

Parental Risk Factors Associated with ASD and Developmental Delay

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Objectives

- Introduction- history of ASD and dev delay research connecting disability to parental characteristics
- ASD is *Multifactorial*: Genetics x environment. ID of risk factors can assist in identifying neurobiologic causes
- Age- Maternal vs Paternal age and ass w/ ASD
- SES- research, results
- Obesity and metabolic conditions: parental obesity ass w/ ASD?
- Conclusions

Introduction

- Autism Spectrum Disorder (ASD) and Pervasive Developmental Delay (PDD) were initially thought of as *non-heritable*
 - Most parents did not have ASD or PDD
 - No distinct chromosomal abnormalities were apparent
 - Sibling recurrence rate (non-twin studies) thought to be low
- Seminal paper in Nature (1977): four of 11 monozygotic pairs (36 percent) concordant for ASD, compared with zero of 10 concordant dizygotic pairs (0 percent), suggesting heritable component
 - Multiple subsequent studies have since repeated/ strengthened this data (British study (1995): 60% MZ twin concordance of ASD)
 - No ASD predisposing gene identified to date
 - Of the MZ twin concordance data, it was later found that 92% of MZ twins have broader range of cognitive and social abnormalities. -> genetic predisposition PLUS environmental factors contribute to outcome

ASD as a Complex Multifactorial Disorder

- No single model to date has emerged to suggest ASD as purely heritable
- Increased prevalence of the disorder over the last decade sparked more interest in non-heritable components
- Unlikely that these new cases are all purely sporadic; current & most accepted theory is that genetic predisposition + environmental insult leads to disorder
- MANY non-heritable, parental and child-related risk factors being studied: **Age of parents, SES of parents, metabolic conditions in parents, psych diagnoses in parents, IVF, perinatal environment, birth weight, birth injuries, low APGARS, etc.**

Parental Age and ASD

- Considerable interest in parental age as risk factor for ASD
- Confirmation of such an association could have important public health implications in light of increasing trends in recent decades regarding both maternal and paternal age.
- Evidence of parental age effects on ASD risk may provide clues to the etiology of this disorder.
- Until recently, no clear study demonstrating great evidence of association between advanced parental age and ASD, with lots of conflicting evidence.

Parental Age and ASD

Advanced Parental Age and the Risk of Autism Spectrum Disorder, Am J Epidemiol, 2008 (Durkin et al.)

- **Population-Based Case-Cohort Study**
 - 10 sites from CDC/Prevention's Autism/DD Monitoring Network
- **Cohort: 253,347 births**
- **Case: 1,251 children aged 8 years with ASD**
- **Analysis: unadjusted and adjusted odds ratio**
 - Identify confounders
 - Model 1: parental age as categorical variable (reference 25-29 y)
 - Model 2: parental age as continuous variable

Parental Age and ASD

Advanced Parental Age and the Risk of Autism Spectrum Disorder, Am J Epidemiol, 2008 (Durkin et al.)

- **Unadjusted Analysis**

- Mean maternal & paternal age significantly higher for ASD
- Reduced for parental age < 20 y
- Increased for maternal age > 35 y; paternal age > 40 y

- **Confounders**

- Low birth order, male gender, preterm birth, advanced maternal education

Parental Age and ASD

Advanced Parental Age and the Risk of Autism Spectrum Disorder, Am J Epidemiol, 2008 (Durkin et al.)

- **Adjusted Analysis**
 - Increased ASD risk for maternal age > 35 y; paternal age > 40 y
 - Decline in ASD risk with increasing birth order
 - Increase ASD risk for preterm birth and male gender still existed
 - No ASD risk for advanced maternal education
- **10-year increase in maternal age = 20% increase in ASD risk**
- **10-year increase in paternal age = 30% increase in ASD risk**
- **First-born offspring of mothers > 35 y & fathers > 40 y (3x)**

Parental Age and ASD

Risk of Autism and Increasing Maternal and Paternal Age in a Large North American Population, Am J Epidemiol, 2009 (Grether et al.)

- **Population-Based Case-Control Study**
 - California singletons born 1989-2002
 - ASD identified by CA Department of Developmental Services
- **Control: 6,506,555 singletons without autism**
- **Case: 23,311 children with DDS-reported autism**
- **Covariates: gender, birth year, education, race, birth weight, GA, parity, SES**
- **Analysis: logistic regression with odds ratio**
 - Model 1: parental age as categorical variable (reference 25-29 y)
 - Model 2: parental age as continuous variable

Table 1. Risk of Department of Developmental Services-reported Autism and Maternal and Paternal Age (Categorical), California Resident Births, 1989–2002

	Singletons Without Autism ^a (n = 6,506,555)		Singletons With Autism ^a (n = 20,701)		Crude Odds Ratio ^a	95% Confidence Interval	Adjusted Odds Ratio ^{a,b}	95% Confidence Interval	Adjusted Odds Ratio ^{a,c}	95% Confidence Interval	
	No.	%	No.	%							
Maternal age, years											
15–19	651,054	10.0	960	4.6	0.49	0.46, 0.52	0.62	0.57, 0.67	0.65	0.59, 0.70	
20–24	1,556,113	23.9	3,531	17.1	0.75	0.72, 0.79	0.84	0.81, 0.88	0.86	0.82, 0.90	
25–29	1,852,900	28.5	5,581	27.0	1.00	Referent	1.00	Referent	1.00	Referent	
30–34	1,558,709	24.0	6,144	29.7	1.31	1.26, 1.36	1.18	1.14, 1.23	1.14	1.10, 1.19	
35–39	738,308	11.3	3,659	17.7	1.64	1.58, 1.72	1.37	1.31, 1.44	1.33	1.27, 1.40	
40–44	149,471	2.3	826	4.0	1.84	1.70, 1.97	1.44	1.33, 1.56	1.43	1.32, 1.55	
Paternal age, years											
15–19	280,837	4.3	385	1.9	0.52	0.47, 0.58	0.74	0.66, 0.83	0.76	0.67, 0.85	
20–24	1,208,883	18.6	2,416	11.7	0.76	0.72, 0.80	0.89	0.84, 0.94	0.89	0.84, 0.94	
25–29	1,717,336	26.4	4,534	21.9	1.00	Referent	1.00	Referent	1.00	Referent	
30–34	1,690,238	26.0	5,944	28.7	1.33	1.28, 1.38	1.17	1.12, 1.22	1.12	1.07, 1.17	
35–39	1,028,251	15.8	4,432	21.4	1.63	1.57, 1.70	1.31	1.25, 1.37	1.23	1.17, 1.30	
40–44	408,114	6.3	2,063	10.0	1.92	1.82, 2.02	1.46	1.38, 1.55	1.39	1.30, 1.47	
45–49	123,373	1.9	649	3.1	1.99	1.84, 2.16	1.50	1.38, 1.64	1.41	1.29, 1.54	
50–54	35,083	0.5	201	1.0	2.17	1.88, 2.50	1.64	1.42, 1.90	1.53	1.32, 1.77	
55–59	10,799	0.2	52	0.3	1.82	1.39, 2.40	1.39	1.06, 1.83	1.35	1.02, 1.77	
60–64	3,641	0.1	25	0.1	2.61	1.76, 3.86	2.00	1.35, 2.97	2.05	1.38, 3.05	

^a Excluded are observations with missing values for child's sex and birth weight, maternal age, maternal race/ethnicity, paternal race/ethnicity, maternal education, paternal education, parity, gestational age, delivery method of payment, and birth year.

^b Adjusted for age of other parent only.

^c Adjusted for child's sex and birth weight, maternal age, paternal age, maternal race/ethnicity, paternal race/ethnicity, maternal education, paternal education, parity, gestational age, delivery method of payment, and birth year.

Parental Age and ASD

Risk of Autism and Increasing Maternal and Paternal Age in a Large North American Population, Am J Epidemiol, 2009

- 10-year increase in maternal age = 38% increase in ASD risk
- 10-year increase in paternal age = 20% increase in ASD risk
- **Subgroup Analyses**
 - Same OR for male and female births
 - Same OR for GA, BW, race, maternal education
 - Some variation in paternal education
 - Risk of ASD associated with maternal age greater across birth year categories
 - **Risk of ASD greater for first-born children**

Parental Age and ASD

- **Public Health Implications**

- Concerns regarding **increasing parental age with firstborn children.**
- One etiology for increasing prevalence of ASD
- Increased toxic load, “hygiene hypothesis”, “stoppage” tendency.

- **Biological Implications**

- Women: hormonal factors, infertility, **assisted reproductive technologies**, nucleotide repeat instability, toxic accumulation
- Men: **de novo sperm mutations**, toxic accumulation, increasing **telomere length**

Rate of *de novo* mutations and the importance of father's age to disease risk

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Mutations generate sequence diversity and provide a substrate for selection. The rate of *de novo* mutations is therefore of major importance to evolution. Here we conduct a study of genome-wide mutation rates by sequencing the entire genomes of 78 Icelandic parent-offspring trios at high coverage. We show that in our samples, with an average father's age of 29.7, the average *de novo* mutation rate is 1.20×10^{-8} per nucleotide per generation. Most notably, the diversity in mutation rate of single nucleotide polymorphisms is dominated by the age of the father at conception of the child. The effect is an increase of about two mutations per year. An exponential model estimates paternal mutations doubling every 16.5 years. After accounting for random Poisson variation, father's age is estimated to explain nearly all of the remaining variation in the *de novo* mutation counts. These observations shed light on the importance of the father's age on the risk of diseases such as schizophrenia and autism.

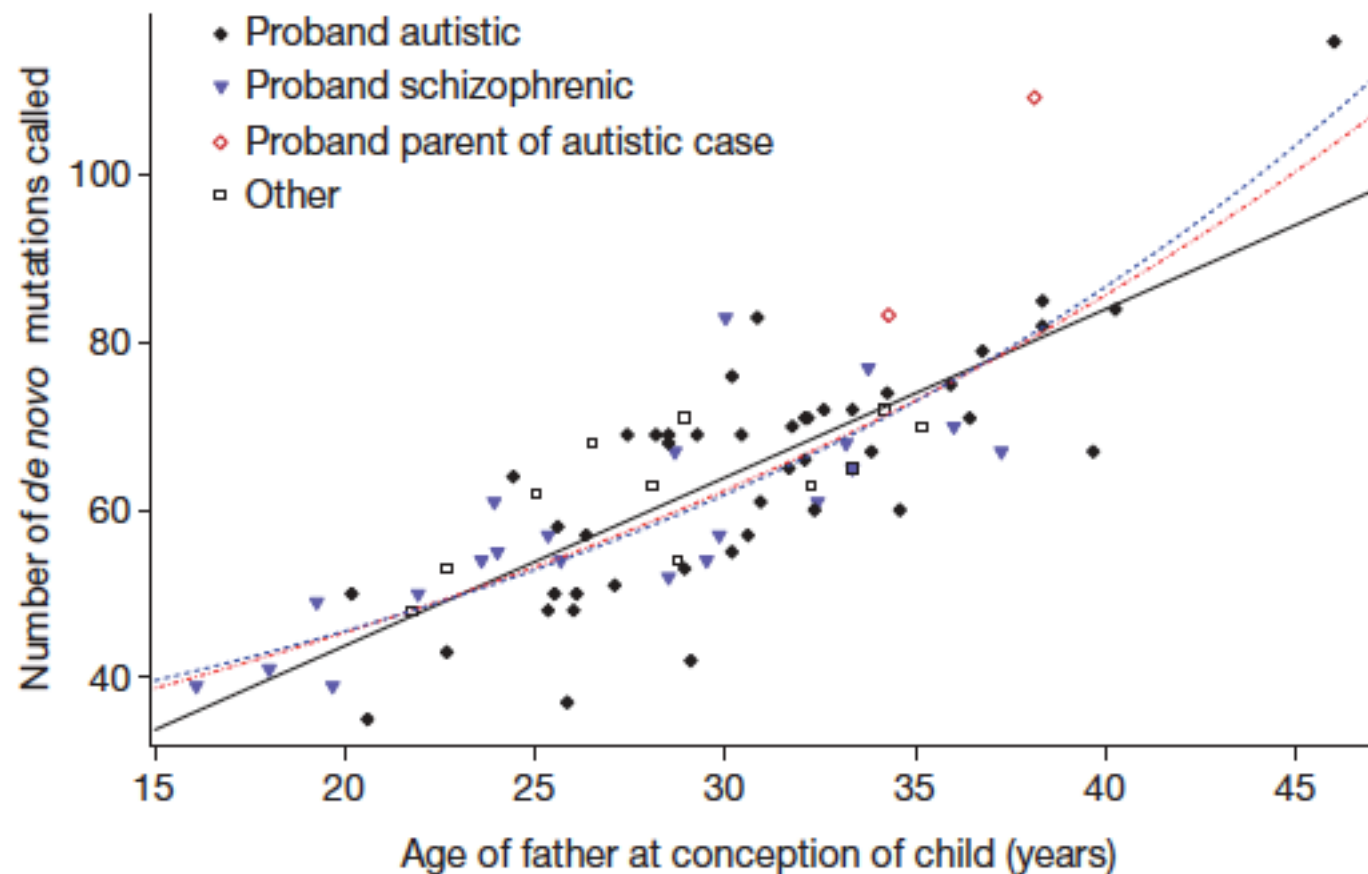


Figure 2 | Father's age and number of *de novo* mutations. The number of *de novo* mutations called is plotted against father's age at conception of child for the 78 trios. The solid black line denotes the linear fit. The dashed red curve is based on an exponential model fitted to the combined mutation counts. The dashed blue curve corresponds to a model in which maternal mutations are assumed to have a constant rate of 14.2 and paternal mutations are assumed to increase exponentially with father's age.

Parental SES and ASD

- Most chronic childhood disorders have an inverse relationship with SES; in other words, *prevalence decreases with increasing SES*
 - SES is usually assessed as parental income, education level and/or occupation
- Not typically the case for ASD, direct proportionality. *Ascertainment bias?*
- To avoid this bias, large population sampling must be performed in such a way that **all SES levels have the same resources and potential for diagnosis to be made**

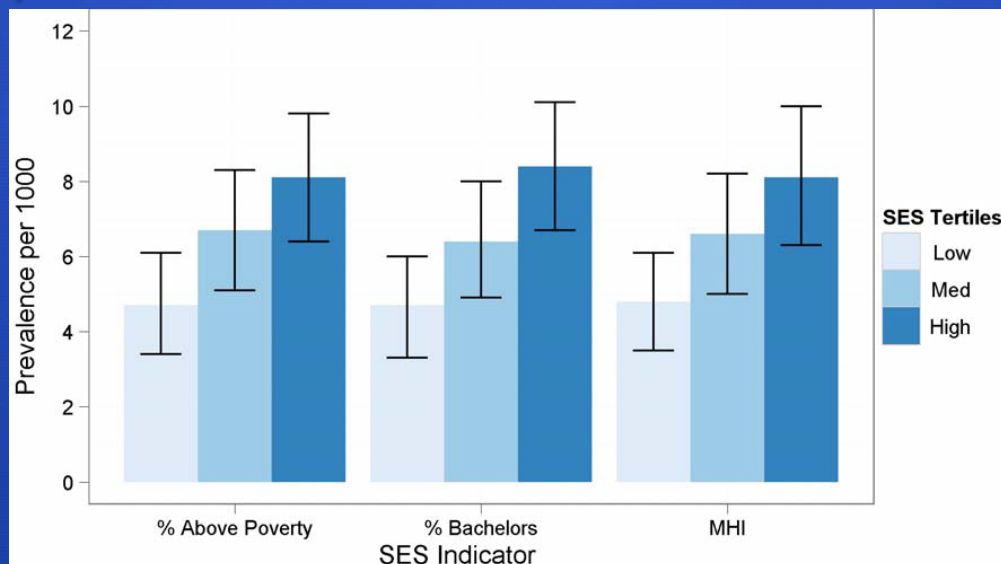
Parental SES and ASD

- Study: *"Socioeconomic Inequality in the Prevalence of Autism Spectrum Disorder: Evidence from a U.S. Cross-Sectional Study"* Durkin et al., PLoS One, 2010
 - Design: Population-based cross-sectional study of 8y.o. kids in 12 states in the Autism and Developmental Disabilities Monitoring (ADDM) network
 - Physicians part of ADDM review charts, determine if child meets ASD or PDD-NOS criteria
 - Three SES categories (low, med, high) based on income and college education

Parental SES and ASD

- **RESULTS:**

- 66% of those kids classified as ASD or PDDNOS already had a pre-existing diagnosis, were more likely to be in the higher SES classes
- However, SES gradient in ASD prevalence was still present in the new diagnosis of ASD, though not as steep.
- SES gradient was present in all ethnic strata, however lower prevalence was seen in the Black, Hispanic and Asian low SES groups when compared to non-hispanic White.



Parental SES and ASD

- **Conclusion/ Critique:**
 - Kids with pre-existing ASD diagnosis were from higher SES regardless of ethnicity; may be due to ascertainment bias
 - However, the significant SES gradient remained (albeit attenuated) when the analysis was restricted to children with no preexisting ASD diagnosis
 - "... suggests the overall SES gradient may not be entirely due to ascertainment bias and points to the possibility that factors associated with socioeconomic advantage might be causally associated with the risk for developing autism."
 - Limitations of the study: limited to participants in ADDM, SES status also estimated by Census block data

Parental Obesity and ASD

- ***"Maternal Metabolic Conditions and Risk for Autism and Other Neurodevelopmental Disorders"*** Krakowiak et al., *Pediatrics*, 2011
 - Population-based study based on CHARGE data (Childhood Autism Risks from Genetics and the Environment)
 - Evaluated whether an association could be made between diabetes (T2D/GDM), hypertension, and obesity during pregnancy, and diagnosis of ASD or DD in their offspring.
 - Two important findings:
 - #1- diabetes, hypertension, and obesity were more common among mothers of children with ASD and DD compared with controls.
 - #2- Among children without ASD, MCs collectively were associated with impairments in visual reception, motor skills, and receptive and expressive language, as well as adaptive communication and socialization

Parental Obesity and ASD

TABLE 2 OR for Autism/ASD or Other Delays in Relation to Diabetes and Related Conditions: CHARGE Study, January 2003–June 2010 (*N* = 1004)

Conditions in Index Pregnancy	ASD		DD		TD		ASD Versus TD		DD Versus TD	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	OR ^a	95% CI	OR ^a	95% CI
Diabetes ^b	48	9.3	20	11.6	20	6.4	1.52	0.82–2.83	2.33	1.08–5.05
Hypertension	19	3.7	6	3.5	4	1.3	2.84	0.94–8.56	3.58	0.93–13.78
Obesity	111	21.5	41	23.8	45	14.3	1.67	1.10–2.56	2.08	1.20–3.61
Any MC(s)	148	28.6	60	34.9	61	19.4	1.61	1.10–2.37	2.35	1.43–3.88

^a Adjusted for mother's age at delivery, race/ethnicity, education level, delivery payer, calendar time, child's age at enrollment and gender, and catchment area. Comparison group had no hypertension or diabetes (T2D or GDM) and also had BMI <25; this group included 267 in ASD, 64 in DD, and 172 in TD groups.

^b T2D or GDM only.

TABLE 4 Assessment Scores of Children of Mothers With and Without any MCs,^a Stratified According to ASD Status

Assessment	ASD (<i>n</i> = 315)					No ASD (<i>n</i> = 276)				
	Any MC		No Conditions		<i>P</i> ^b	Any MC		No Conditions		<i>P</i> ^b
	LS Mean	SE	LS Mean	SE		LS Mean	SE	LS Mean	SE	
MSEL										
Visual reception T score	26.98	1.41	28.31	1.03	0.37	41.57	1.72	46.66	1.25	.01
Fine motor T score	27.11	1.18	27.79	1.00	0.58	38.98	1.72	44.32	1.24	.01
Receptive language T score	24.68	1.09	25.92	0.86	0.28	37.34	1.48	42.32	1.11	.004
Expressive language T score	23.72	0.96	25.16	0.84	0.16	36.33	1.38	42.21	1.10	<.001
Composite Standard score	57.59	1.79	59.49	1.44	0.31	80.35	2.61	90.11	1.94	.001
VABS										
Communication standard score	63.71	1.47	66.04	1.23	0.13	85.87	2.11	92.38	1.55	.01
Socialization standard score	67.16	1.32	66.50	1.04	0.62	87.63	1.78	95.10	1.43	<.001
Motor skills standard score	75.00	1.83	74.35	1.57	0.73	86.15	2.51	92.06	1.84	.04
Composite standard score	62.62	1.55	62.87	1.20	0.86	84.09	2.32	91.68	1.77	.005

^a Any MCs group includes mothers with diabetes (T2D or GDM), hypertension, or a BMI ≥ 30 ; no conditions group consists of mothers with no diabetes (T2D or GDM) or hypertension and who have a BMI < 25 ; this comparison group consisted of 267 in ASD and 236 in non-ASD strata.

^b Adjusted for mother's age at delivery, race/ethnicity, education level, delivery payer, calendar time, child's age at enrollment and gender, and catchment area.

Conclusions

- **Advanced parental age associated with increased ASD risk**
 - First-born children at highest risk
 - Related to assistive reproductive technologies, de novo sperm mutations, toxic accumulations
- **SES advantage associated with increased ASD risk**
- **Maternal metabolic conditions associated with increased ASD and DD risk**
 - Diabetes, HTN, obesity
- **Further longitudinal studies need to be performed**
- **Huge potential for research into biological etiologies**