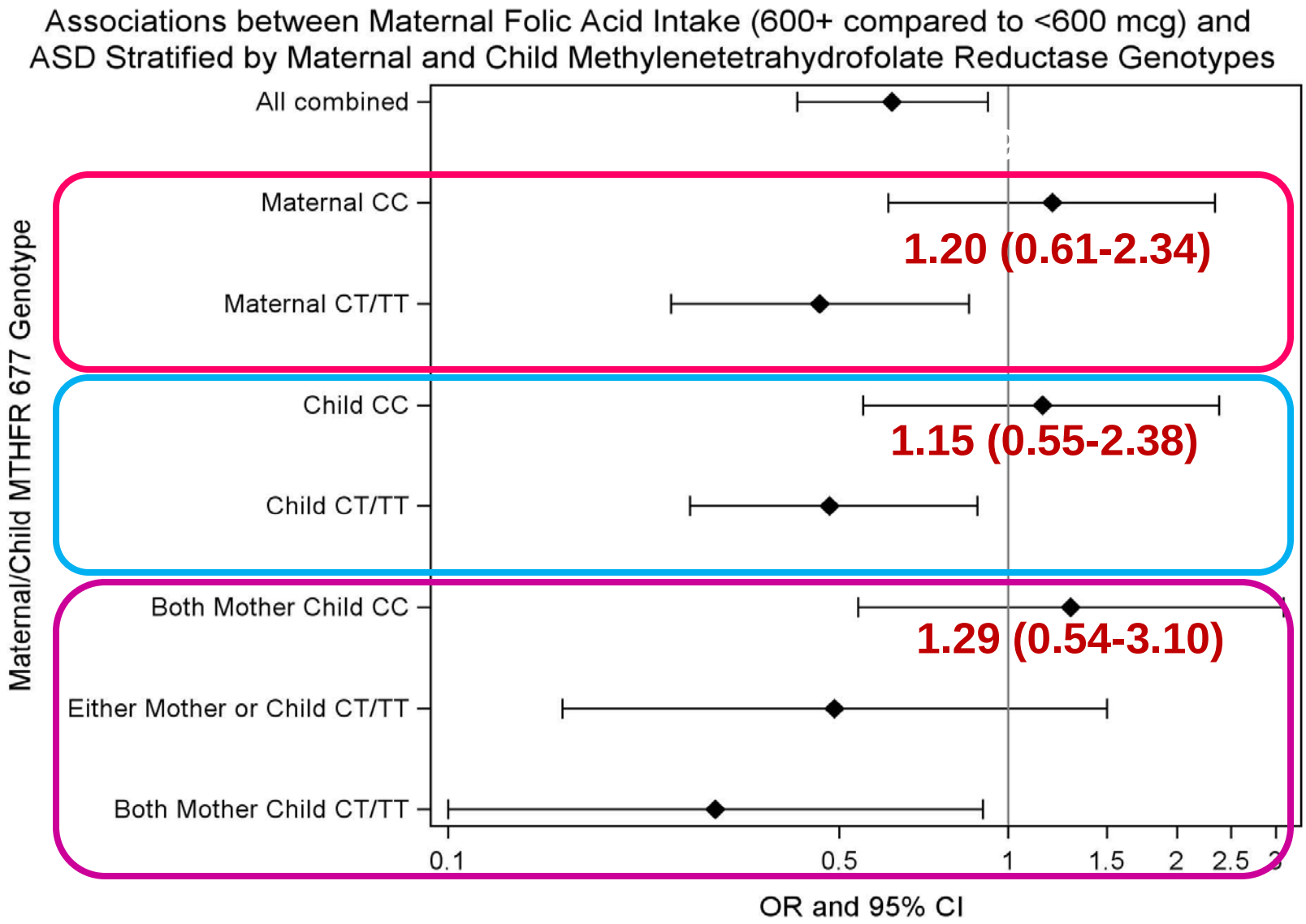
Adjusted for: maternal education level and child's birth year

Folic Acid (P1) and ASD

Folic Acid Intake (µg/d)	OR (95% CI)	P
0	Reference	
< 500	0.35 (0.10, 1.24)	0.10
500 – 800	0.27 (0.06, 1.36)	0.11
800 – 1000	0.25 (0.05, 1.22)	0.09
1000+	0.18 (0.04, 0.94)	0.04

Adjusted for: maternal education level and child's birth year, and log transformed total **vitamins A, B6, C and D** from supplements and cereals; estimates were not substantially different when further adjusting for: log transformed **vitamin E, vitamin B12, iron, or calcium** from supplements and cereals, or when adjusting for prenatal vitamin use in the first month of pregnancy. Estimates are based on 183 TD and 317 ASD due to missing data on additional nutrient variables. Though risk estimates are not presented, DD was included in the model as an outcome

Associations between Folic Acid and ASD Stratified by MTHFR 677



Comments

- Effect Size, timing, and effect modification by MTHFR 677 Similar to that observed for NTDs
- Evidence for ASD origins in early pregnancy (Rodier et al, 1997)
- Folic Acid During Early Pregnancy Associated With:
  - Fewer Behavioral Problems at 18 Mos (Roza et al, 2009)
  - Lower Risk for Severe Language Delay at 3 Yrs (Roth et al, 2011)
  - Improved Verbal & Verbal-executive Function, Attention, and Social Competence at 4 Yrs (Julvez et al, 2009)
  - Reduced Hyperactivity and Fewer Peer Problems at 8 Yrs (Schlotz et al, 2010)
- Link between Short IPI and ASD → Folate depletion (Cheslack-Postava et al, 2011)

Interactions between Prenatal vitamin intake and Pyrethroid Pesticide exposure

Self-Reported Indoor Pyrethroid Pesticide Use

- Reported use of products to control ants, flies, cockroaches or pet pests such as fleas and ticks
- Asked product type (spray, bait, etc.), brand name, whether application was indoors, outdoors, or on pet, and about use of professional pest control services
- Determined active ingredient(s); where ambiguous, researched product databases to probabilistically assign active ingredients

Irva Hertz-Picciotto, Lora Delwiche

Prenatal Vitamins X Pyrethroid Pesticides: Self-reported Indoor Use

Pyrethroid Pesticide Exposure During Pregnancy	Periconceptional Prenatal Vitamin		No Periconceptional Prenatal Vitamin	
	aOR (95% CI)*	P	aOR (95% CI)*	P
None	Reference		1.8 (1.1 - 2.9)	.02
Any	2.3 (1.3 - 4.1)	.01	3.7 (1.6 - 8.9)	.003

*** Adjusted for maternal education, age, and birthplace**

Prenatal Vitamins X Pyrethroid Pesticides: Pesticide Use Report (PUR)

Geocode CHARGE addresses by month (-6 months to birth) (ArcGIS)

→ **Download PUR data (1998-2008)**

→ **Map CHARGE addresses to PUR square mile grid (ArcGIS)**

→ **Sum pesticides applied to grid within buffer by day (SAS)**

→ **Model in linear and logistic regression (SAS)**

Janie Shelton

Pyrethroid Pesticides X Prenatal Vitamins

Pyrethroids	Prenatal Vitamin +	Prenatal Vitamin -
6 mos prior to pregnancy	1.35 (0.73-2.50)	2.09 (0.91-4.82)
N3 to 3 months	1.31 (0.72-2.39)	2.33 (0.97-5.60)
First half of pregnancy	1.37 (0.74-2.52)	1.31 (0.56-3.08)
Second half of pregnancy	1.54 (0.77-3.08)	1.80 (0.67-4.87)
Pregnancy	1.26 (0.72-2.21)	1.30 (0.59-2.83)
Type 1		
6 mos prior to pregnancy	1.49 (0.59-3.76)	1.74 (0.56-5.42)
N3 to 3 months	1.07 (0.50-2.29)	1.91 (0.52-7.10)
First half of pregnancy	0.92 (0.41-2.08)	0.96 (0.24-3.81)
Second half of pregnancy	1.77 (0.39-7.92)	5.03 (1.10-22.96)
Pregnancy	0.99 (0.48-2.02)	1.56 (0.51-4.75)
Type 2		
6 mos prior to pregnancy	1.25 (0.66-2.38)	2.68 (1.06-6.80)
N3 to 3 months	1.37 (0.73-2.56)	2.58 (1.03-6.49)
First half of pregnancy	1.57 (0.80-3.08)	1.32 (0.54-3.19)
Second half of pregnancy	1.26 (0.60-2.67)	1.33 (0.46-3.78)
Pregnancy	1.29 (0.71-2.37)	1.37 (0.61-3.07)

Comments

- Animal studies folate x environmental exposures
  - Folic acid and BPA
- Epigenetic mechanisms
- Recall an issue, but interactions in expected directions

MARBLES Prospective Study

*M*arkers of *A*utism *R*isk in *B*abies —
*L*earning *E*arly *S*igns

PI: Irva Hertz-Picciotto

MARBLES Study

- Mothers of a child with autism planning another pregnancy or pregnant with another child
- Over 200 mothers enrolled, goal 450
- Survey data, biologic and environmental samples from home visits throughout pregnancy until child is 3 yrs
- Child assessed at the M.I.N.D. Institute
- Serum/Plasma: Folate, B12, B6, Choline, Hcy
- FFQs Analyzed

Acknowledgements

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  - Irva Hertz-Picciotto - PI of CHARGE, MARBLES
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  - Hooman (USC) - Genotyping
  - Janie Shelton - PUR Pesticide Exposure
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- CHARGE & MARBLES Participants & Staff