Pre- and Perinatal Risk Factors of Autism Spectrum Disorders

Raz Gross, MD, MPH

Arrow Project Meeting

Sheba Medical Center

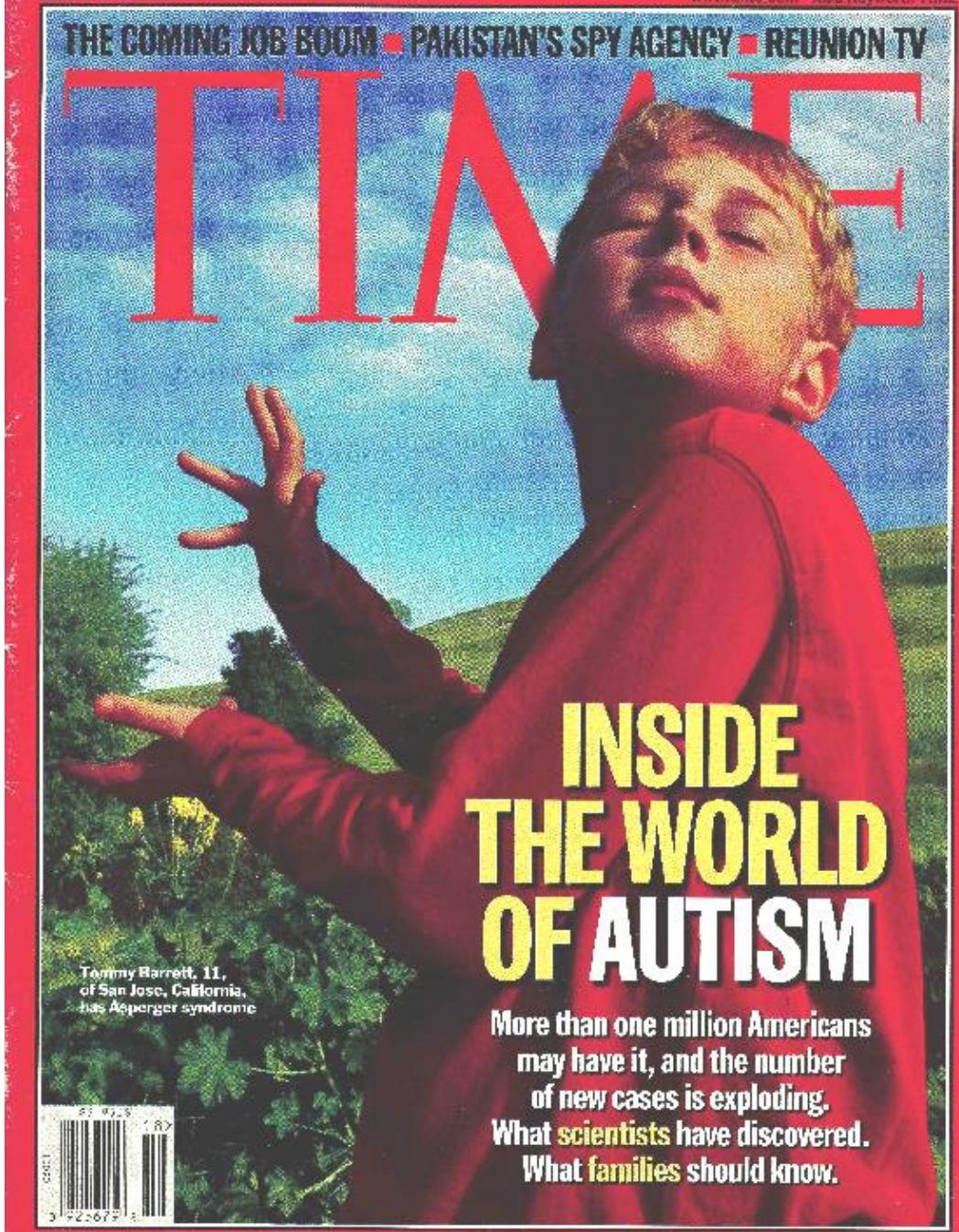
February 10, 2017

MAY 6, 2002

www.time.com AOL Keyword: TIME

THE COMING JOB BOOM ■ PAKISTAN'S SPY AGENCY ■ REUNION TV

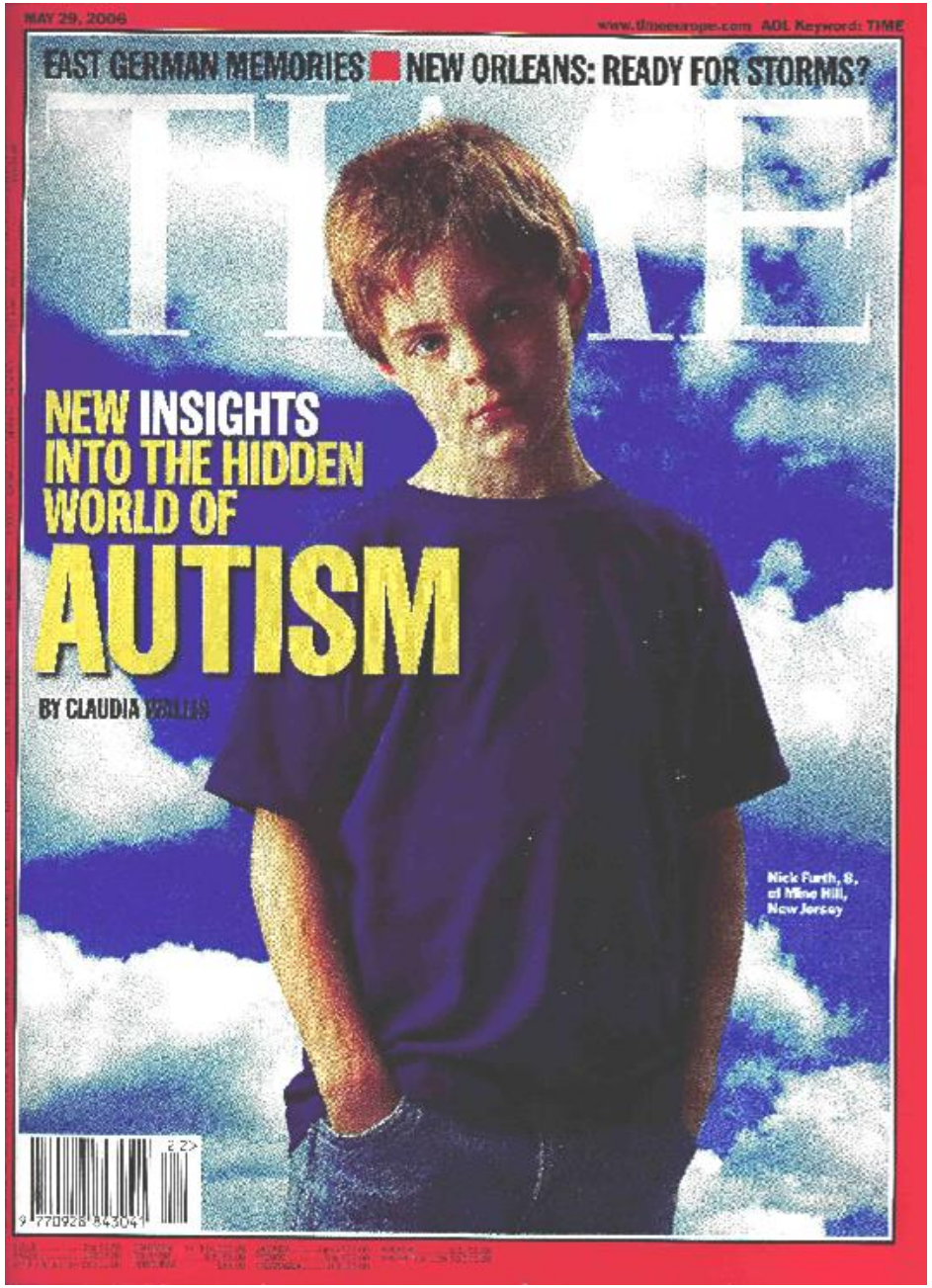
TIME

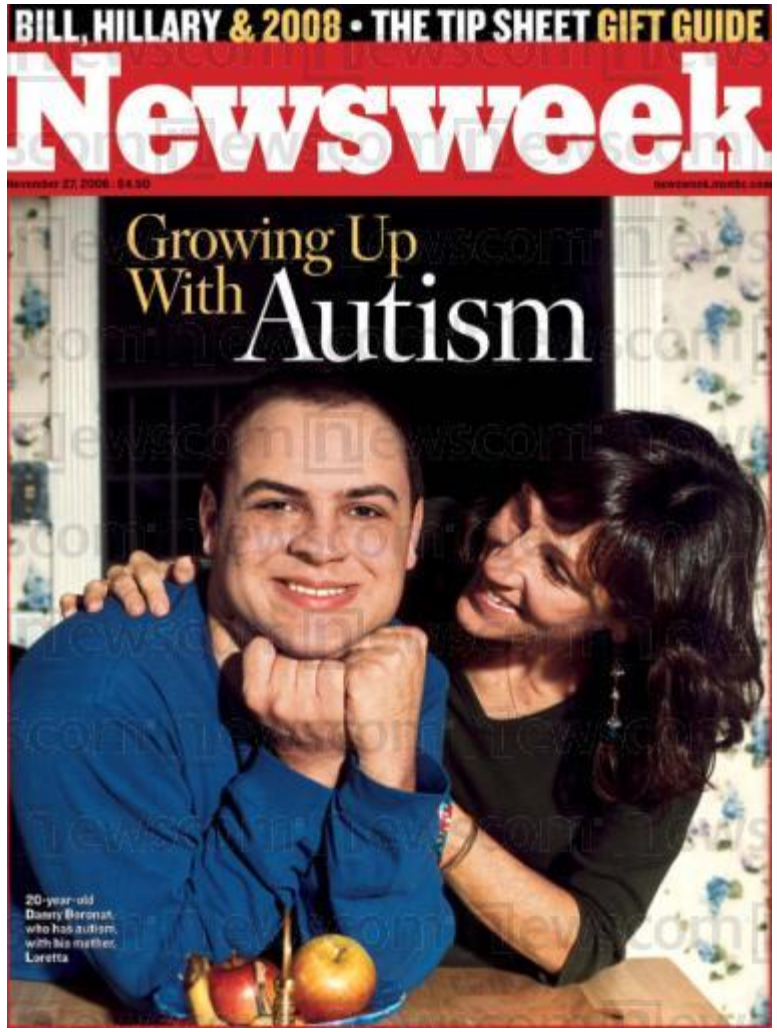


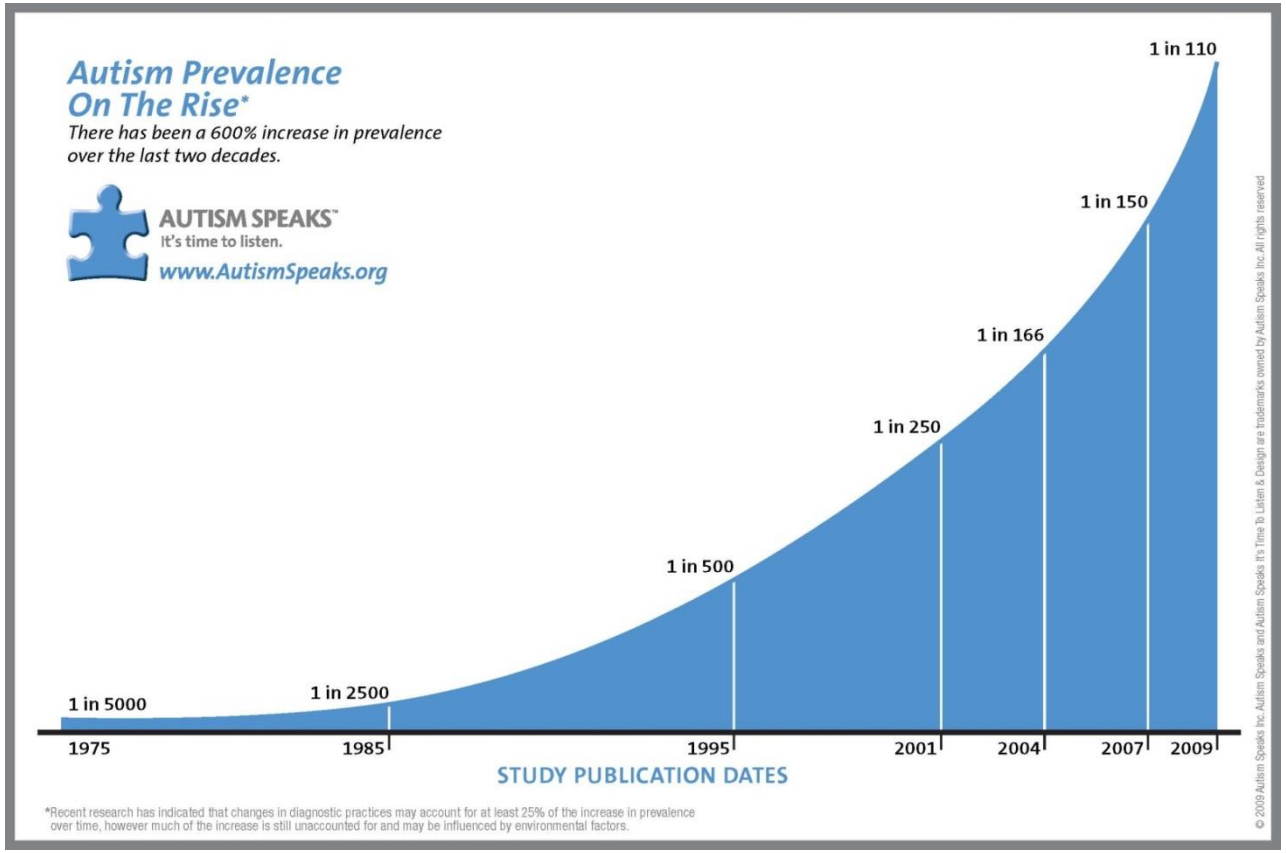
Tommy Barrett, 11, of San Jose, California, has Asperger syndrome

INSIDE THE WORLD OF AUTISM

More than one million Americans may have it, and the number of new cases is exploding. What scientists have discovered. What families should know.


MAY 29, 2006
www.timeeurope.com AOL Keyword: TIME
EAST GERMAN MEMORIES
NEW ORLEANS: READY FOR STORMS?
TIME
NEW INSIGHTS INTO THE HIDDEN WORLD OF
AUTISM
BY CLAUDIA WALLIS
Nick Furth, 8, of Mine Hill, New Jersey


BILL, HILLARY & 2008 • THE TIP SHEET GIFT GUIDE
Newsweek
Growing Up With Autism
20-year-old Danny Beronat, who has autism, with his mother, Loretta


Autism Prevalence
On The Rise*
There has been a 600% increase in prevalence
over the last two decades.
AUTISM SPEAKS™
It's time to listen.
www.AutismSpeaks.org
1 in 5000
1 in 2500
1 in 500
1 in 250
1 in 166
1 in 150
1 in 110
1975
1985
1995
2001
2004
2007
2009
STUDY PUBLICATION DATES
*Recent research has indicated that changes in diagnostic practices may account for at least 25% of the increase in prevalence over time, however much of the increase is still unaccounted for and may be influenced by environmental factors.
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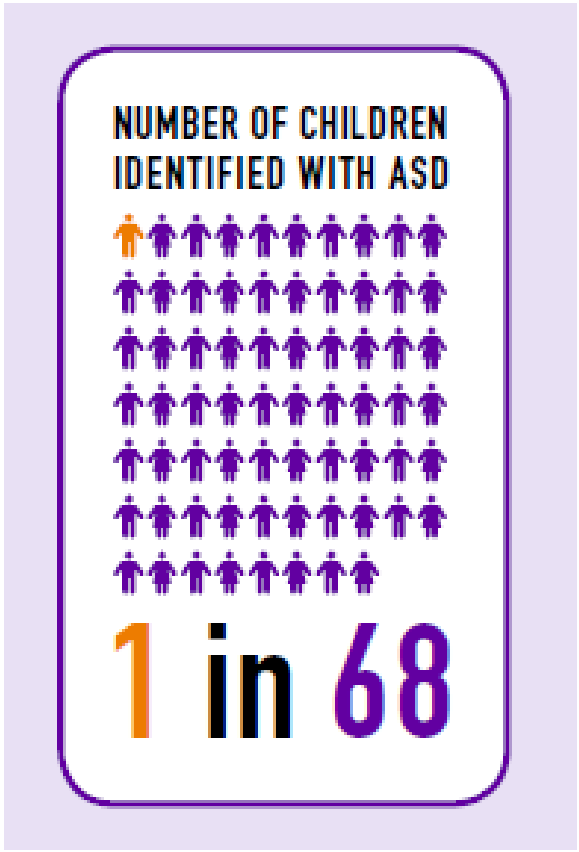
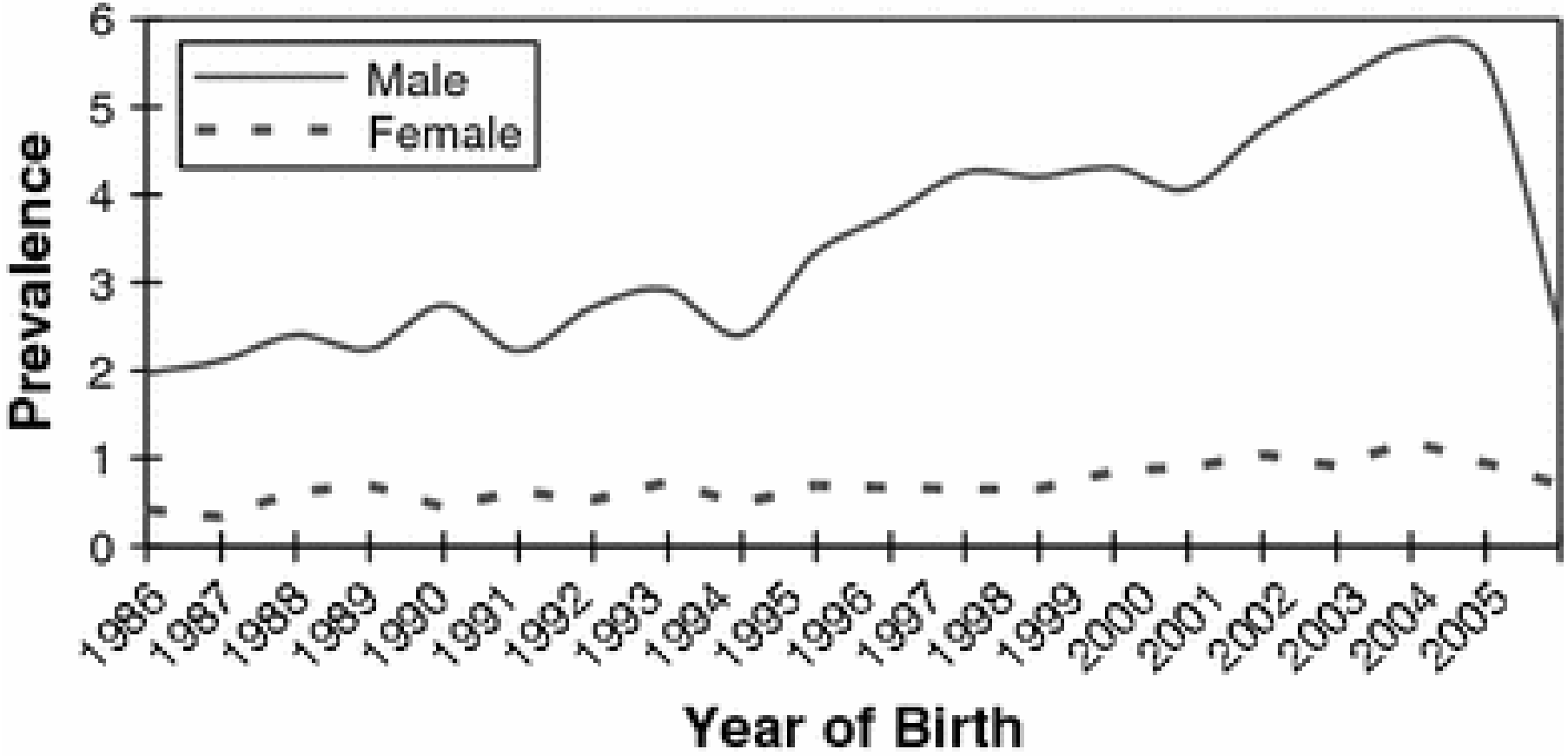

NUMBER OF CHILDREN
IDENTIFIED WITH ASD
1 in 68

Identified Prevalence of Autism Spectrum Disorder

ADDM Network 2000-2010
Combining Data from All Sites

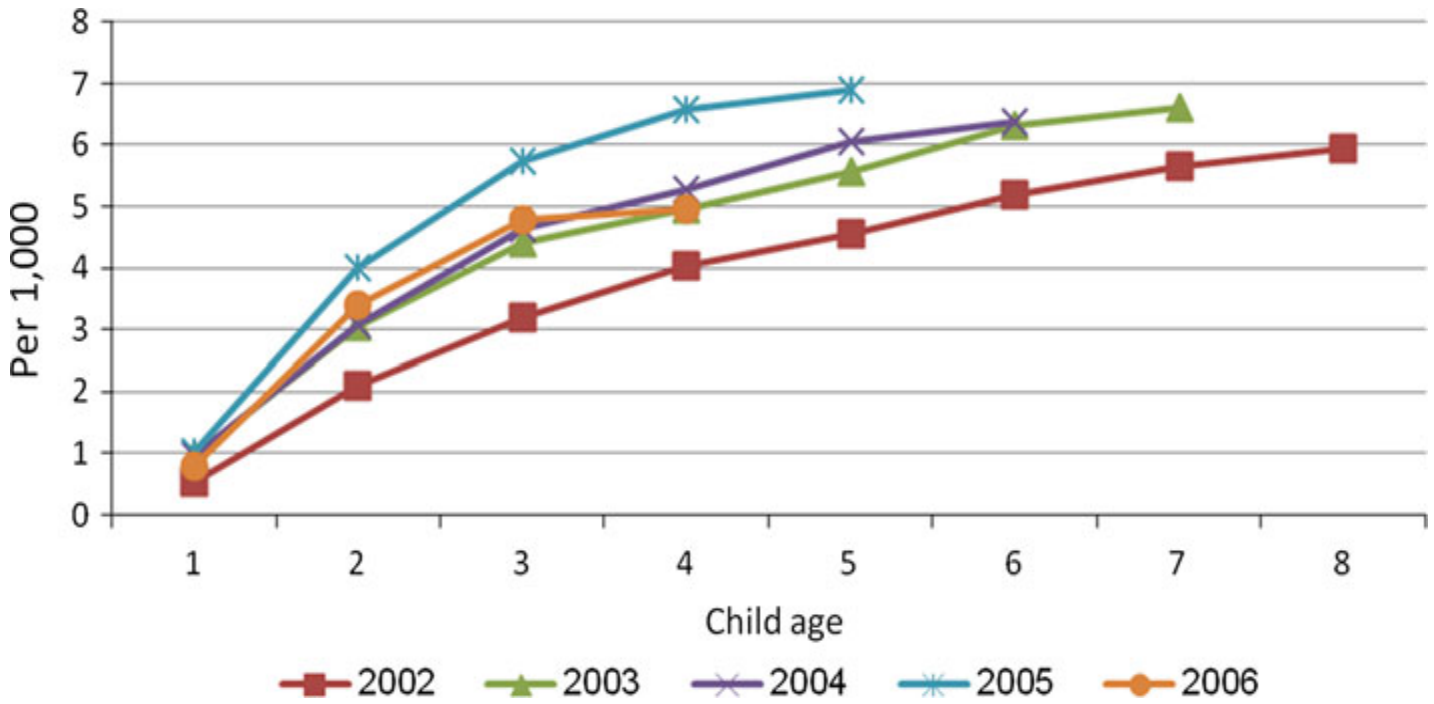
Surveillance Year	Birth Year	Number of ADDM Sites Reporting	Prevalence per 1,000 Children (Range)	This is about 1 in X children...
2000	1992	6	6.7 (4.5 – 9.9)	1 in 150
2002	1994	14	6.6 (3.3 – 10.6)	1 in 150
2004	1996	8	8.0 (4.6 – 9.8)	1 in 125
2006	1998	11	9.0 (4.2 – 12.1)	1 in 110
2008	2000	14	11.3 (4.8 – 21.2)	1 in 88
2010	2002	11	14.7 (5.7 – 21.9)	1 in 68

Source: CDC, 2015



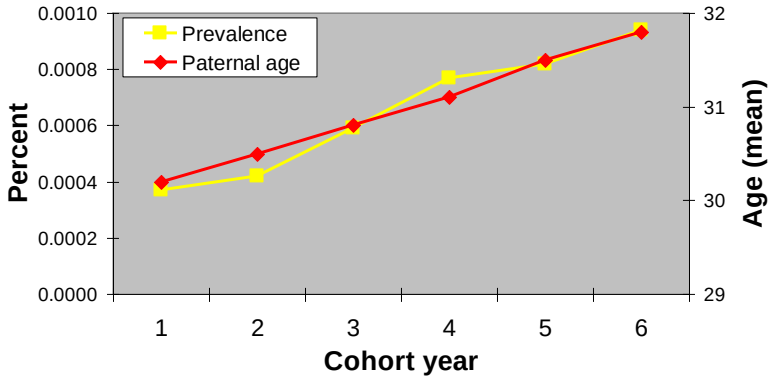
Gal G, Abiri L, Reichenberg A, Gabis L, Gross R.
Time trends in reported autism spectrum disorders in Israel, 1986-2005.
J Autism Developmental Dis. 2012; 42(3):428-31.

Davidovitch et al. J Autism Dev Disord (2013)



Maccabi HMO data

Annual Increase in Paternal Age and Prevalence of ASD (in Israel)



ORIGINAL ARTICLE

Advancing Paternal Age and Autism

Abraham Reichenberg, PhD; Raz Gross, MD, MPH; Mark Weiser, MD; Michealine Bresnahan, PhD; Jeremy Silverman, PhD; Susan Harlap, MBBS; Jonathan Rabinowitz, PhD; Cory Shulman, PhD; Dolores Malaspina, MD; Gad Lubin, MD; Haim Y. Knobler, MD; Michael Davidson, MD; Ezra Susser, MD, DrPH

Context: Maternal and paternal ages are associated with neurodevelopmental disorders.

Objective: To examine the relationship between advancing paternal age at birth of offspring and their risk of autism spectrum disorder (ASD).

Design: Historical population-based cohort study.

Setting: Identification of ASD cases from the Israeli draft board medical registry.

Participants: We conducted a study of Jewish persons born in Israel during 6 consecutive years. Virtually all men and about three quarters of women in this cohort underwent draft board assessment at age 17 years. Paternal age at birth was obtained for most of the cohort; maternal age was obtained for a smaller subset. We used the smaller subset (n=132 271) with data on both paternal and maternal age for the primary analysis and the larger subset (n=318 506) with data on paternal but not maternal age for sensitivity analyses.

Main Outcome Measures: Information on persons coded as having *International Classification of Diseases, 10th Revision* ASD was obtained from the registry. The registry identified 110 cases of ASD (incidence, 8.3 cases per 10 000 persons), mainly autism, in the smaller subset with complete parental age data.

Results: There was a significant monotonic association between advancing paternal age and risk of ASD. Offspring of men 40 years or older were 5.75 times (95% confidence interval, 2.65-12.46; $P<.001$) more likely to have ASD compared with offspring of men younger than 30 years, after controlling for year of birth, socioeconomic status, and maternal age. Advancing maternal age showed no association with ASD after adjusting for paternal age. Sensitivity analyses indicated that these findings were not the result of bias due to missing data on maternal age.

Conclusions: Advanced paternal age was associated with increased risk of ASD. Possible biological mechanisms include de novo mutations associated with advancing age or alterations in genetic imprinting.

Arch Gen Psychiatry. 2006;63:1026-1032

Multinational Registry-based Analyses of Autism Risk Factors and Trends:

The International Collaboration for Autism Registry Epidemiology (iCARE)

Tracing the Origins of Autism

A Spectrum of New Studies

iCARE Concept

- Integration of multiple existing population-based data systems

iCARE Sites and Roles

Site	Site Role				
	Data Contributor	IT Operations	Data Management Core	Project Lead	Founding Collaborator
Denmark					
Finland					
Israel					
Norway					
Spain					
Sweden					
USA/Columbia University					
USA/CDC					
Western Australia					

iCARE Consortium Characteristics

Site	Population Size	Birth Years	Births/Year	Coverage	Health Care Provision
Denmark	5.5 mill	1980-2007	62,000	Nation	Public
Finland	5.4 mill	1987-2008	60,000	Nation	Public
Israel	7.6 mill	1987-2006	125,000	Nation	Public
Norway	4.8 mill	1980-2005	55,000	Nation	Public
Sweden	9.4 mill	1980-2008	107,000	Nation	Public
Western Australia	1.9 mill	1983-1999	24,000	State	Public and private

iCARE Consortium Characteristics

	1987-1996 Births					
	ASD			Autistic Disorder		
Site	N	Prevalence (per 1000)	Sex ratio	N	Prevalence (per 1000)	Sex ratio
Denmark (2009)*	6,116	9.5	3.7	1,277	2.0	5.0
Finland** (2009)*	3,579	7.0	3.5	670	1.3	---
Sweden (2009)*	10,340	9.2	2.2	3,235	2.9	2.6
Israel (2007)*	1,281	1.7	---	---	---	---
Norway (2005)*	985	1.7	3.9	455	0.8	3.1
Western Australia (2004)*	770	3.3	5.9	531	2.3	5.9

* Year of follow-up
** 1987-1994 births

iCARE Consortium Characteristics

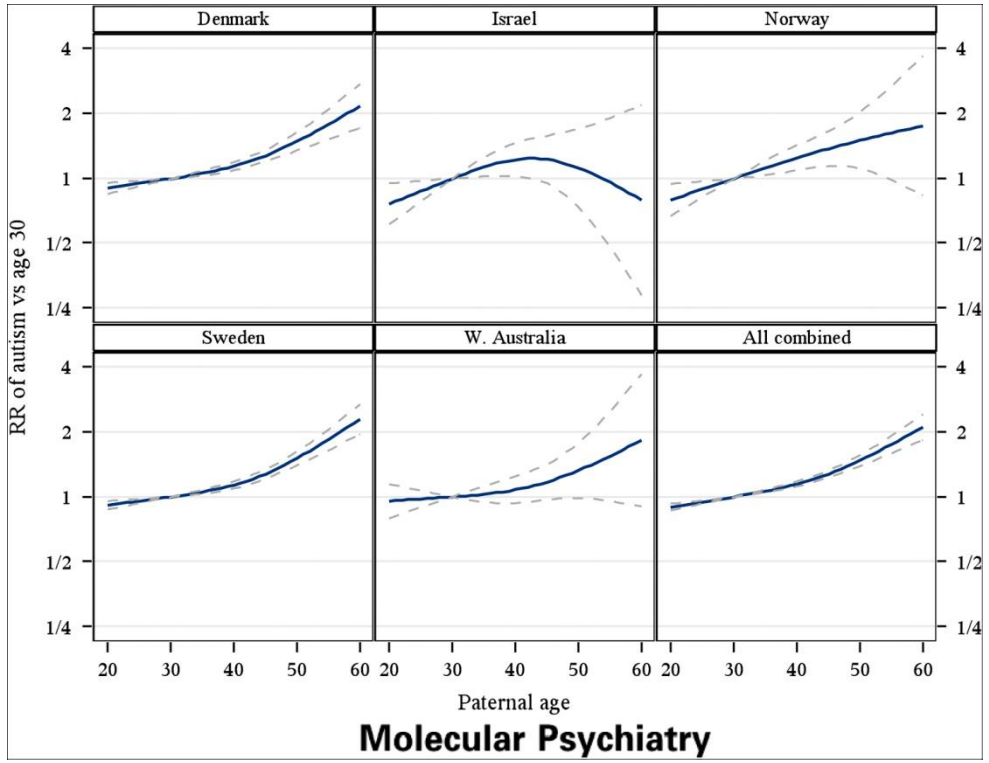
	1997-2004 Births					
	ASD			Autistic Disorder		
Site	N	Prevalence (per 1000)	Sex ratio	N	Prevalence (per 1000)	Sex ratio
Denmark (2009)*	4,218	8.0	4.7	1,633	3.1	4.8
Sweden (2009)*	4,236	5.8	3.4	2,186	3.0	3.5
Israel** (2007)*	1,521	2.8	---	---	---	---
Norway*** (2005)*	266	1.1	4.8	172	0.7	5.4
Western Australia**** (2004)*	364	5.2	4.9	279	4.0	4.6

* Year of follow-up
** 1997-2002 births
*** 1997-2000 births
**** 1997-1999 births

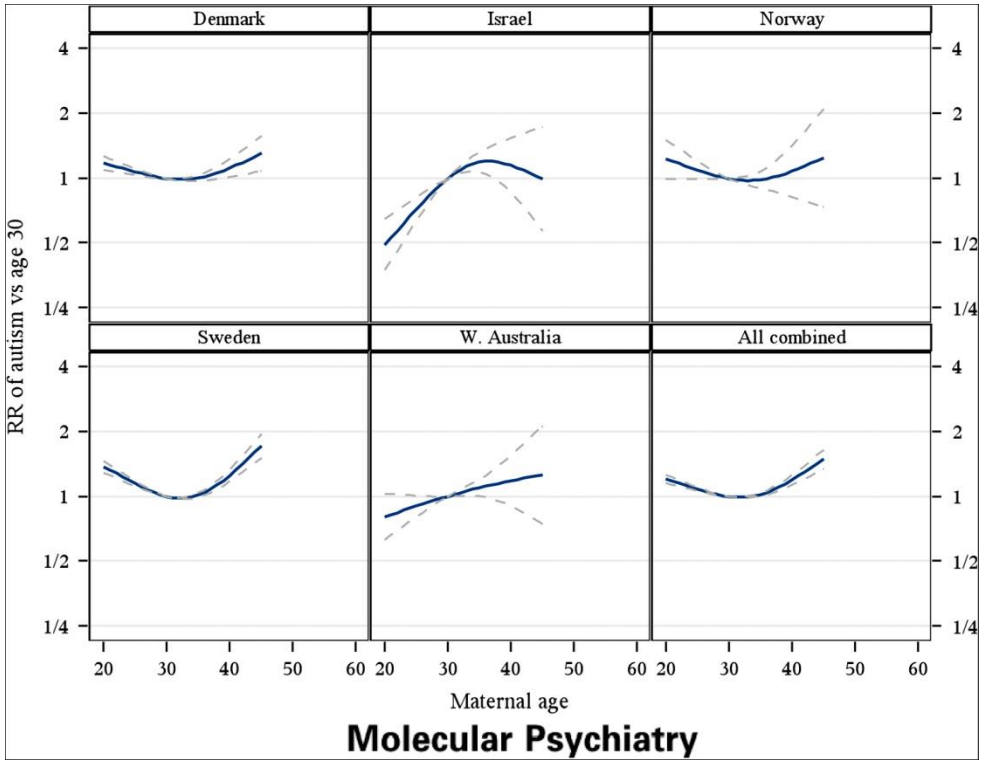
Benefits of Multi-site Approach

- **Assemble birth cohort data sets**
  - Can adopt different study designs to suit analysis
- **Integration enhances statistical power of analyses**
  - Individual strata of exposure or outcome
  - Independent effects of multiple risk factors
- **Uniform analytic methodology can be applied to:**
  - Pooled, multi-site data
  - Individual, site-by-site, comparisons
    - May reveal etiologic mechanisms

Facilitates results comparison and interpretation



Molecular Psychiatry (2016) **21**, 693-700;
doi:10.1038/mp.2015.70



Molecular Psychiatry (2016) **21**, 693-700;
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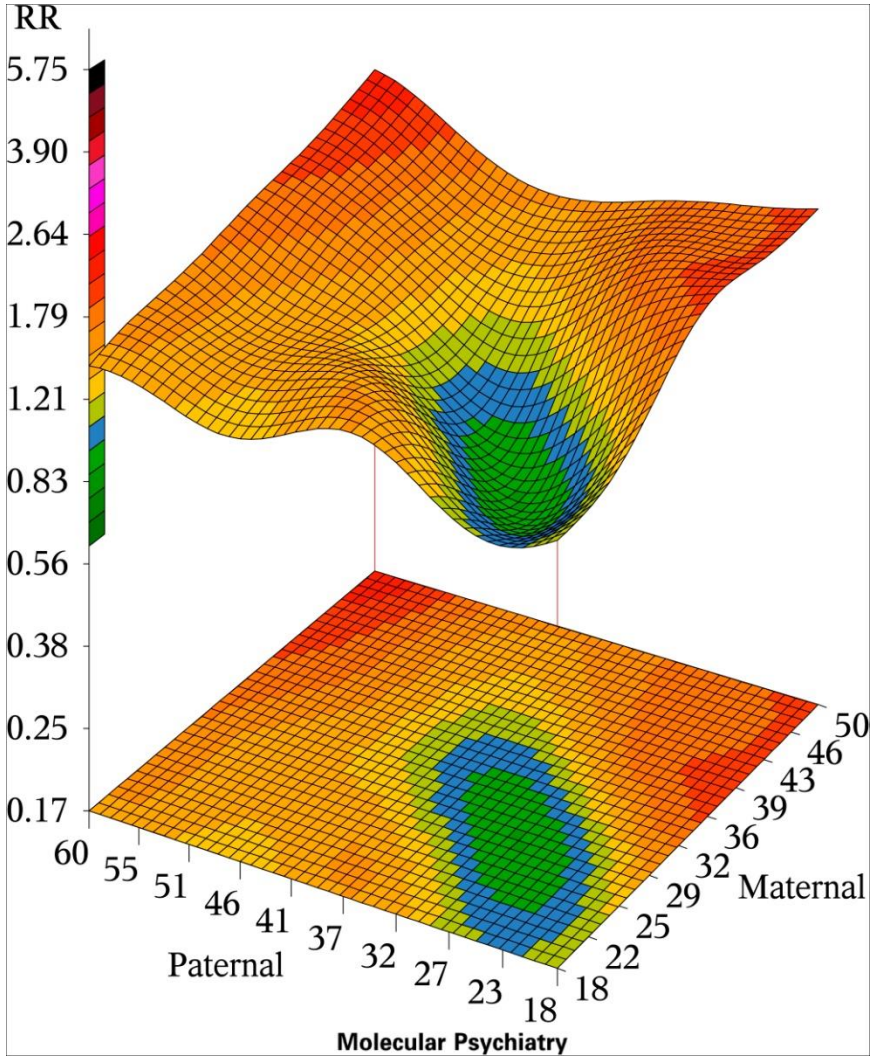

Molecular Psychiatry (2016) **21**, 693-700;
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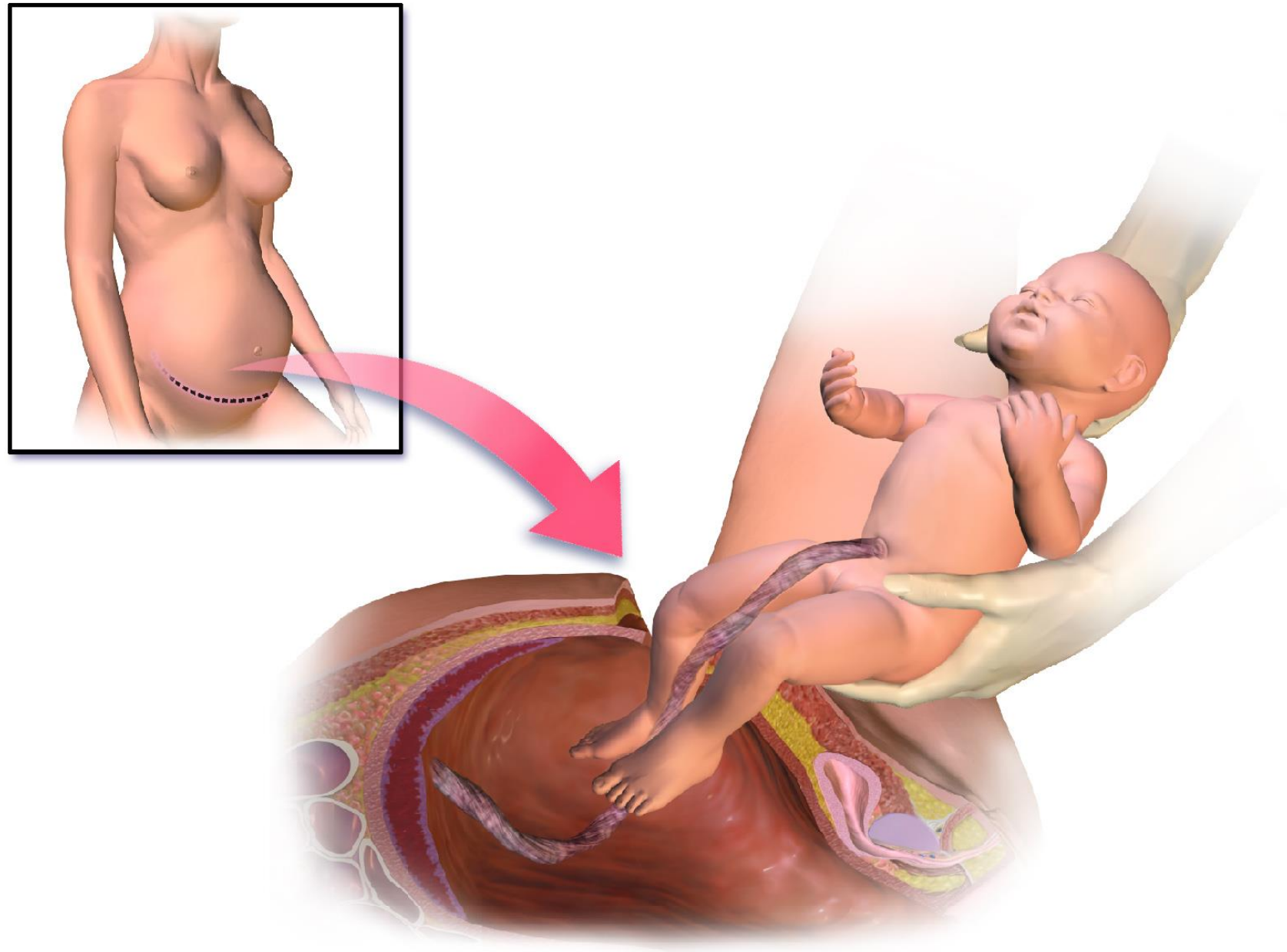
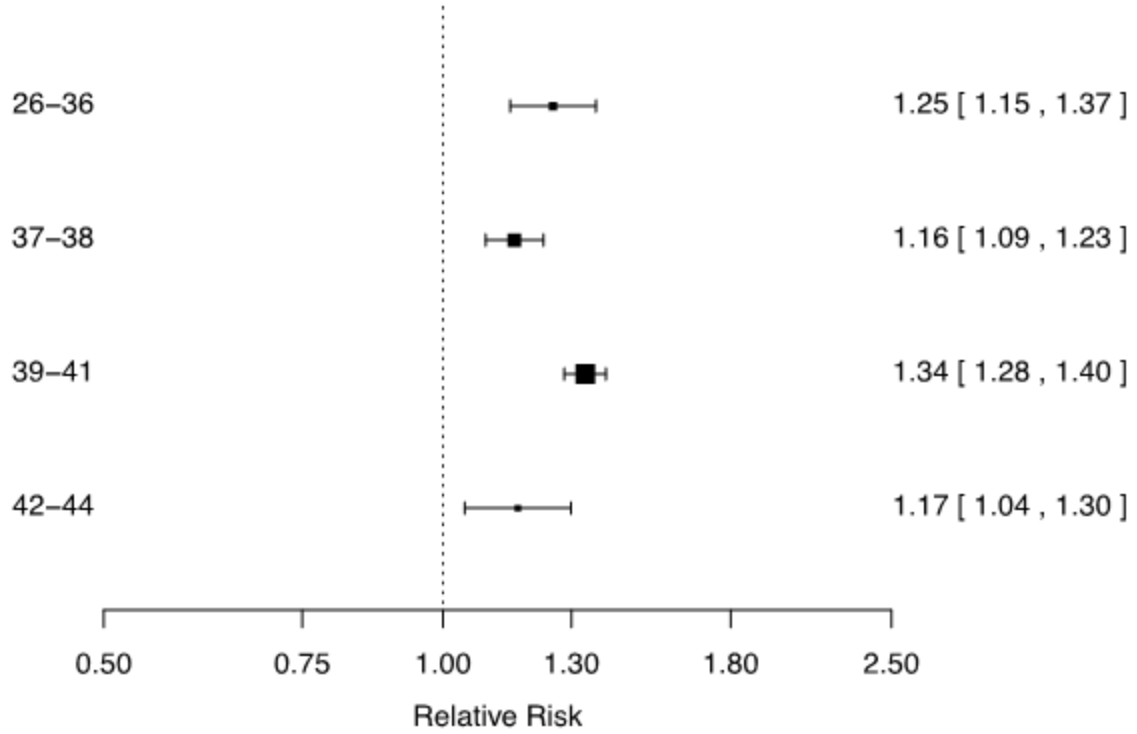


Figure 1 Relative risk (RR) and two-sided 95% confidence intervals for autism spectrum disorder following Cesarean section compared with vaginal delivery overall and in gestational age subgroups (weeks 26-36, 37-38, 39-41, and 42-44).



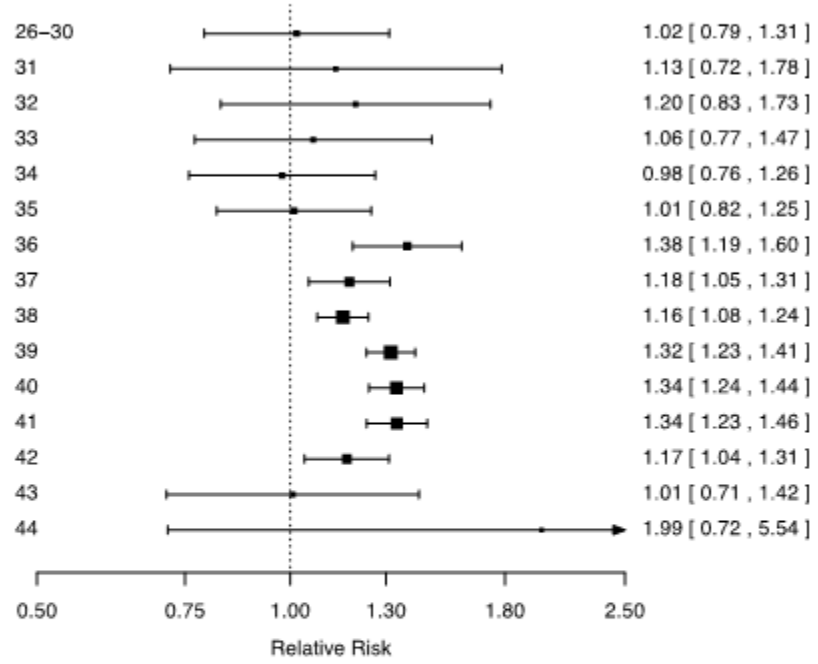
Each RR was estimated from logistic regression adjusting for site (Denmark, Finland, Norway, Sweden, Western Australia), sex, birth year (1984-89, 1990-1994, 1995-99, and 2000-2004) and maternal age (<25, 25-29, 30-34, 35-39, ≥40).

Autism Risk in Caesarean Section

Benjamin Hon Kei Yip, Helen Leonard, Sarah Stock, Camilla Stoltenberg, Mika Gissler, Raz Gross, Diana Schendel, Sven Sandin. International J Epi. Dec 26, 2016.

ASD: C-Section vs. Vaginal Delivery by Week of Gestation

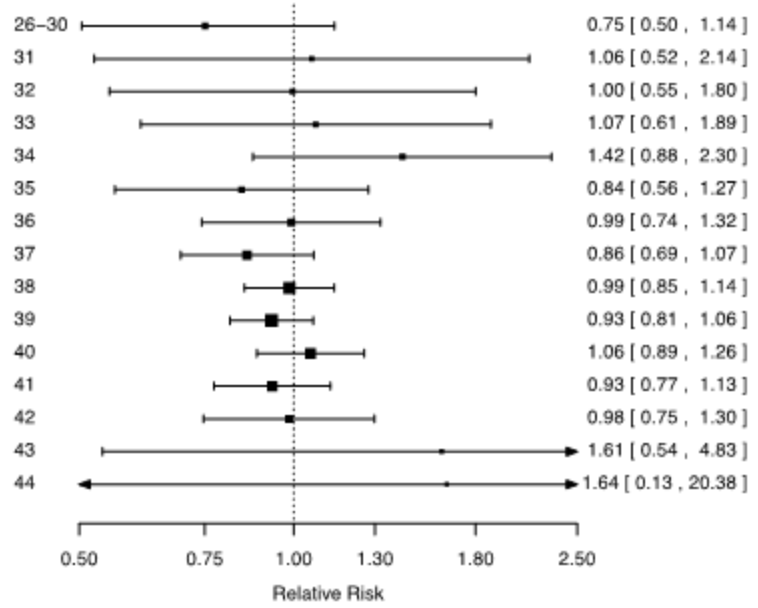
Figure 2 Relative risk (RR) and two-sided 95% confidence intervals for autism spectrum disorder following Caesarean section compared with vaginal delivery by week of gestation (weeks 26-30 as one group).



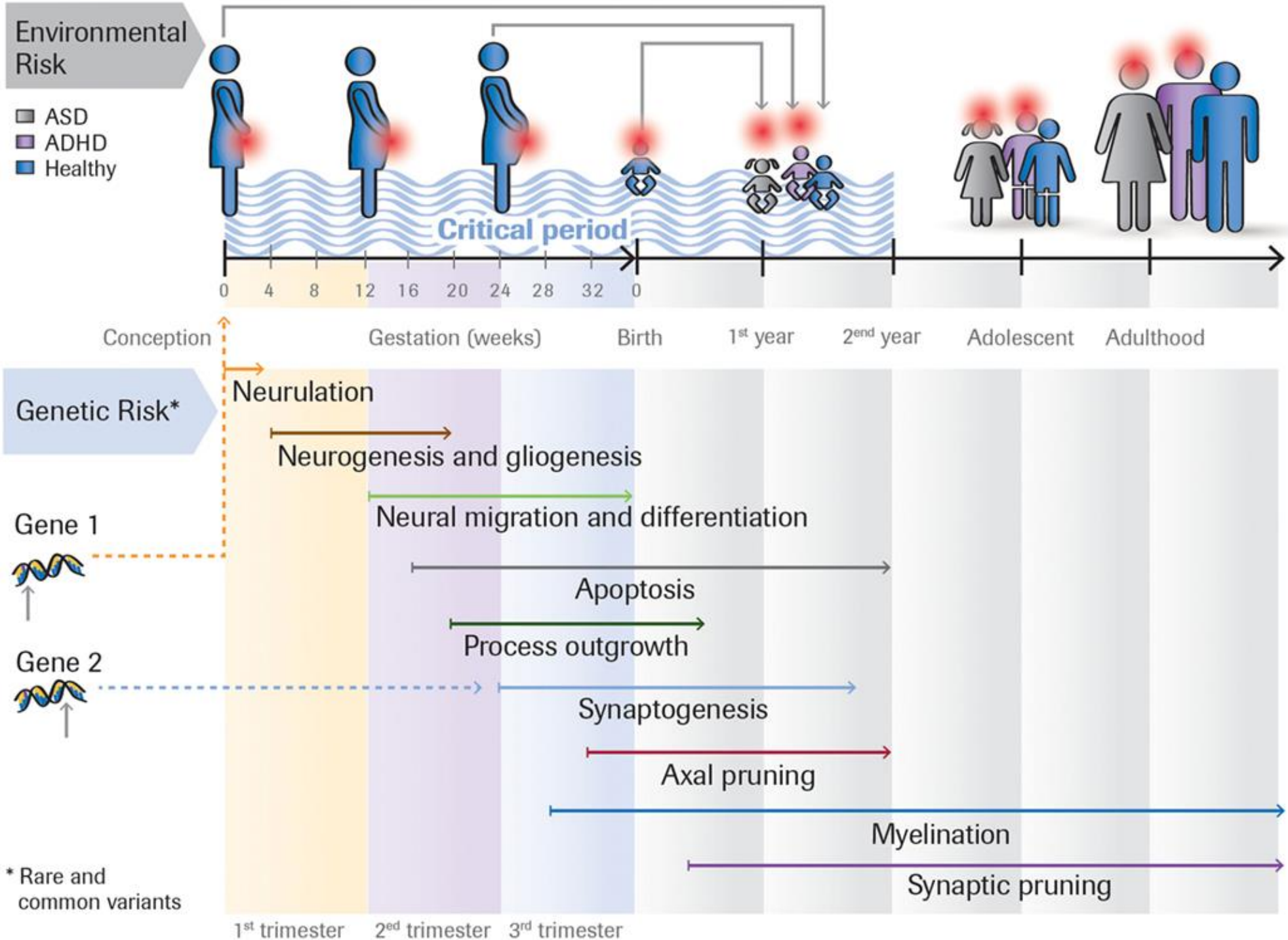
Each RR was estimated from logistic regression adjusting for site (Denmark, Finland, Norway, Sweden, Western Australia), sex, birth year (1984-89, 1990-1994, 1995-99, and 2000-2004) and maternal age (<25, 25-29, 30-34, 35-39, ≥40).

ASD: Emergency vs. Elective C-Section by Week of Gestation

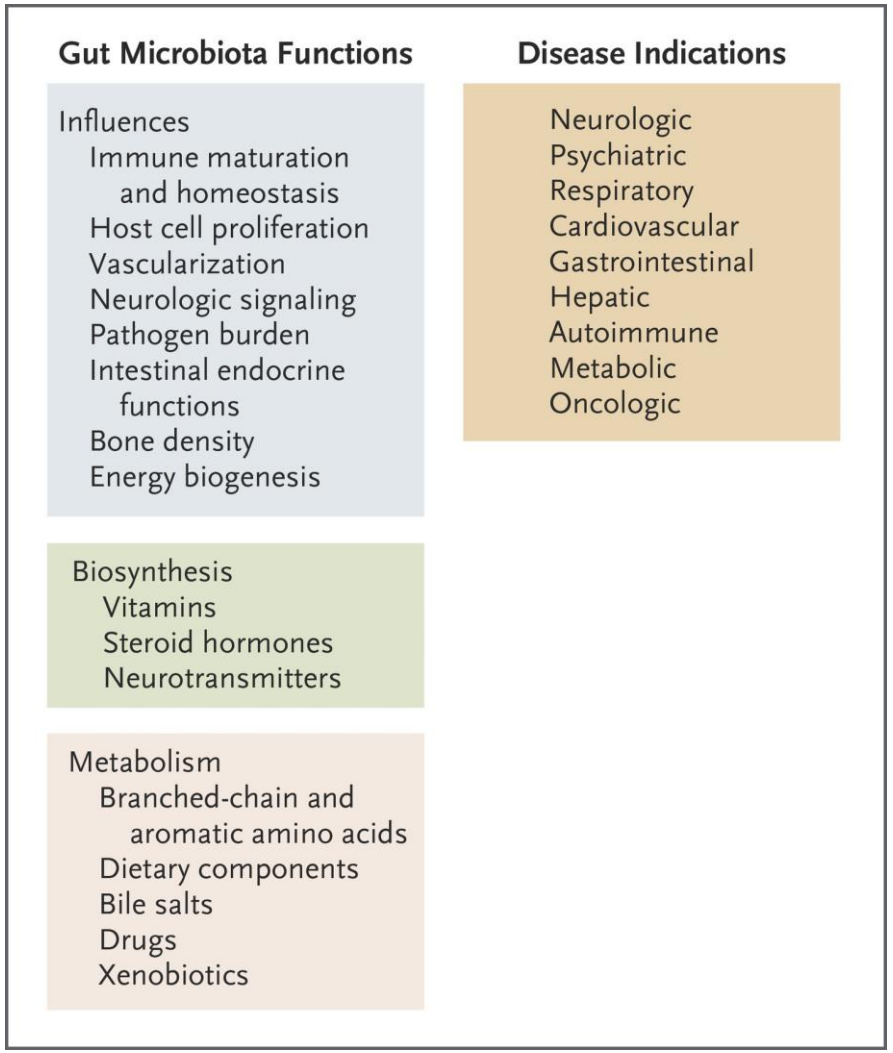
Figure 3 Relative risk (RR) and two-sided 95% confidence intervals for autism spectrum disorder following emergency Caesarean section compared with elective caesarean section by week of gestation (weeks 26-30 as one group).



Each RR was estimated from logistic regression adjusting for site (Denmark, Finland, Norway, Sweden, Western Australia), sex, birth year (1984-89, 1990-1994, 1995-99, and 2000-2004) and maternal age (<25, 25-29, 30-34, 35-39, ≥40).

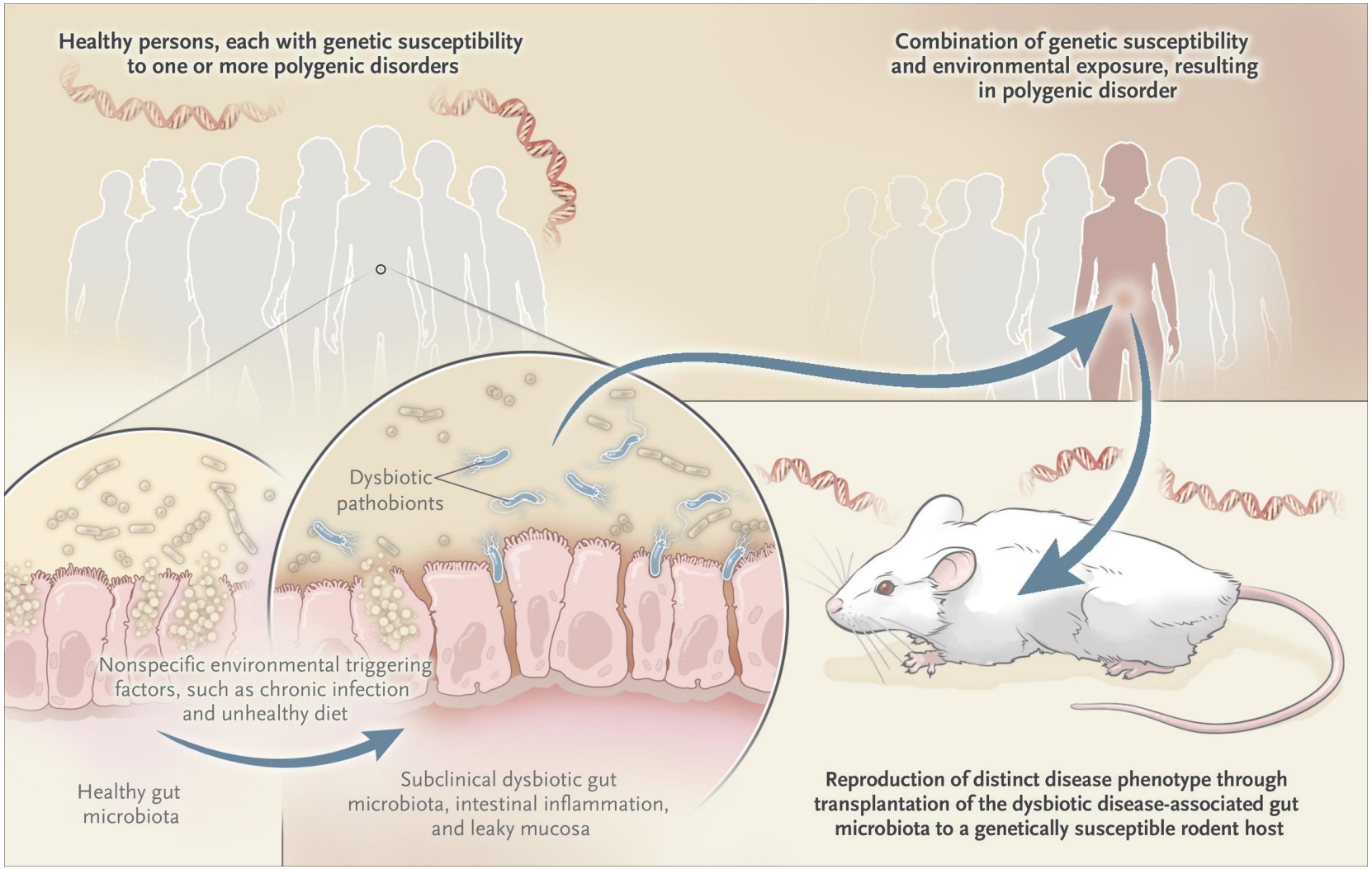


Loth E et al. Frontiers In Psychiatry. 2016



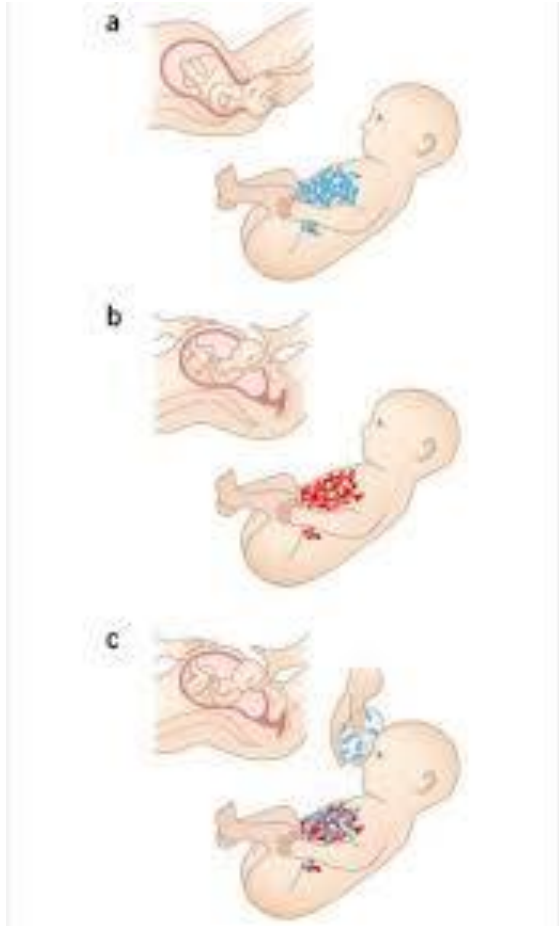
Lynch SV et al. 2016

The NEW ENGLAND JOURNAL of MEDICINE

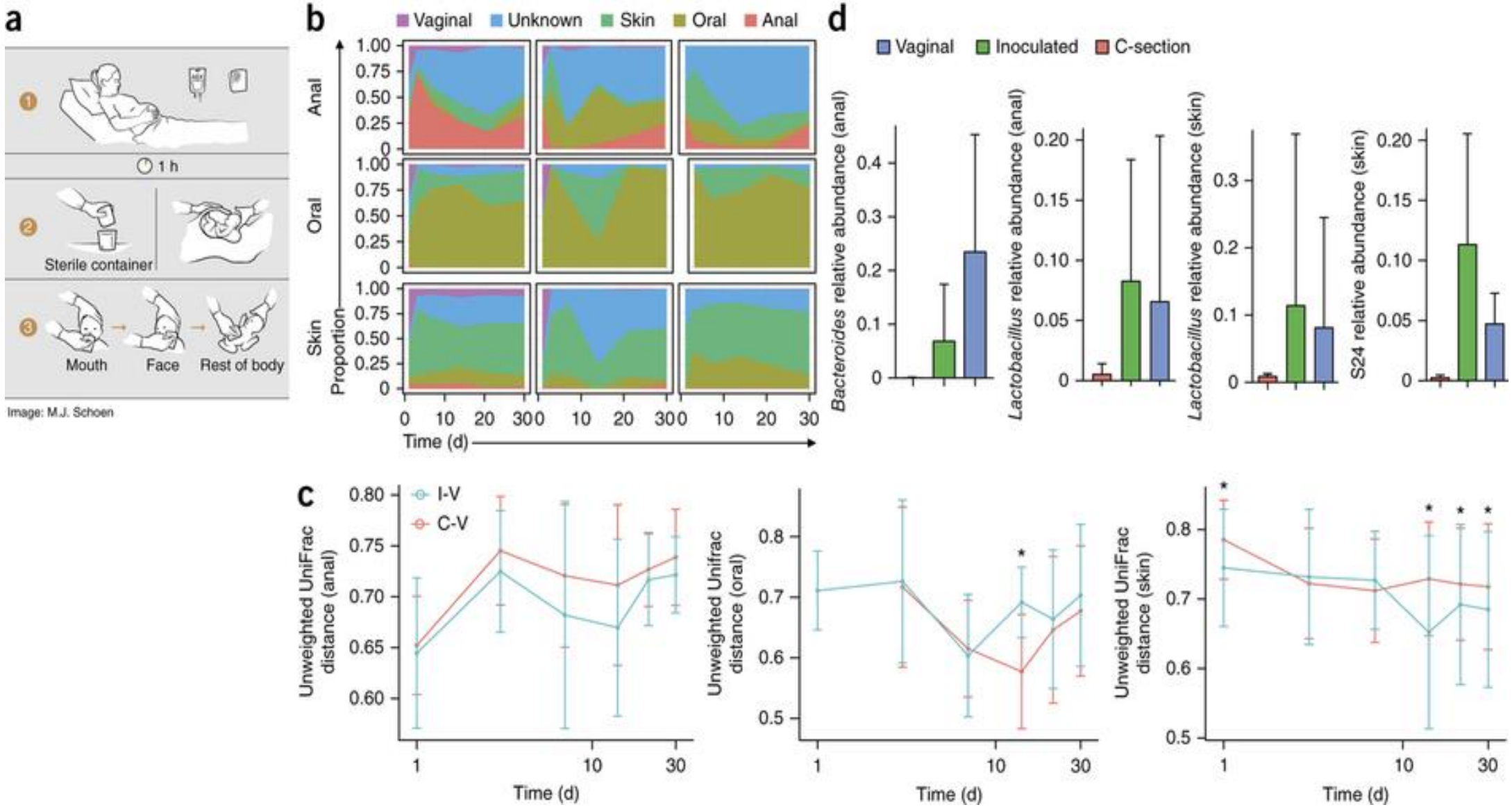


Lynch SV et al. 2016

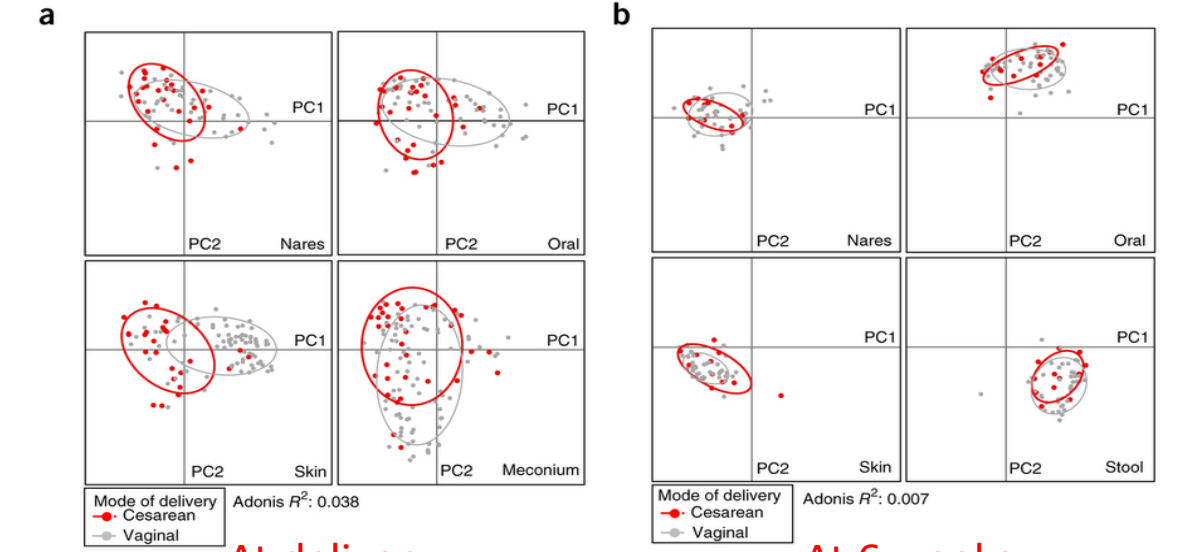
The NEW ENGLAND JOURNAL of MEDICINE



Khoruts A. Nature Med. 2016

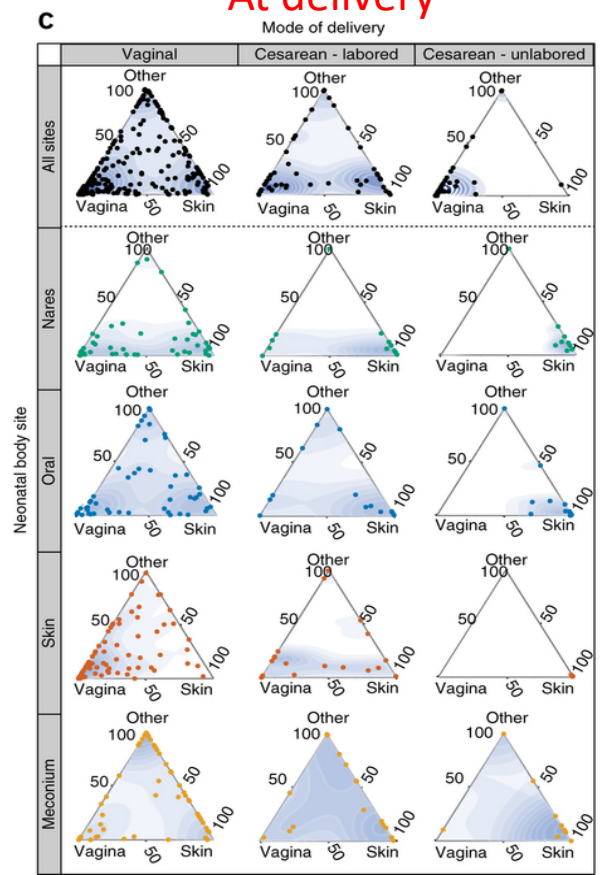


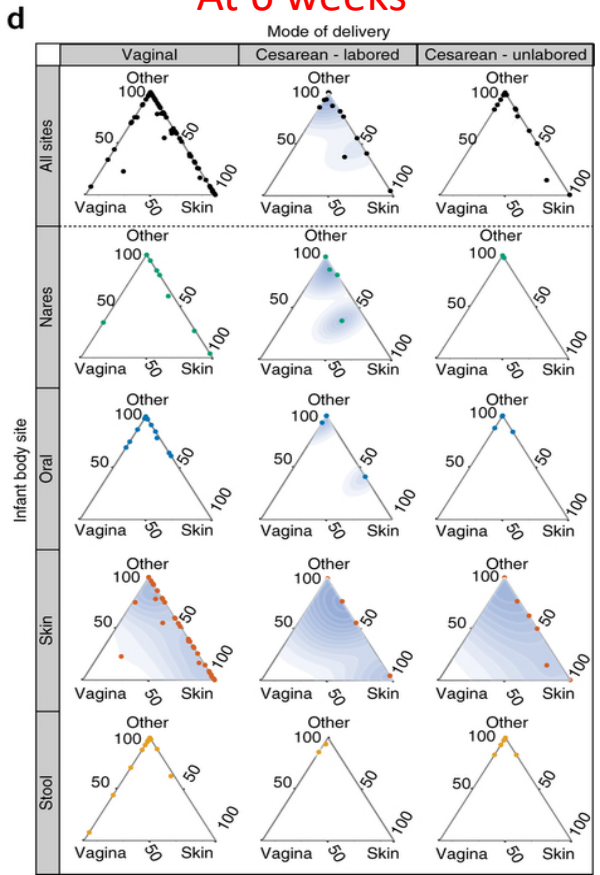
Dominguez-Bello MG et al. Nature Med. 2016



At delivery

At 6 weeks





Chu et al. Nat Med, 2017


Children conceived between January and May have higher-than-average rates of developmental conditions, whereas those conceived between June and December have lower-than-average rates.
J
F
M
A
M
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J
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S
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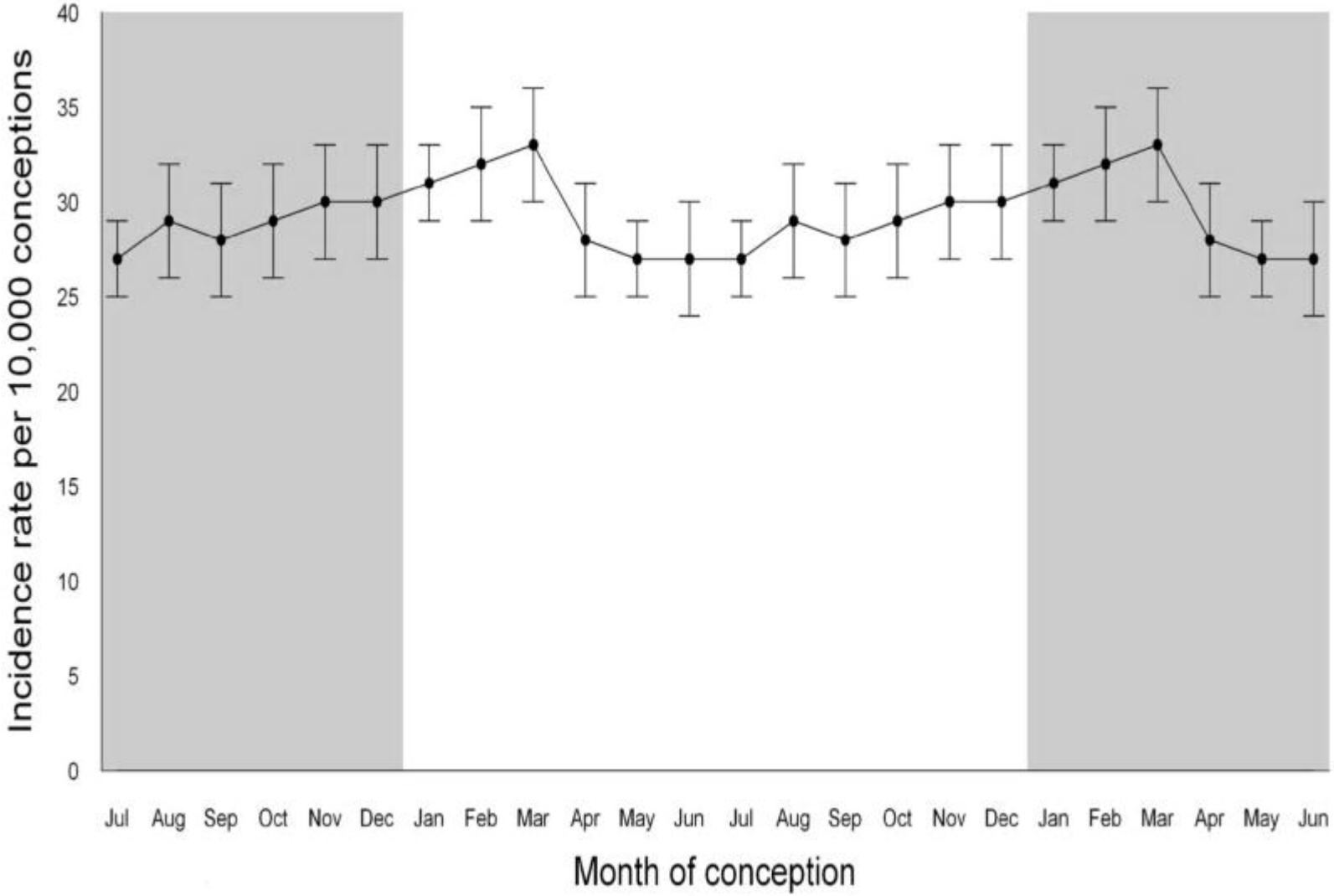
Viruses (Influenza)
Pesticides
Vitamin D



Zerbo et al. Epidemiology. 2011

From: Month of Conception and Learning Disabilities: A Record-Linkage Study of 801,592 Children

Am J Epidemiol. 2016;184(7):485-493. doi:10.1093/aje/kww096

ASD

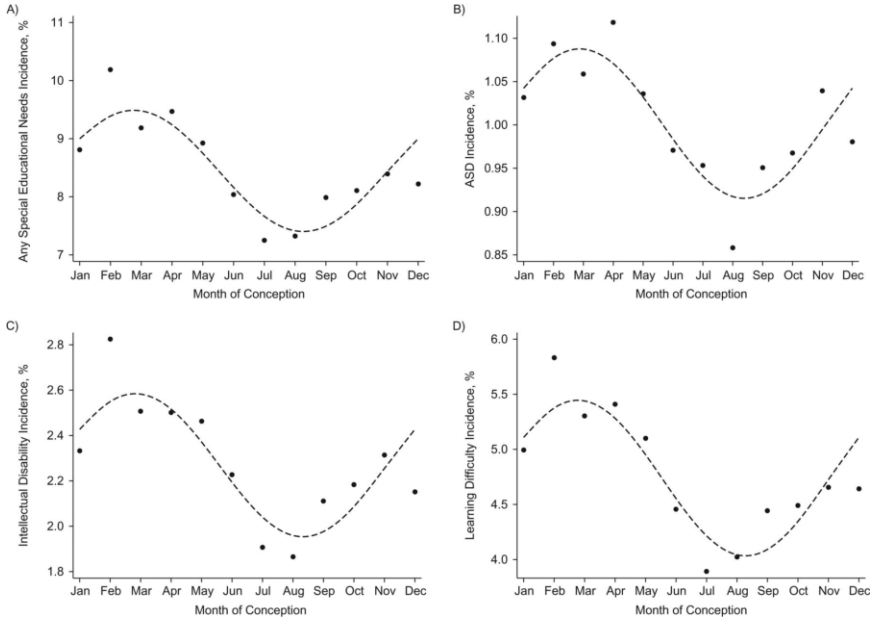
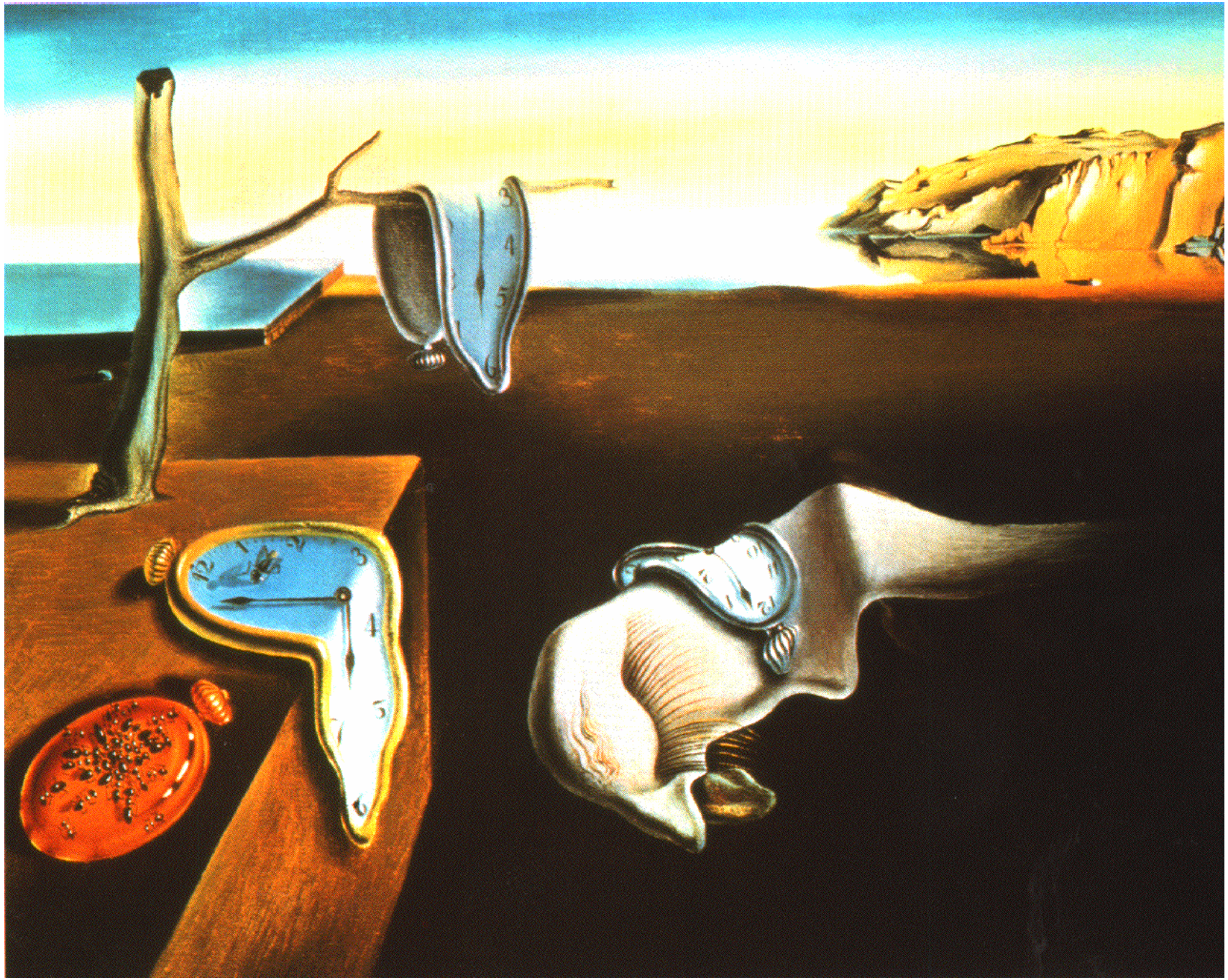


Figure Legend:
Crude monthly incidence (dots) and pure cosinor models (dashed lines) of additional educational support needs, Scotland, United Kingdom, 2006–2011.



AUTISM SPEAKS™

It's time to listen.

המוסד לביטוח לאומי


NOBEL FORUM
Nobels väg 1
PORTTELEFON
Nobelkansliet
Ann-Margreth Jörnvall
Agneta Sjövall

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