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FROM RESEARCH TO CLINICAL PRACTICE. LINKING THE EXPERTISE
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SaludMadrid Hospital General Universitario Gregorio Marañón Comunidad de Madrid IiSGM cibersam Centro de Investigación Biomédica En Red de Salud Mental

Developmental trajectories in early-onset psychoses: open windows for prevention?

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Outline

- Prevention in psychiatry
- Psychosis (psychiatric disorders) as the reflection of abnormal developmental trajectories
- Shifting the focus towards prevention and early intervention in developmentally sensitive periods
- Implications and priorities for the future

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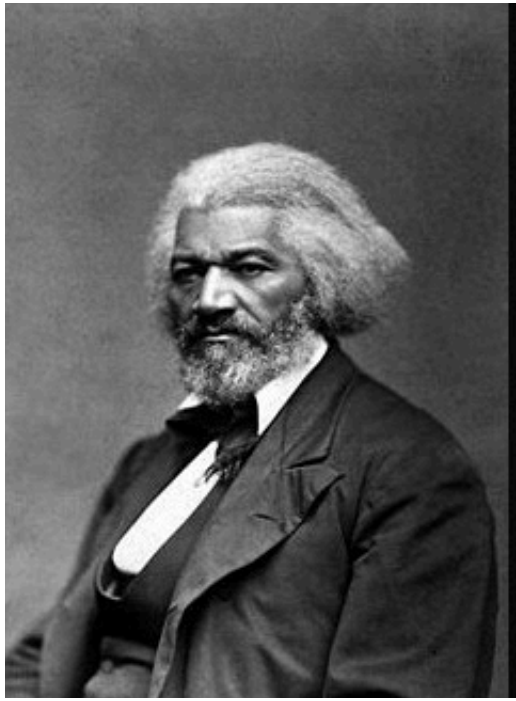

It is easier to build strong children than to repair broken men.

(Frederick Douglass)

What is prevention?

Whole population through public health policy	Whole population: selected groups and healthy individuals	Selected individuals, high risk patients	Patients
PRIMORDIAL PREVENTION Establish or maintain conditions to minimize hazards to health	**PRIMARY PREVENTION** Prevent disease well before it develops. Reduce risk factors	**SECONDARY PREVENTION** Early detection of disease (screening and intervention for pre-diabetes)	**TERTIARY PREVENTION** Treat established disease to prevent deterioration
Advocacy for social change to make physical activity easier	Primary care advice as part of routine consultation	e.g. primary care risk factor reduction for those at risk of chronic disease, falls, injury	e.g. exercise advice as part of cardiac rehabilitation

Cure

Prevention

Efficacy of preventive interventions in medicine: Prevention of diabetes

The New England Journal of Medicine

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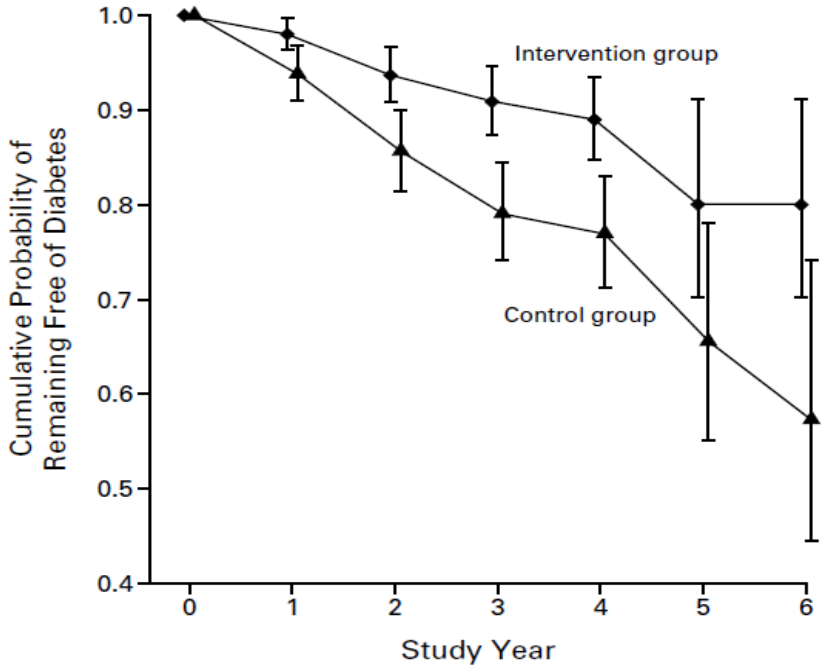
VOLUME 344 · MAY 3, 2001 · NUMBER 18

PREVENTION OF TYPE 2 DIABETES MELLITUS BY CHANGES IN LIFESTYLE AMONG SUBJECTS WITH IMPAIRED GLUCOSE TOLERANCE

JAAKKO TUOMILEHTO, M.D., PH.D., JAANA LINDSTRÖM, M.S., JOHAN G. ERIKSSON, M.D., PH.D., TIMO T. VALLE, M.D., HELENA HÄMÄLÄINEN, M.D., PH.D., PIRJO ILANNE-PARIKKA, M.D., SIRKKA KEINÄNEN-KIUKAANNIEMI, M.D., PH.D., MAURI LAAKSO, M.D., ANNE LOUHERANTA, M.S., MERJA RASTAS, M.S., VIRPI SALMINEN, M.S., AND MATTI UUSITUPA, M.D., PH.D., FOR THE FINNISH DIABETES PREVENTION STUDY GROUP



SUBJECTS AT RISK						
Total no.	507	471	374	167	53	27
Cumulative no. with diabetes:						
Intervention group	5	15	22	24	27	27
Control group	16	37	51	53	57	59

Figure 1. Proportion of Subjects without Diabetes during the Trial.
The vertical bars show the 95 percent confidence intervals for the cumulative probability of remaining free of diabetes. The relative risk of diabetes for subjects in the intervention group, as compared with those in the control group, was 0.4 ($P<0.001$ for the comparison between the groups).

Efficacy of preventive interventions in medicine: Prevention of cancer

The cervical cancer epidemic that screening has prevented in the UK

Julian Peto, Clare Gilham, Olivia Fletcher, Fiona E Matthews

Lancet 2004; 364: 249–56

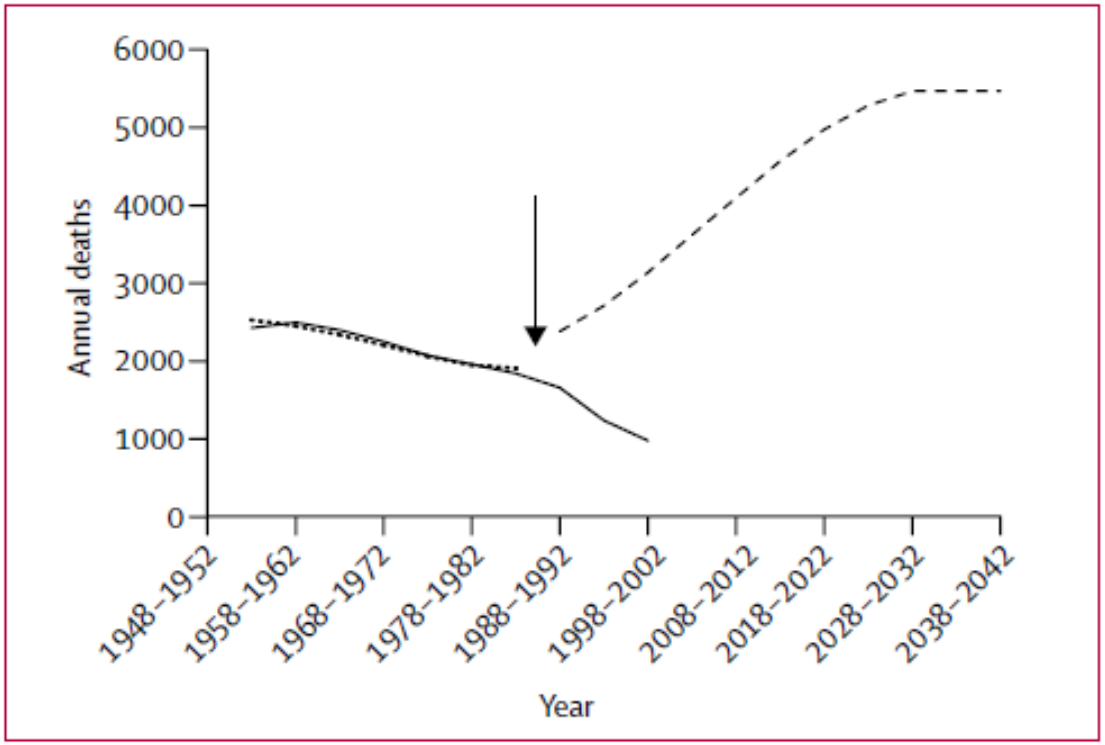
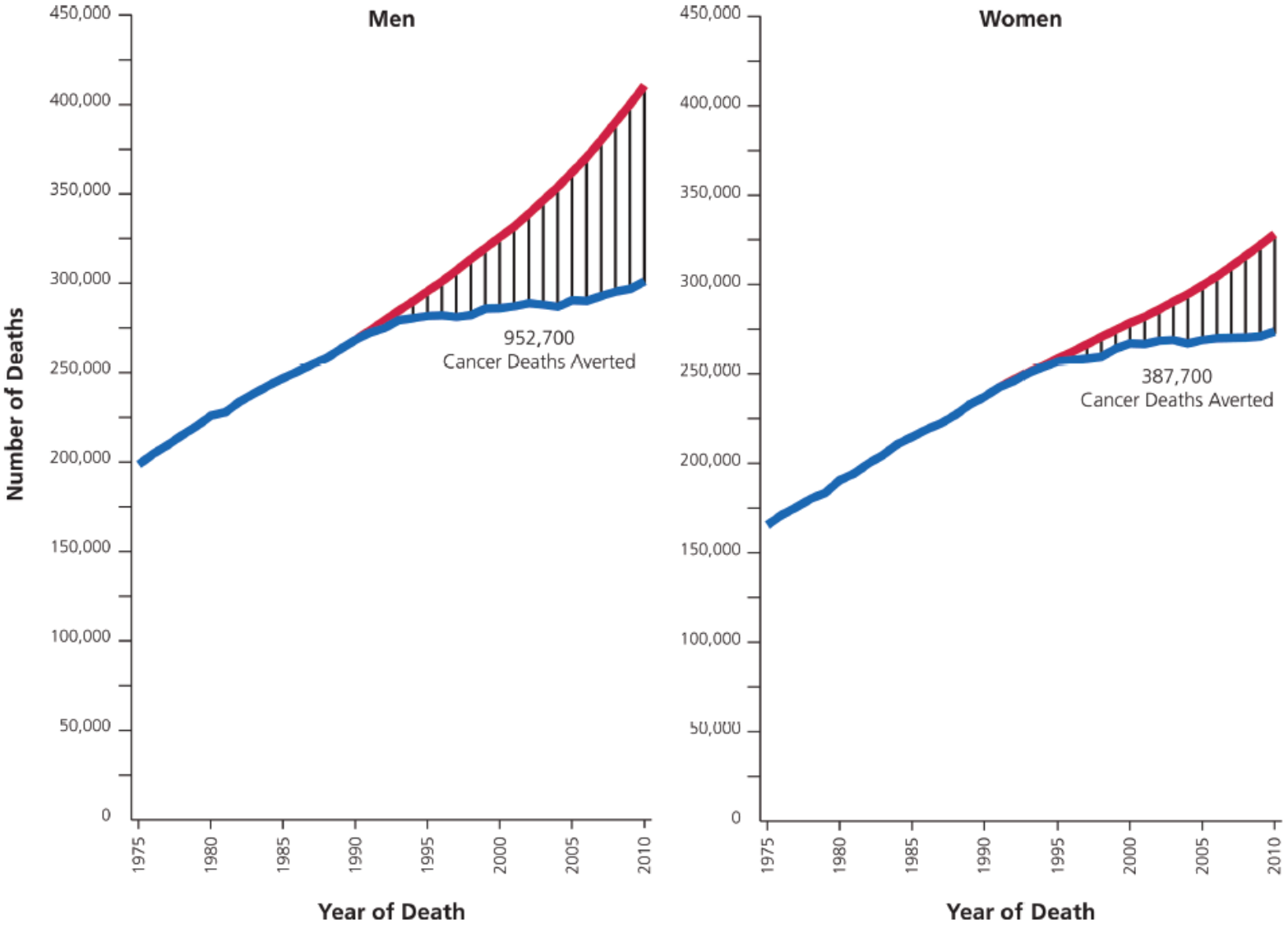


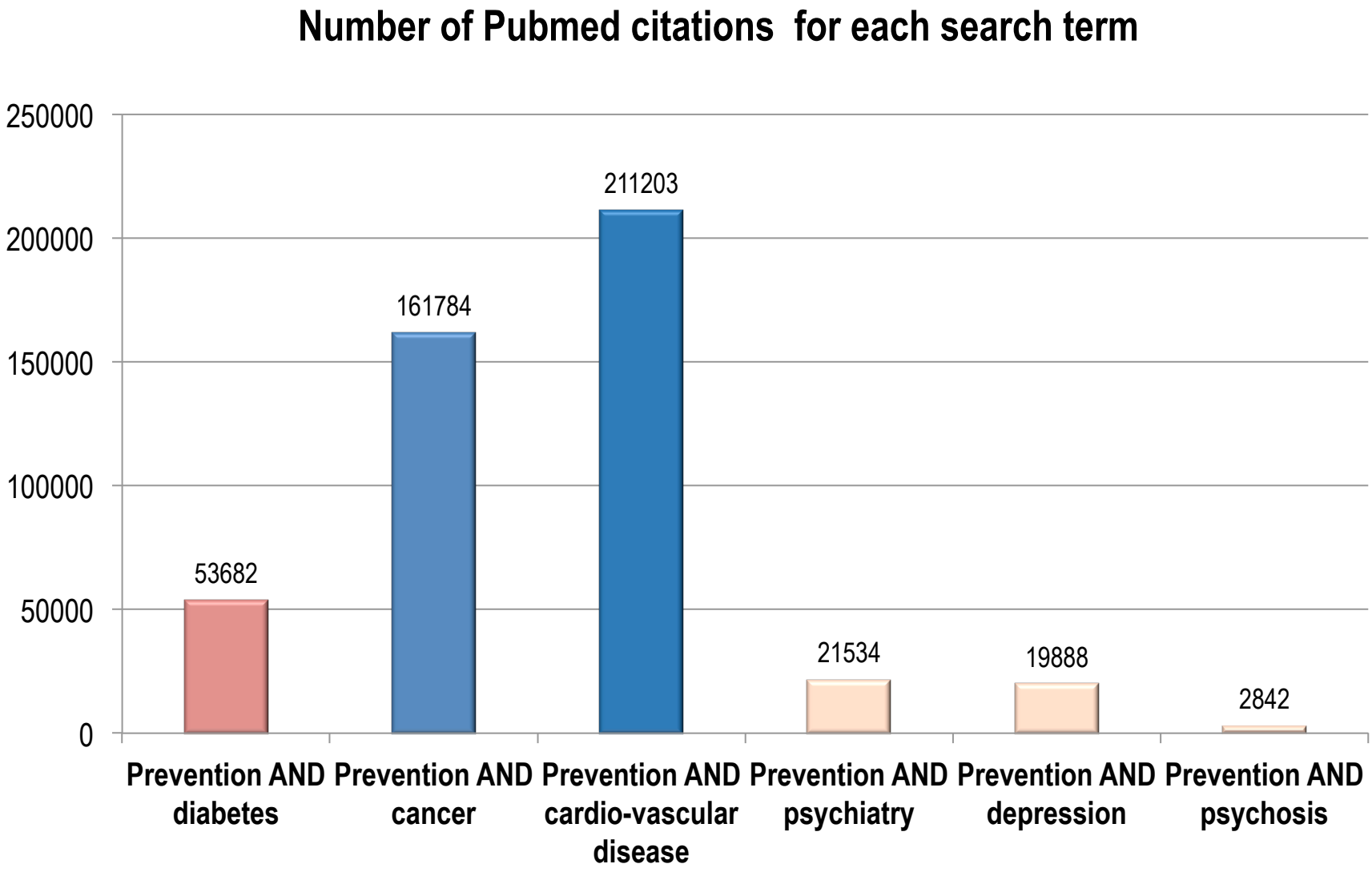
Figure 4: Projected cervical cancer deaths in women younger than 85 years without any screening (England and Wales)



Rebecca Siegel, MPH[1]; Jiemin Ma, PhD[2,*]; Zhaohui Zou, MS[3]; Ahmedin Jemal, DVM, PhD[4]

CA CANCER J CLIN 2014;64:9–29

Prevention in psychiatry: A neglected topic?



Prevention in psychiatry, a neglected topic

VIEWPOINT

Use of Clinical Preventive Services in Infants, Children, and Adolescents

Coleen A. Boyle, PhD
National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia.

James M. Perrin, MD
Division of General Pediatrics, Center for Child and Adolescent Health Research and Policy, MassGeneral Hospital for Children, Boston, Massachusetts; and Harvard Medical School, Pediatrics, Boston, Massachusetts.

Virginia A. Moyer, MD, MPH
American Board of Pediatrics, Chapel Hill, North Carolina.

At each stage from birth to young adulthood, the use of clinical preventive services (CPSs) provides an opportunity to intervene early to improve outcomes for many costly and complex conditions and to modify important disease-defining risk factors.[1] A number of important provisions of the Affordable Care Act (ACA) will provide impetus to improve the use of CPSs, in particular, the provision that such services are now covered without cost sharing.[2]

The Centers for Disease Control and Prevention (CDC) has collected baseline data and reported detailed information on a select set of CPSs for children to serve as a benchmark to measure change following ACA implementation.[3]

The selected CPSs were identified by the CDC because they represent important public health issues for which CPSs exist, the service was underused before ACA implementation, and national data (largely parent and self-report or provider office-based surveys) were available to establish a baseline (defined as prior to 2012). Other important CPSs for children were not included in the report because of the lack of

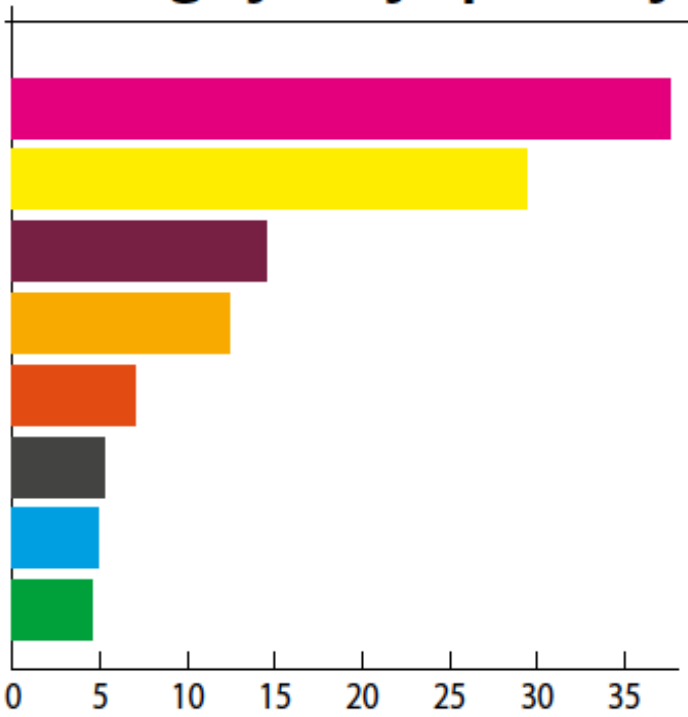
In infancy and early childhood, although 98% of all newborns were screened for hearing loss, 50% of children with a failed newborn hearing screen lacked documentation of a follow-up audiology evaluation. Without initiation of early diagnosis and subsequent communication services, the benefits of newborn hearing screening can be diminished.[4] Only 21% of all infants and toddlers were assessed in a standardized way for developmental delays. A higher percentage of parents (52%) reported informal monitoring (ie, discussion and questioning by the health care practitioner about parental concerns), but informal screening is less likely to result in appropriate identification of children with delays.[5] About one-third of children aged 1 to 2 years had screening for lead poisoning.

In early and middle childhood, when major chronic disease risk factors begin to emerge, key findings from the report indicate that between 56% and 86% of children did not receive preventive dental care, including topical fluoride application and dental sealants. Some dental services offered by physicians (eg, oral fluoride supplementation in preschool children and pediatric oral

JAMA Published online September 10, 2014

Prevention in psychiatry, a neglected topic

Average yearly spend by research activity (£m)



37.6	Underpinning research
29.4	Aetiology
14.5	Evaluation of treatments & therapeutic interventions
12.4	Health & social care services research
7.0	Development of treatments & therapeutic interventions
5.2	Detection, screening and diagnosis
4.9	Management of disease and conditions
4.5	Prevention of disease & conditions & promotion of wellbeing

On average, less than 4% of UK mental health research (£4.5m) goes directly on prevention.

UK Mental Health Research Funding Report. MQ Landscape Analysis. April, 2015

Reasons for lack of prevention in mental health

- It is not possible

- It is too expensive

Efficacy of primary prevention in child and adolescent mental health

Table III. Mean Effect Sizes and 95% Confidence Intervals for Primary Prevention

Type of program	*n*	Mean effect[a]	95% CI
Environment-centered			
School-based	15	0.35	0.30–0.43
Parent training	10	0.16	–0.04–0.36
Transition programs			
Divorce	7	0.36	0.15–0.56
School entry/change	8	0.39	0.27–0.58
First-time mothers	5	0.87	0.66–1.07
Medical/dental procedure	26	0.46	0.35–0.58
Person-centered programs			
Affective education			
Children 2–7	8	0.70	0.49–0.91
Children 7–11	28	0.24[b]	0.18–0.31
Children over 11	10	0.33	0.18–0.48
Interpersonal problem solving			
Children 2–7	6	0.93	0.66–1.19
Children 7–11	12	0.36	0.23–0.48
Children over 11	0	—	—
Other person-centered programs			
Behavioral approach	26	0.49	0.38–0.59
Nonbehavioral approach	16	0.25	0.06–0.44

[a] All means differ significantly from zero except for Parent training.
[b] Only category in which mean effects are heterogeneous.

Can treatment of childhood disorders prevent adult mental disorders?

Does Stimulant Therapy of Attention-Deficit/Hyperactivity Disorder Beget Later Substance Abuse? A Meta-analytic Review of the Literature

Timothy E. Wilens, MD*‡; Stephen V. Faraone, PhD*‡; Joseph Biederman, MD*‡; and Samantha Gunawardene, BS*

Study	Protective Effect (OR)	
	OR	95% CI
Meta-analysis of drug studies		
Lambert[15]	0.47	0.22–1.0
Biederman[14]	3.9	1.8–8.1
Huss[26]	2.2	0.99–5.1
Loney[25]	1.1	0.46–2.8
Molina[21]	4.6	1.5–14.5
Barkley	0.83	0.29–2.3
Meta-analysis of alcohol studies		
Lambert[15]	0.6	0.32–1.1
Biederman[14]	8.1	3.9–17.2
Loney[25]	3.6	1.7–7.4
Molina[21]	6.6	1.4–30.2
Barkley	0.98	0.36–2.7

ORs>1 indicate protective effect of stimulant use

Pooled OR=1.9.
CI [1.1-3.6], p=0.037

Pediatrics 2003;111;179-185

Reasons for lack of prevention in mental health

- It is not possible
- It is too expensive

Prevention in psychiatry pays off

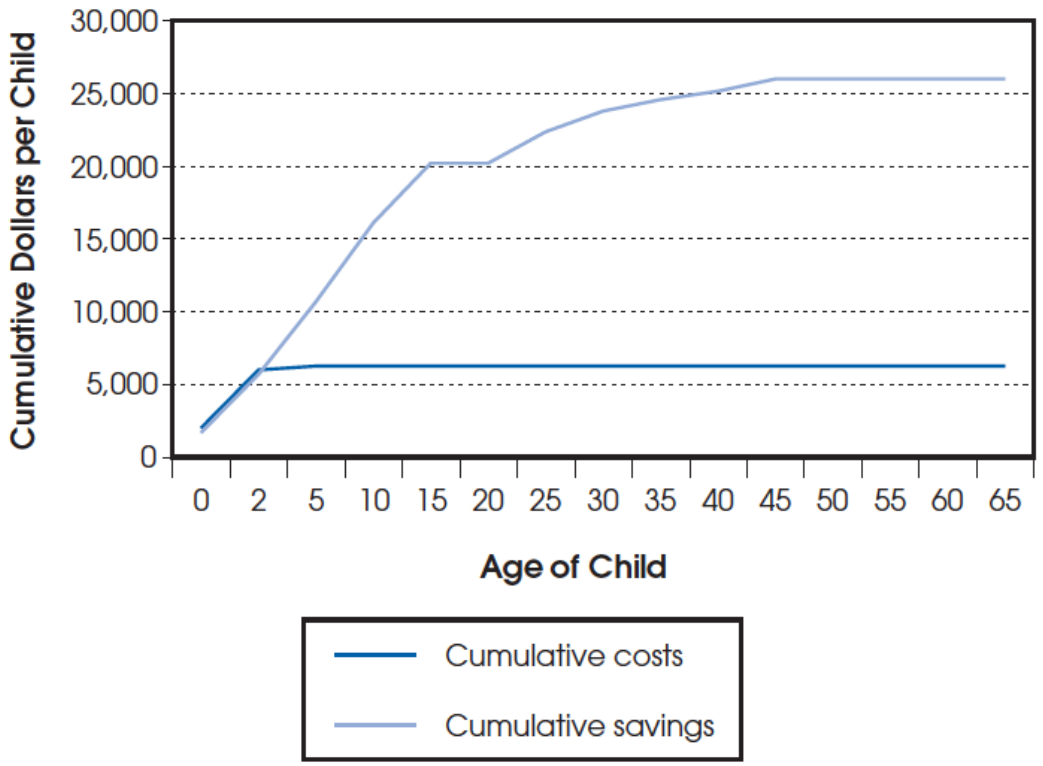
Table 13: Total returns on investment (all years): economic pay-offs per £1 expenditure [a]

	NHS	Other public sector	Non-public sector	Total
Early identification and intervention as soon as mental disorder arises				
Early intervention for conduct disorder	1.08	1.78	5.03	7.89
Health visitor interventions to reduce postnatal depression	0.40	–	0.40	0.80
Early intervention for depression in diabetes	0.19	0	0.14	0.33
Early intervention for medically unexplained symptoms [b]	1.01	0	0.74	1.75
Early diagnosis and treatment of depression at work	0.51	–	4.52	5.03
Early detection of psychosis	2.62	0.79	6.85	10.27
Early intervention in psychosis	9.68	0.27	8.02	17.97
Screening for alcohol misuse	2.24	0.93	8.57	11.75
Suicide training courses provided to all GPs	0.08	0.05	43.86	43.99
Suicide prevention through bridge safety barriers	1.75	1.31	51.39	54.45
Promotion of mental health and prevention of mental disorder				
Prevention of conduct disorder through social and emotional learning programmes	9.42	17.02	57.29	83.73
School-based interventions to reduce bullying	0	0	14.35	14.35
Workplace health promotion programmes	–	–	9.69	9.69
Addressing social determinants and consequences of mental disorder				
Debt advice services	0.34	0.58	2.63	3.55
Befriending for older adults	0.44	–	–	0.44

Knapp, McDaid and Parsonage, 2011

An example of a cost-efficient preventive intervention in children

Cumulative Costs and Savings for High-Risk Families in Elmira, NY, Nurse Home Visitation Program by Age of Child



Source: Reprinted with permission from Karoly, L.A., Greenwood, P.W., Everingham, S.S., et al. *Investing in our children: What we know and don't know about the costs and benefits of early childhood interventions.* Santa Monica, CA: RAND Corporation, 1998.

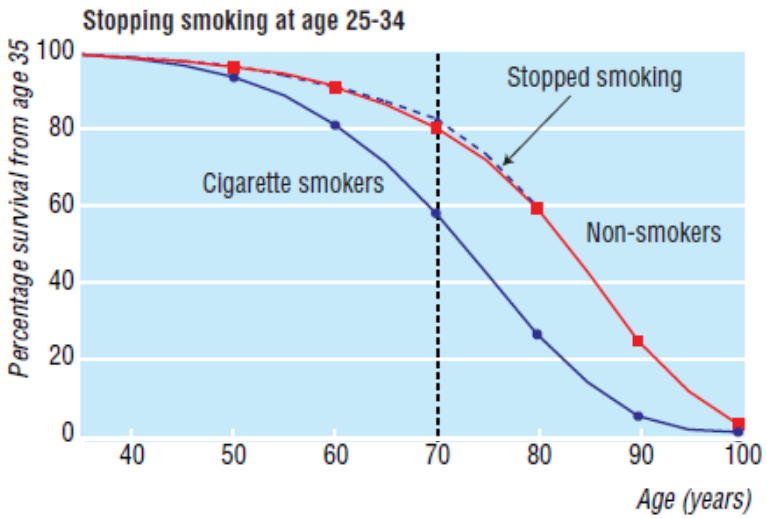
Reasons for lack of prevention in mental health

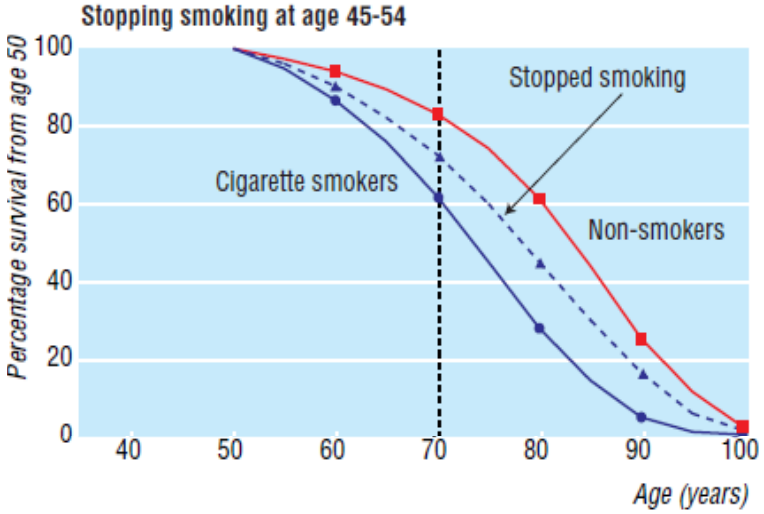
- It is not possible
- It is too expensive

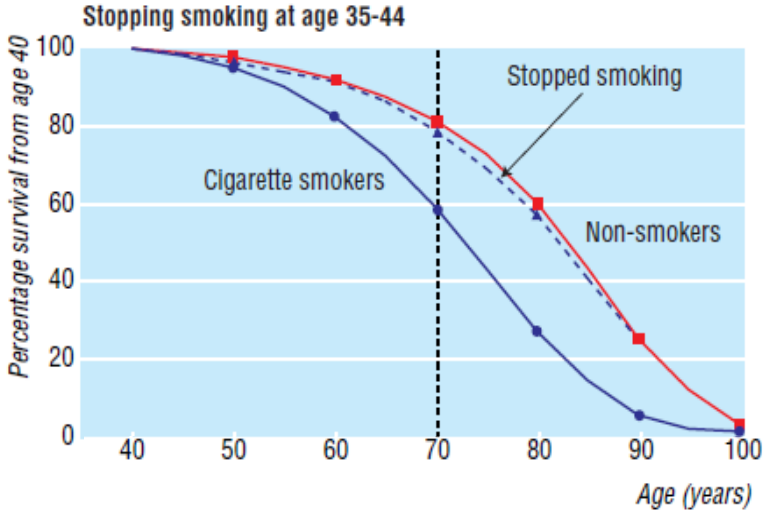
Why we get it all (or almost all) wrong?

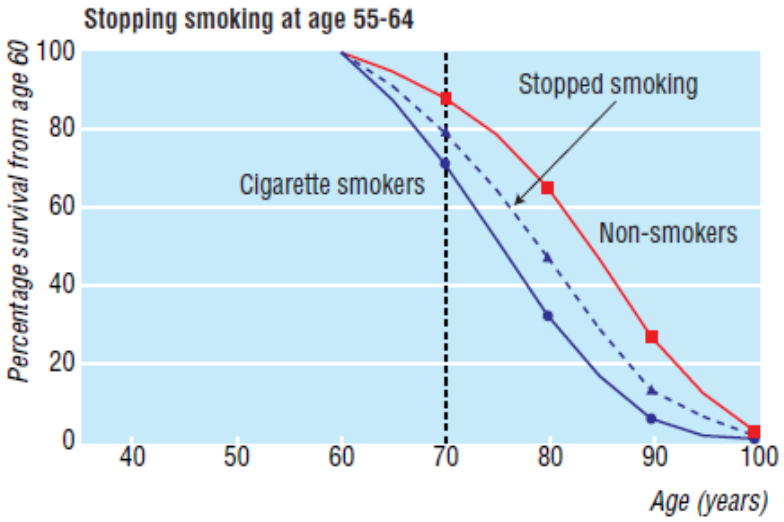
- *We act too late*

Efficacy of preventive interventions in medicine: Reduction in mortality by quitting smoking





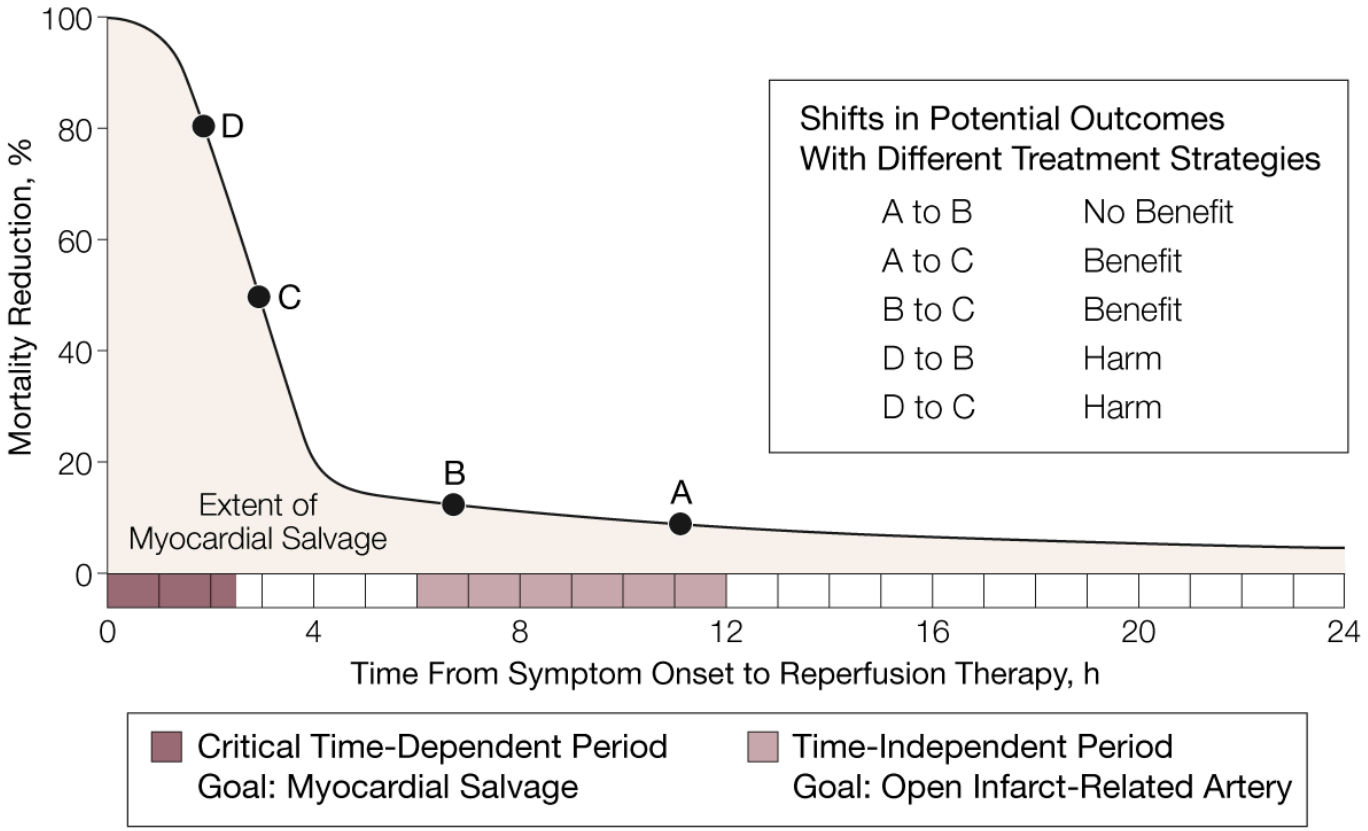




Doll et al., BMJ 2004

Critical periods for intervention

Theoretical Model of the Relationship Among the Duration of Symptoms of Acute MI Before Reperfusion Therapy, Mortality Reduction, and Extent of Myocardial Salvage



Gersh et al.,

JAMA, February 23, 2005—Vol 293, No. 8

Speakers's notes to the previous slide:

Critical periods of intervention: **For myocardial infarction the ultimate goal of treatment and the optimal therapeutic option also depend on the time point when the intervention strategy is implemented**.

Mortality reduction as a benefit of reperfusion therapy is greatest in the first 2 to 3 hours after the onset of symptoms of acute myocardial infarction (MI), most likely a consequence of myocardial salvage. The exact duration of this critical early period may be affected by several factors, including the presence of functioning collateral coronary arteries, ischemic preconditioning, myocardial oxygen demands, and duration of sustained ischemia. After this early period, the magnitude of the mortality benefit is much reduced, and as the mortality reduction curve flattens, time to reperfusion therapy is less critical. If a treatment strategy, such as facilitated percutaneous coronary intervention (PCI), is able to move patients back up the curve, a benefit would be expected. The magnitude of the benefit will depend on how far up the curve the patient can be shifted. The benefit of a shift from points A or B to point C would be substantial, but the benefit of a shift from point A to point B would be small. A treatment strategy that delays therapy during the early critical period, such as patient transfer for PCI, would be harmful (shift from point D to point C or point B). **Between 6 and 12 hours after the onset of symptoms, opening the infarct-related artery is the primary goal of reperfusion therapy, and primary PCI is preferred over fibrinolytic therapy.**

Eur Child Adolesc Psychiatry
DOI 10.1007/s00787-013-0434-6

EDITORIAL

Why psychogeriatrics starts right after adolescence

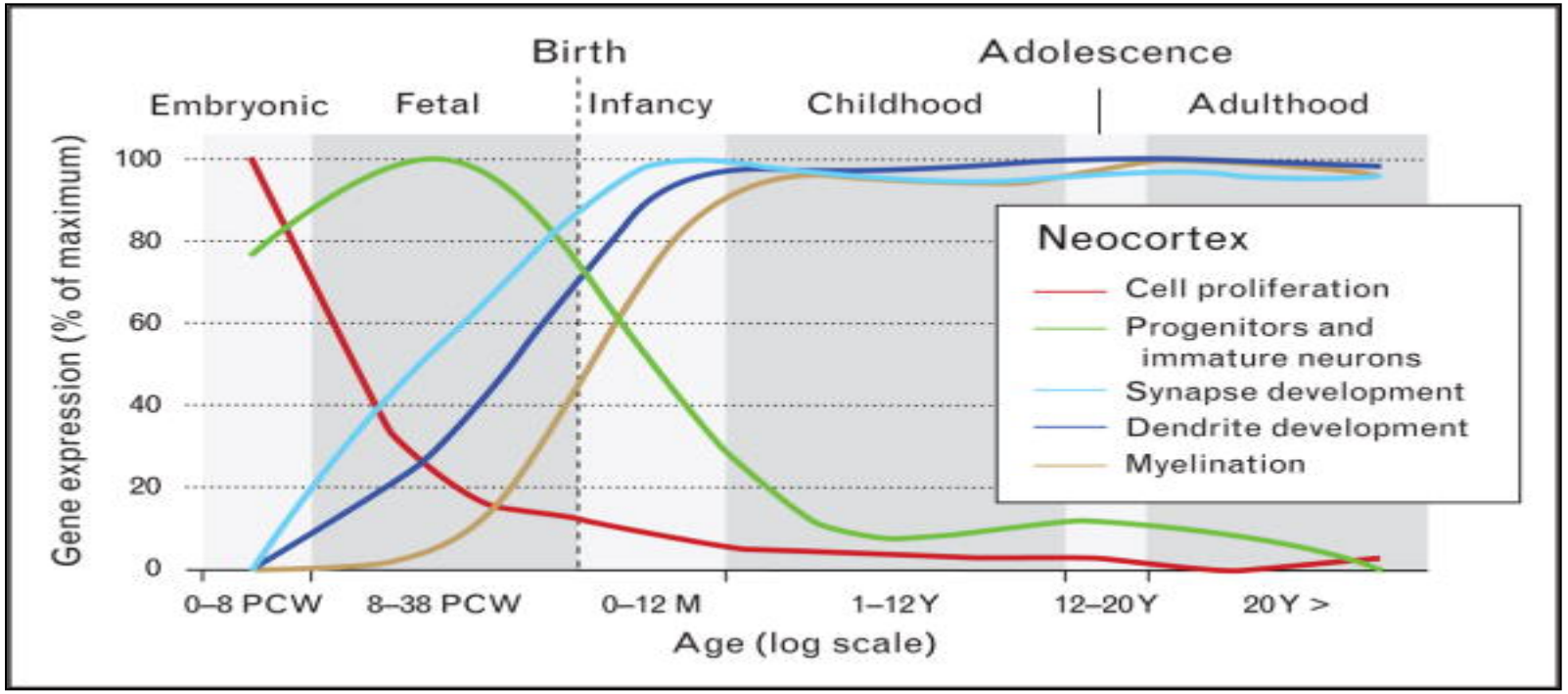
Mara Parellada

© Springer-Verlag Berlin Heidelberg 2013

The borders between pediatric and adult medical specialties are always somewhat artificial, and based on spurious considerations, such as usually attaining the age of majority, i.e., 18 years; however, the borders between so-called child and adolescent (C&A) psychiatry and adult

females at 11.8 years [2]. The visual, auditory, and limbic cortices, which myelinate early, show a more linear pattern of aging than the frontal and parietal neocortices, which continue myelination into adulthood. Except for the posterior temporal regions, which have a more protracted

Critical periods for intervention

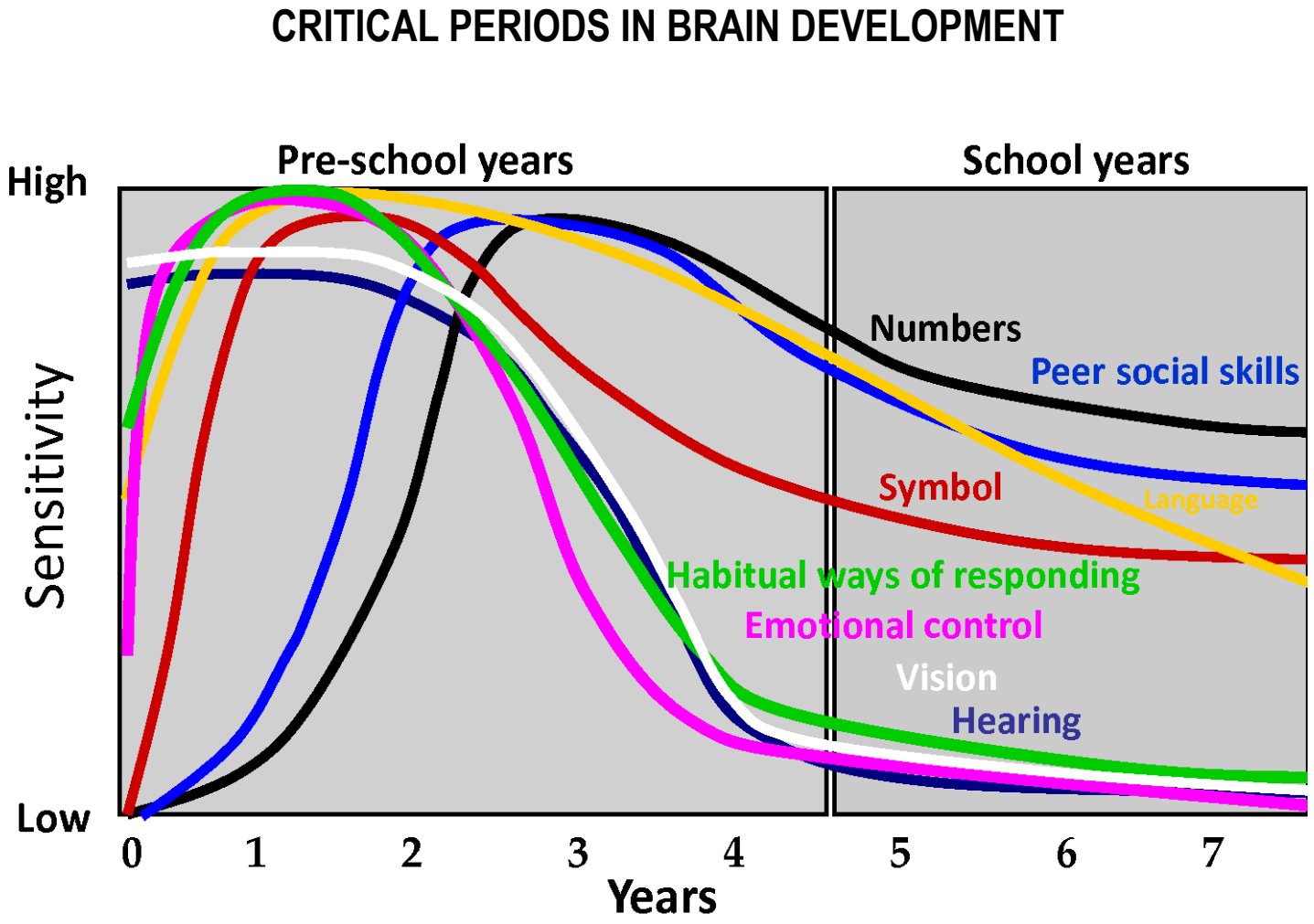


Graph developed by Council for Early Child Development (Nash 1997, Early Years Study 1999, Shonkoff 2000)

Speaker's notes to the previous slide:

The onset of the first psychiatric symptoms in children may be already too late. In subjects with vulnerability, symptoms arise according to the stage of development (pathoplasty). For example at age 6, the most common forms of manifestation of vulnerability will be inattention-hyperactivity, anxiety and cognitive difficulties, as other cognitive functions are still immature. **As time goes by, this vulnerability can crystallise into different phenotypic expressions**. This means that it is difficult to establish the moment "before" the illness arises, when prevention could take place, as ADHD symptoms for instance may already represent an early manifestation of an adult disorder such as BD or schizophrenia.

Critical periods for intervention



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Critical periods for intervention

AN EXAMPLE: EARLY INTERVENTION IN AUTISM

TABLE 3.
Treatment Outcomes for Children in Groups 1 and 2 and for the Total Sample

		Percent (and number) of children who	
Group	Total	Achieved Positive Treatment Outcome	Remained in Comprehensive Intervention Program
Group 1—Program entry at 60 months or earlier	100% (9)	67% (6)	33% (3)
Group 2—Program entry after 60 months	100% (9)	11% (1)	89% (8)
Total	100% (18)	39% (7)	61% (11)

$\chi^2 (1) = 5.86, p < .02$

Fenske et al., ***Analysis and Intervention in Developmental Disabilities***, Vol. 5, pp. 49–58, 1985

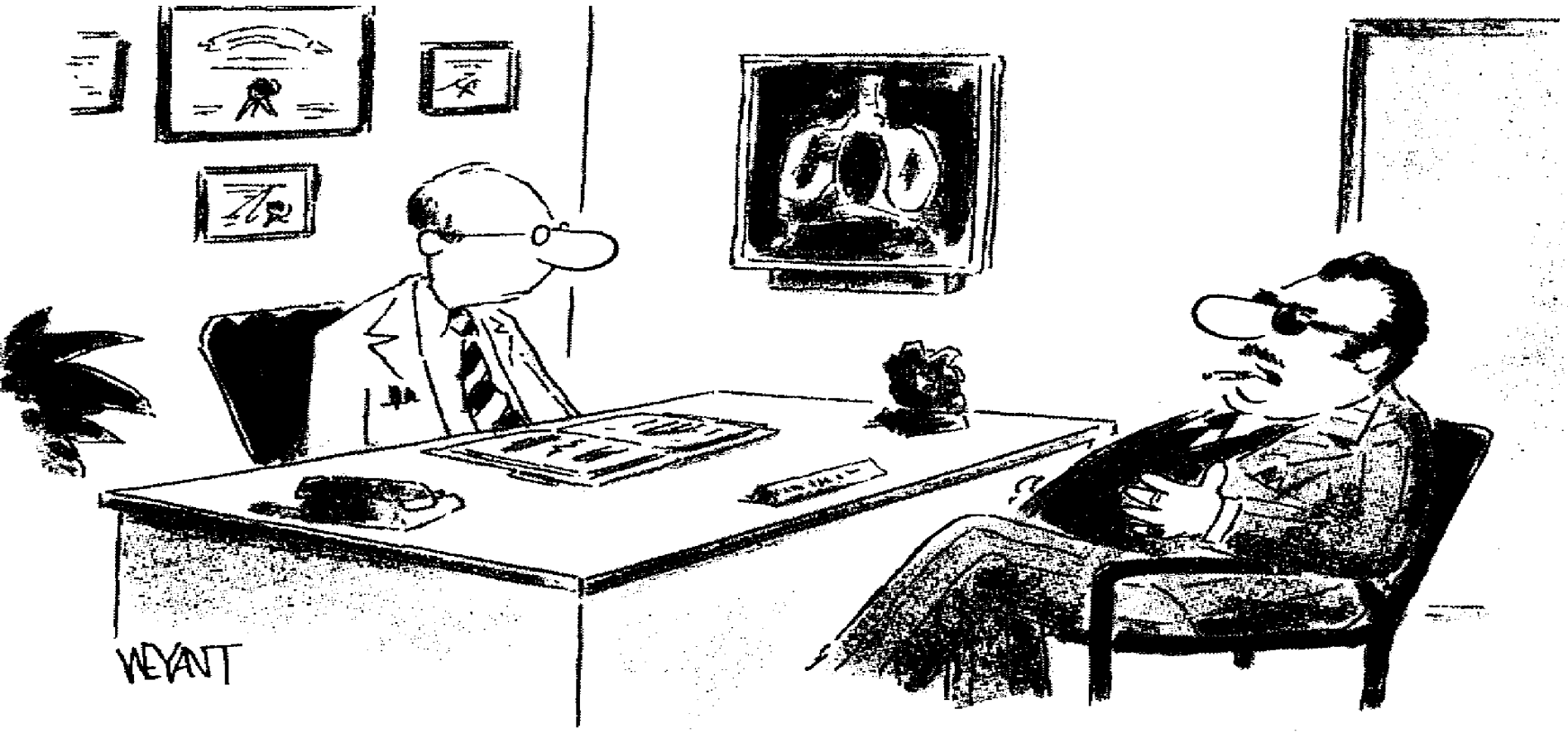
Speaker's notes to the previous slide:

This study compared treatment outcomes in nine autistic children who began receiving intensive behavioural intervention prior to 60 months of age with outcomes in nine other children who entered the same intervention programme after 60 months of age. The 18 children in the sample included all children served by the Princeton Child Development Institute's day school and treatment programme during the period 1975-83 who were diagnosed with autism and who had either (a) achieved positive discharge or (b) been enrolled in the programme for 24 months or longer and needed to continue receiving programme services. Age at programme entry was found to be strongly related to positive treatment outcome (i.e. children's continuing to live with their natural parents and attend mainstream school classes). This investigation underlines the importance of early behavioural intervention for children with autism.

Why do we get it all (or almost all) wrong?

- *We act too late*

- *Prevention is a politician's decision:*
  - *They are adults*
  - *They think this is something they will never use*
  - *Its pays off in the long term (and cannot be sold in the next 4 years)*



"So, Doc, what would it take to make my little 'problem' disappear?"

Don Juan de Palafox y Mendoza

“Kingdoms that govern with remedies rather than prevention are headed for disaster”

(June 26, 1600 – October 1, 1659)

Why do we get it all (or almost all) wrong?

- *We act too late*

- *Prevention is a politician's decision:*
  - *They are adults*
  - *They think this is something they will never use*
  - *Its pays off in the long term (and cannot be sold in the next 4 years)*

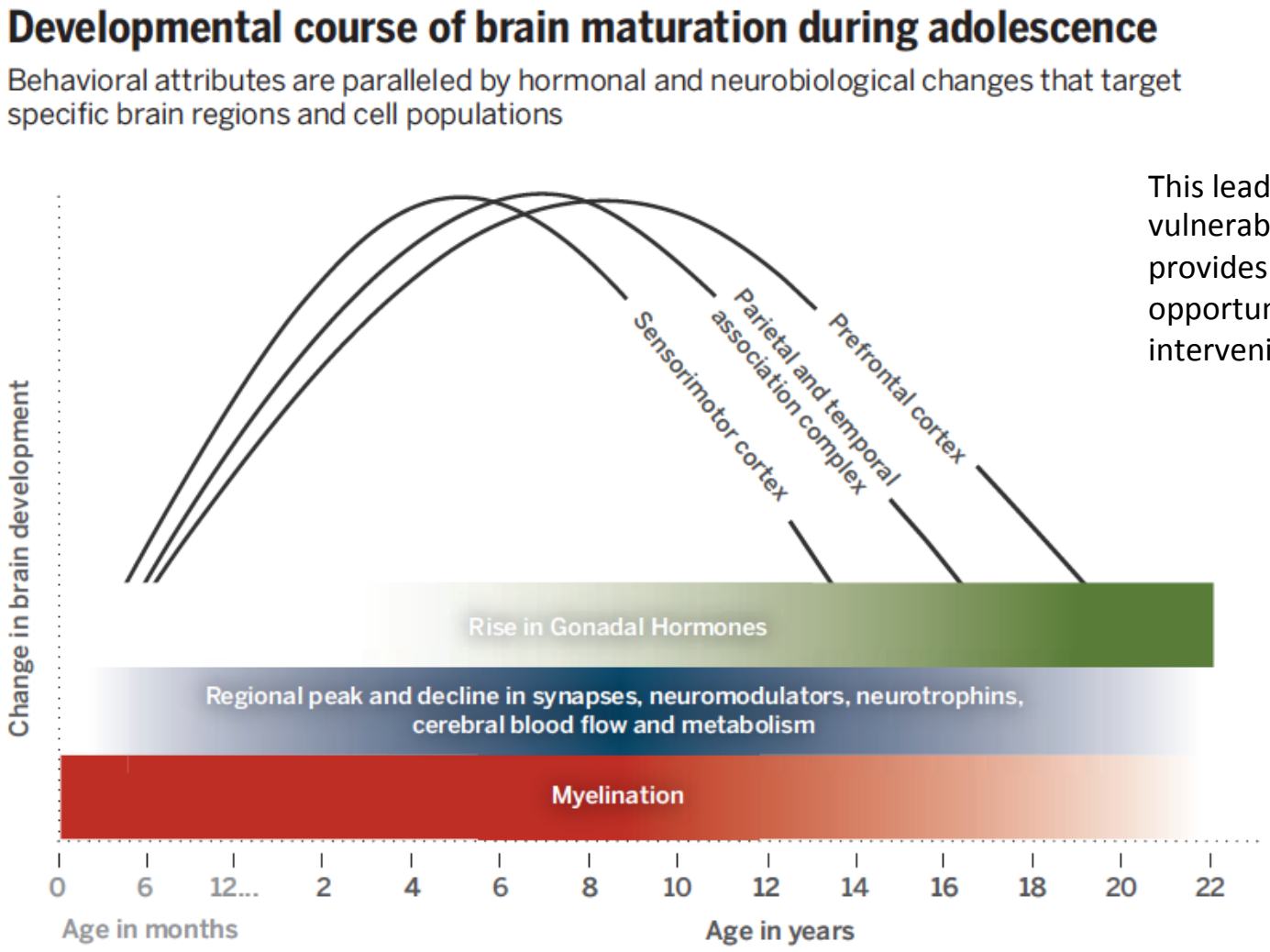
- *Lack of integration between child and adult services*


NO ADULTS
ALLOWED UNLESS
ACCOMPANIED
BY CHILDREN
SEC. 3.02 PARK CODE

Outline

- Prevention in psychiatry
- Psychotic (psychiatric disorders) as the reflection of abnormal developmental trajectories
- Shifting the focus towards prevention and early intervention in developmentally sensitive periods
- Implications and priorities for the future

Childhood and adolescence as phases of major changes



This leads to increased vulnerability but also provides windows of opportunity for intervening.

Lee, Heimer et al.,

SCIENCE sciencemag.org 31 OCTOBER 2014 • VOL 346 ISSUE 6209

Early developmental signs in psychosis

Newborn-3 months

Infancy
3-12 months

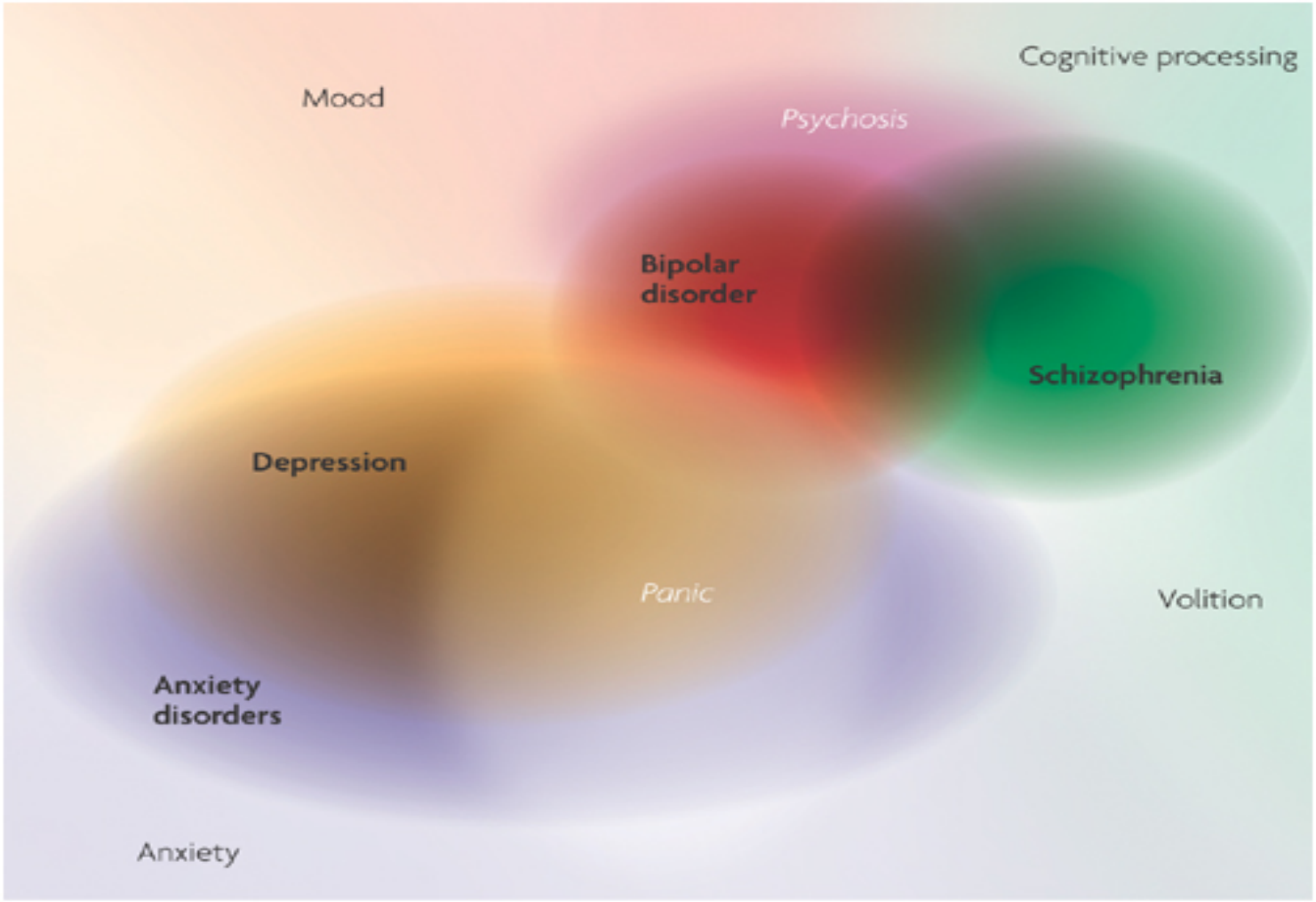
Toddler- Pre-schooler
1-4 years

Elementary school
5-12 years

	Newborn-3 months	Infancy 3-12 months	Toddler- Pre-schooler 1-4 years	Elementary school 5-12 years
Neuromotor and Minor Physical Anomalies		Sitting, walking, and standing delays	Potty training delays	Poor coordination and clumsiness, unusual movements
Speech/Language/ Hearing			Delays in speech and in receptive language, hearing impairments	Poor abnormal speech acquisition and quality; abnormal language including echolalia, meaningless laughter
Socioemotional Behavior			Preference for solitary play; less joy, more negative affect	More internalizing and externalizing disorders, psychotic symptoms at age 11-14
Cognition			Poorer IQ scores	Poorer IQ scores, declines in IQ scores from 4-7 years, poorer performance in other cognitive tasks

Adapted from Liu et al. Schizophrenia Bulletin, 2015.

What are we trying to prevent when we try to prevent psychosis?



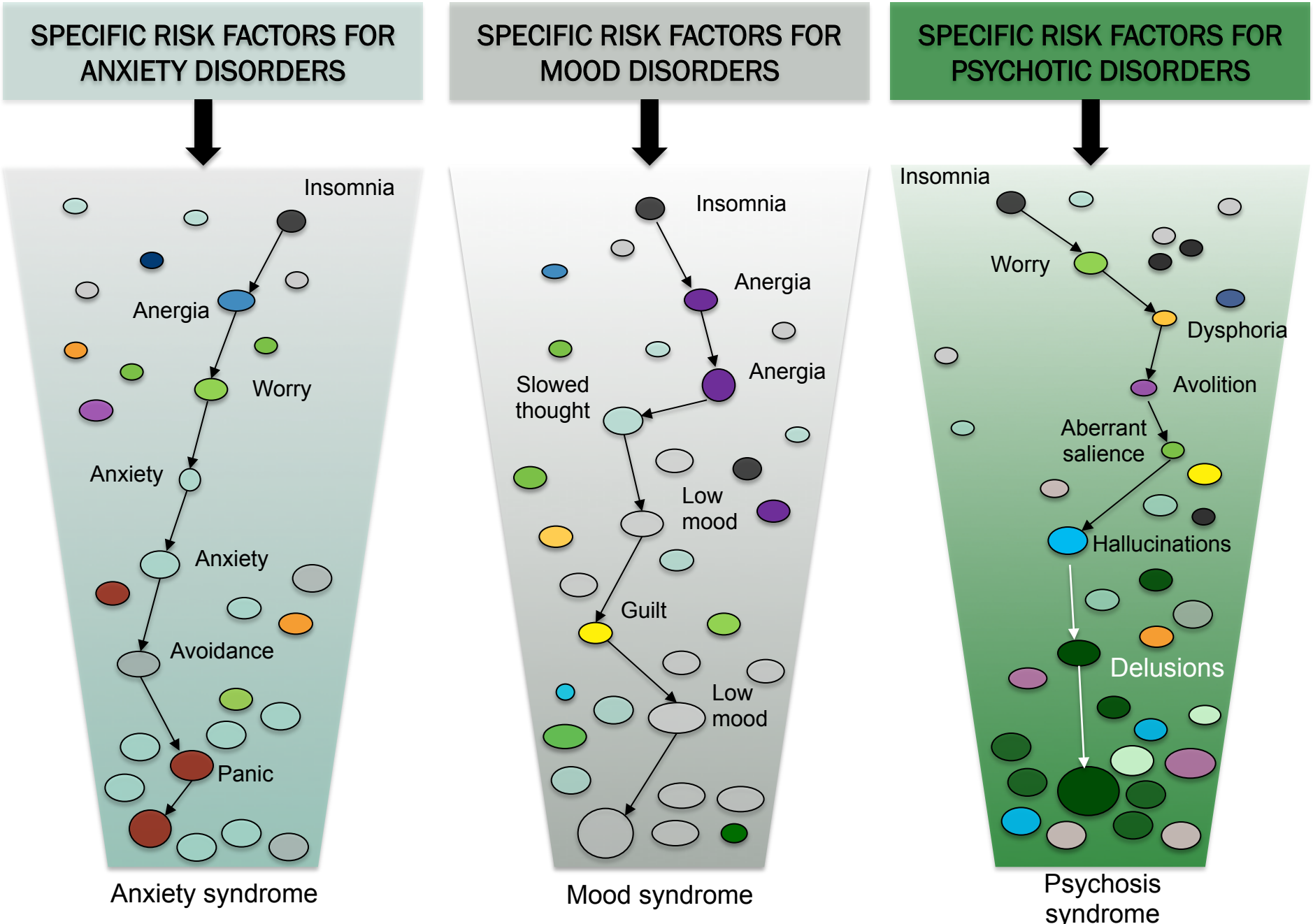
Burmeister et al.,

Speaker's notes to the previous slide:

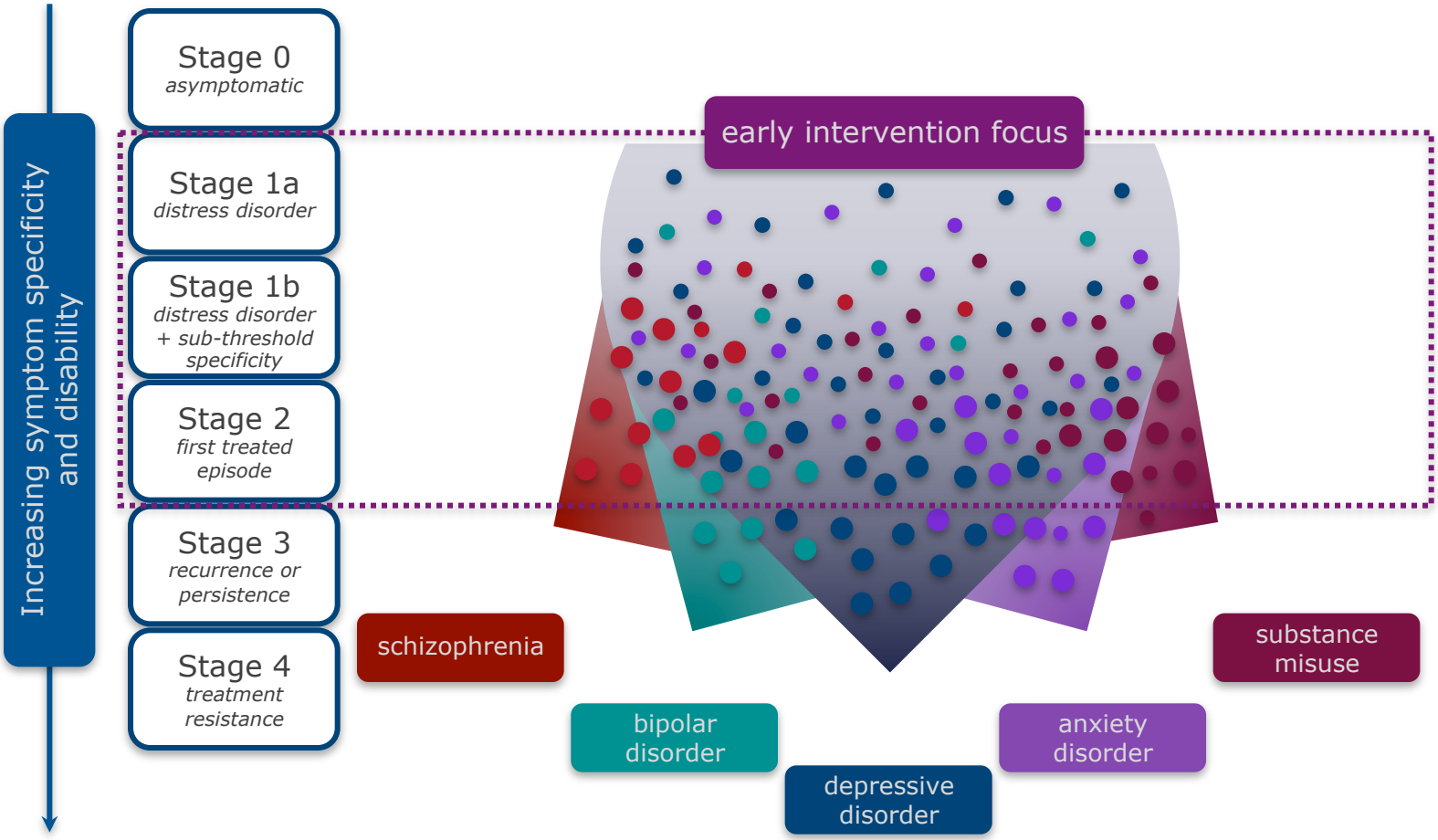
Psychiatric disorders often overlap and might be extremes of personality traits.

Genetic vulnerabilities for psychiatric disorders are shown as emerging from the extreme end of normal population variations of personality, illustrated as different background shades of mood, anxiety, cognitive processing and volition. Genetic factors affecting levels of these underlying traits, in interaction with additional genetic and environmental factors, can lead to psychiatric disorders subsequently shown here are bipolar disorder, schizophrenia, depression and anxiety disorders — the symptoms and genetic risk factors of which are in part unique and in part overlapping. Psychosis and panic are pathological traits and are not a formal diagnostic category, but are associated with several psychiatric diagnoses. Because not all disorders can be covered in two dimensions; interactions and overlaps exist in many more dimensions than can be represented here (for example, depression and anxiety are also present in schizophrenia).

Risk factor silos and the pathways to specific (DSM5) conditions



Early manifestations of mental disorders are non-specific: pluripotentiality and staging



"The principle could be that we should allow no more specificity in the diagnostic term or label than is necessary to guide treatment selection."

Shared genetic risk factors among neurodevelopmental disorders

Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis

*Cross-Disorder Group of the Psychiatric Genomics Consortium**

Summary

Background Findings from family and twin studies suggest that genetic contributions to psychiatric disorders do not in all cases map to present diagnostic categories. We aimed to identify specific variants underlying genetic effects shared between the five disorders in the Psychiatric Genomics Consortium: autism spectrum disorder, attention deficit-hyperactivity disorder, bipolar disorder, major depressive disorder, and schizophrenia.

Methods We analysed genome-wide single-nucleotide polymorphism (SNP) data for the five disorders in 33 332 cases and 27 888 controls of European ancestory. To characterise allelic effects on each disorder, we applied a multinomial logistic regression procedure with model selection to identify the best-fitting model of relations between genotype

Lancet 2013; 381: 1371–79

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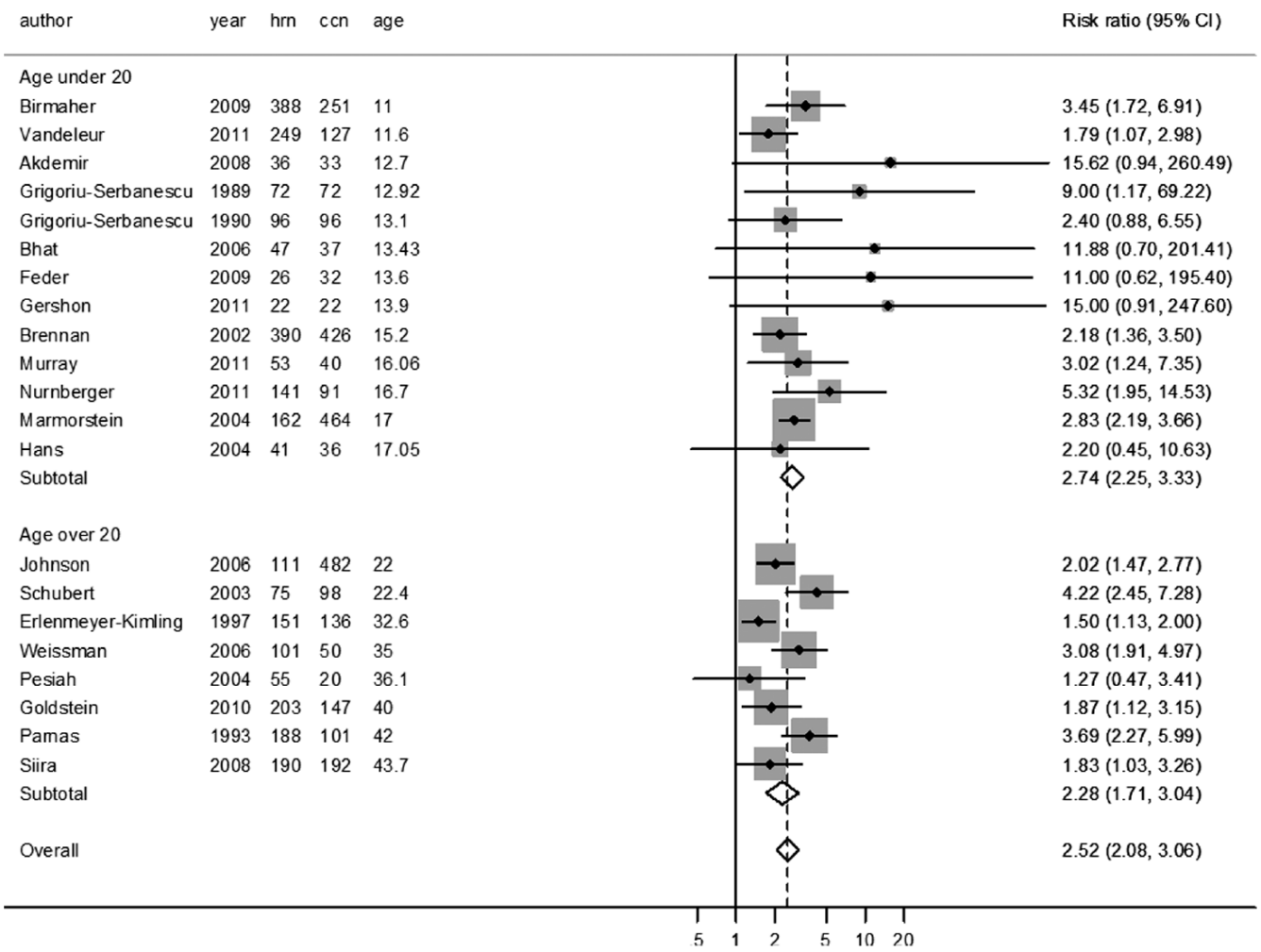
This online publication has been corrected. The corrected version first appeared at thelancet.com on April 19, 2013

PGC, Lancet, 2013

Speaker's notes to the previous slide:

- Genes involved in neuroplasticity provide susceptibility for the development of schizophrenia, BD and schizoaffective disorder.
- Fig. 1. Simplified hypothesised relationship between specific susceptibility genes (above the black line) and clinical phenotype (below the line) using the model outlined in Craddock and Owen. The overlapping ellipses represent overlapping sets of genes: red influencing susceptibility to phenotypes with prominent schizophrenia-like features, blue to prominent mood features, and green to phenotypes with a prominent mix of both types of feature. These assignments are based on current data and are likely to require revision as more data accumulate.

Psychopathology in the offspring of patients with schizophrenia, bipolar disorder or depression

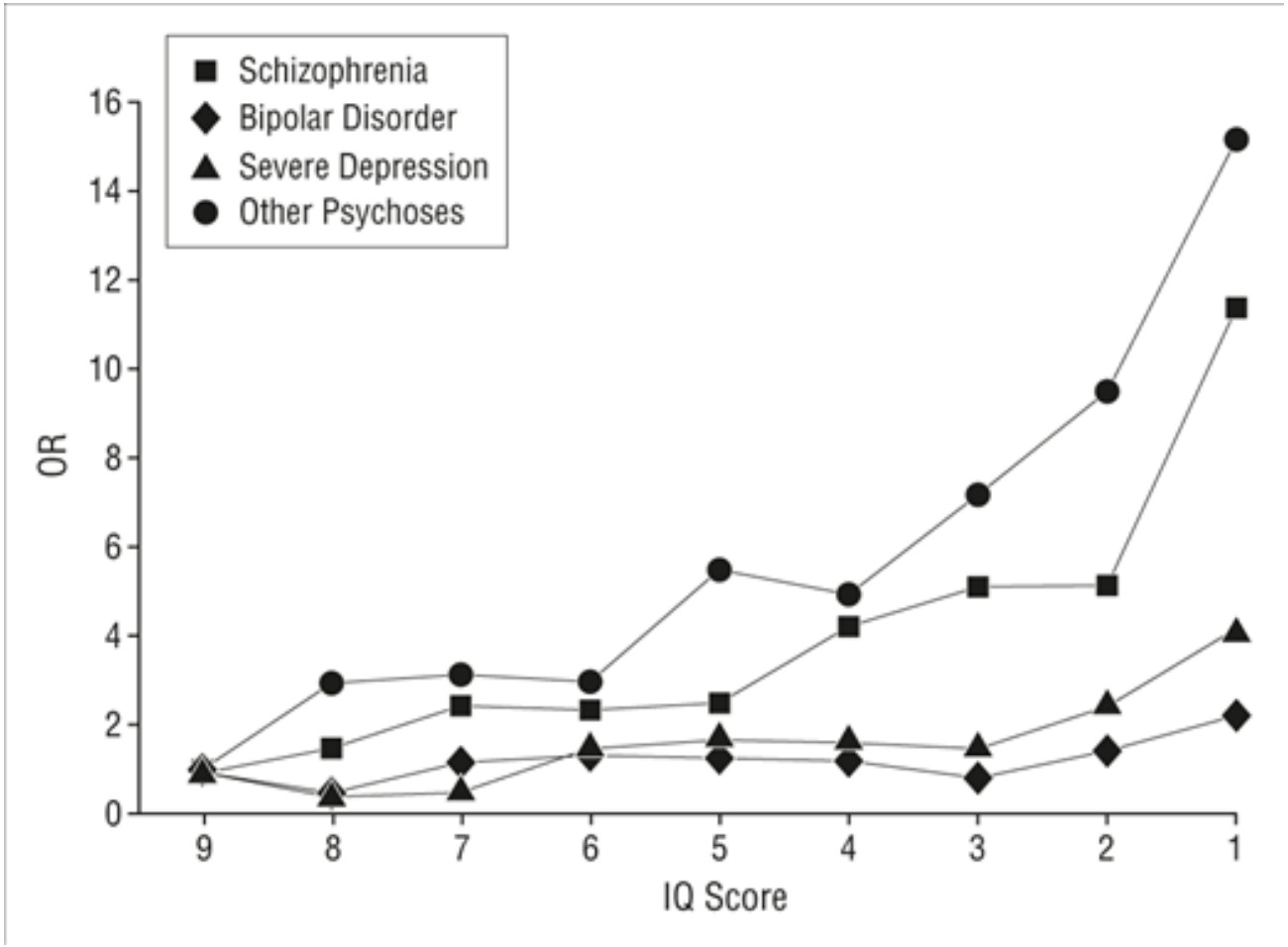


Rasic et al., Schiz Bulletin 2014

Speaker's notes to the previous slide:

- Meta-analyses of absolute and relative rates of mental disorders in offspring of parents with schizophrenia, bipolar disorder, **or depression** in family high-risk studies published by December 2012. *Results:* We included 33 studies with 3863 offspring of parents with SMI and 3158 control offspring.
- **Offspring of parents with SMI had a 32% probability of developing SMI by early adulthood** (95% CI: 24%–42%) by adulthood (age >20). This risk was more than twice that of control offspring (**risk ratio [RR] 2.52**; 95% CI 2.08–3.06, *P* < .001). High-risk offspring had a significantly increased rate **of the disorder present in the parent (RR = 3.59**; 95% CI: 2.57–5.02, *P* < .001) **and of other types of SMI (RR = 1.92**; 95% CI: 1.48–2.49, *P* < .001). **The risk of mood disorders was significantly increased among offspring of parents with schizophrenia (RR = 1.62**; 95% CI: 1.02–2.58; *P* = .042). The risk of schizophrenia was significantly increased in offspring of parents with bipolar disorder (RR = 6.42; 95% CI: 2.20–18.78, *P* < .001) but not among offspring of parents with depression (RR = 1.71; 95% CI: 0.19–15.16, *P* = .631).

Children with low IQ are at risk of psychosis and other mental disorders



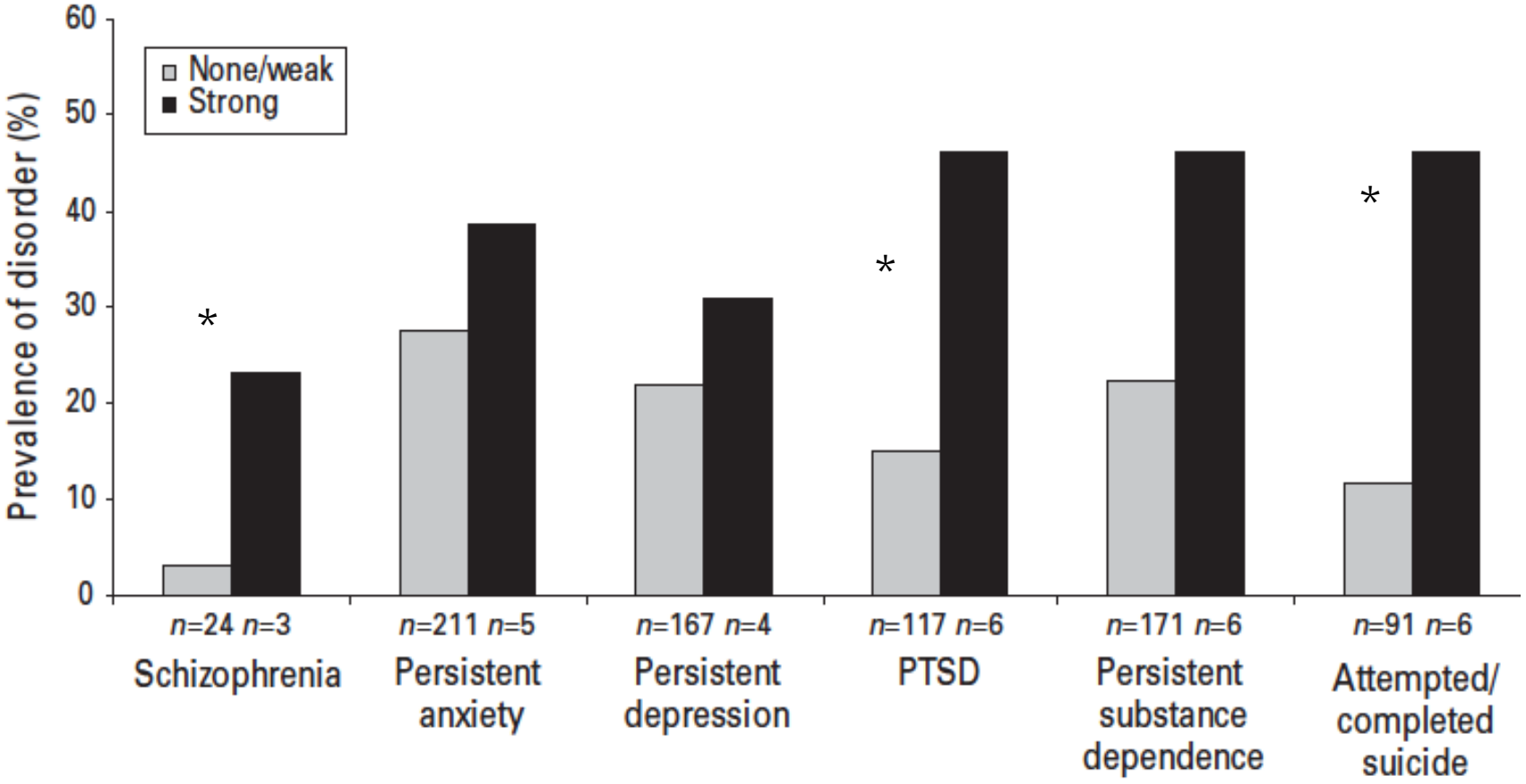
Zammit et al., Arch Gen Psychiatry. 2004;61(4):354-360.

Speaker's notes to the previous slide:

- Adjusted odds ratios (ORs) plotted against IQ scores for schizophrenia, bipolar disorder, severe depression, and other non-affective psychoses. Highest IQ score (coded as 9) is the baseline category (OR = 1.0).

- **Participants** Population-based sample of 50 087 male subjects. Data were available on IQ score at conscription and on other social and psychological characteristics.
- **Main Outcome Measures** *International Classification of Diseases, Eighth Revision* or *Ninth Revision* diagnoses of schizophrenia, bipolar disorder, severe depression, and other non-affective psychoses.
- **Results** There was no association between premorbid IQ score and risk of bipolar disorder. **Lower IQ was associated with increased risk of schizophrenia, severe depression, and other non-affective psychoses.** Risk of schizophrenia was increased in subjects with average IQ compared with those with high scores, indicating that risk is spread across the whole IQ range.

Psychotic symptoms in childhood as a marker of general vulnerability



H. L. Fisher et al.

Psychological Medicine (2013), **43**, 2077–2086.

Schizophrenia Bulletin vol. 41 no. 4 pp. 963–970, 2015
doi:10.1093/schbul/sbu119
Advance Access publication September 5, 2014

Risk of Schizophrenia Increases After All Child and Adolescent Psychiatric Disorders: A Nationwide Study

Cecilie Frejstrup Maibing[*,1,4], Carsten Bøcker Pedersen[2–4], Michael Eriksen Benros[1,2,4], Preben Bo Mortensen[2,4], Søren Dalsgaard[2,4–6], and Merete Nordentoft[1,6]

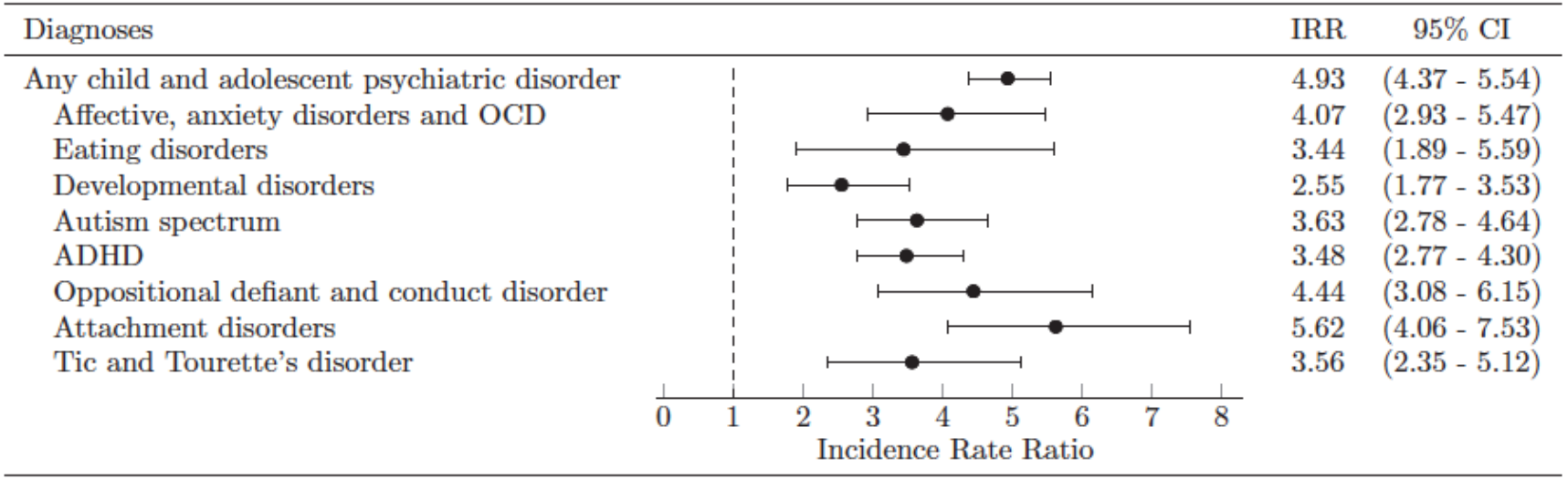


Fig. 1. Risk of schizophrenia spectrum disorders >5 years after onset of child and adolescent psychiatric disorders.

Speaker's notes to the previous slide:

- Methods: Danish nationwide registers were linked to establish a cohort consisting of all individuals born during 1990–2000 and the cohort was followed until
- 31 December 2012. Data were analysed using survival analyses and adjusted for calendar year, age, and sex.

- Results: A total of 25,138 individuals with child and adolescent psychiatric disorders were identified, of whom 1232 individuals were subsequently diagnosed with schizophrenia spectrum disorders. The risk of schizophrenia spectrum disorders was highly elevated, particularly within the first year after onset of the child or adolescent psychiatric disorder, and remained significantly elevated for >5 years with an **incidence rate ratio of 4.93** (95% confidence interval: 4.37–5.54).We utilized the cumulated incidences and found that among individuals diagnosed with a child or adolescent psychiatric disorder **between ages 0–13 years and 14–17 years, 1.68% and 8.74 %, respectively, will be diagnosed with a schizophrenia spectrum disorder within <8 years**

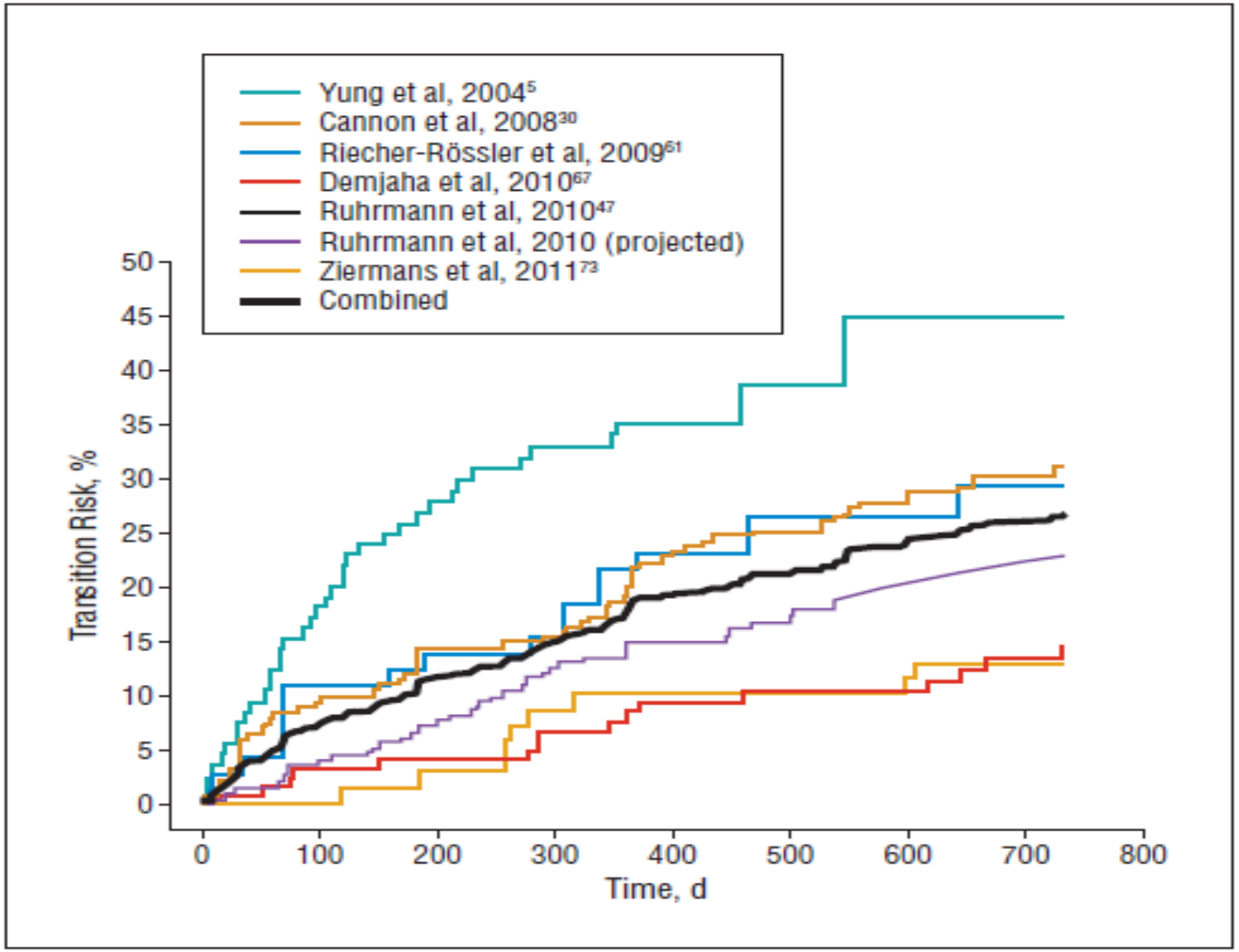
Are “prodromal” subjects healthy people at high risk for psychosis?

Table 2
SCID diagnoses.

SCID-IV diagnosis	Clinical high risk (N=360)	Control (N=108)	Significance of χ^2
Depression — current	41.4%	1.7%	<0.0001
Depression — lifetime	35.1%	5.6%	<0.0001
Lifetime alcohol	10.7%	1.1%	<0.0001
Current cannabis abuse	5.8%	1.1%	<0.05
Lifetime cannabis abuse	12.8%	2.8%	<0.001
Current OCD	7.8%	0%	<0.0001
Lifetime OCD	4.6%	0%	<0.01
Current PTSD	2.6%	0%	<0.05
Lifetime PTSD	4.1%	0%	<0.01
Current panic	13.3%	0.6%	<0.0001
Lifetime panic	9.3%	0%	<0.0001
Current social phobia	13.6%	0%	<0.0001
Lifetime social phobia	7.5%	0.6%	<0.0001
Current specific phobia	11.0%	0%	<0.0001
Lifetime specific phobia	6.4%	0.6%	<0.01
Current GAD or NOS	20.3%	2.2%	<0.0001
Lifetime GAD or NOS	9.0%	0.6%	<0.001
Current attention-deficit/hyperactivity	15.7%	1.7%	<0.0001
Lifetime attention-deficit/hyperactivity	10.8%	2.2%	<0.01
Current learning disorder NOS	2.3%	0%	<0.05
Current avoidant	10.4%	0%	<0.0001
Lifetime avoidant	4.6%	0%	<0.01
Current schizotypal	18.3%	0%	<0.0001
Lifetime schizotypal	7.2%	0%	<0.0001
Current borderline	3.8%	0%	<0.01

J. Addington et al. / Schizophrenia Research 142 (2012) 77–82

Transition rates in patients at ultra-high risk of psychosis are about one-third



Fusar-Poli et al., *Arch Gen Psychiatry. 2012;69(3):220-229*

Outcomes of Nontransitioned Cases in a Sample at Ultra-High Risk for Psychosis

TABLE 3. Course of Nonpsychotic Disorders in Young People at Ultra-High Risk for Psychosis at Baseline

	Entire Cohort (N=203)[a]		1993–2000 Subsample (N=61)[a]		2001–2003 Subsample (N=77)		2004–2006 Subsample (N=65)	
Status of Nonpsychotic Disorder	N	%	N	%	N	%	N	%
Present at baseline								
Any disorder	173	90.1	47	94.0	73	94.8	53	81.5
Any mood disorder	145	71.4	33	54.1	61	79.2	51	78.5
Any anxiety disorder	81	39.9	21	34.4	34	44.2	26	40.0
Any substance use disorder	42	21.9	17	34.0	21	27.3	4	6.1
Remitted								
Any disorder	50	26.0	12	24.0	22	28.6	16	24.6
Any mood disorder	67	33.0	13	21.3	31	40.3	23	35.4
Any anxiety disorder	48	23.6	13	21.3	22	28.6	13	20.0
Any substance use disorder	20	10.4	7	14.0	12	15.6	1	1.5
Incident								
Any disorder	72	37.5	24	48.0	24	31.2	24	36.9
Any mood disorder	19	9.3	9	14.8	4	5.2	6	9.2
Any anxiety disorder	36	17.7	13	21.3	11	14.3	12	18.5
Any substance use disorder	33	17.2	7	14.0	12	15.6	14	21.5
Persistent or recurrent								
Any disorder	99	51.6	29	58.0	40	51.9	30	46.1
Any mood disorder	78	38.4	20	32.8	30	39.0	28	43.1
Any anxiety disorder	33	16.2	8	13.1	12	15.6	13	20.0
Any substance use disorder	22	11.5	10	20.0	9	11.7	3	4.6
Never present								
Any disorder	14	7.3	5	10.0	3	3.9	6	9.2
Any mood disorder	39	19.2	19	31.1	12	15.6	8	12.3
Any anxiety disorder	86	42.3	27	44.3	32	41.6	27	41.5
Any substance use disorder	117	60.9	26	52.0	44	57.1	47	72.3

Lin, Wood, Nelson et al., Am J Psychiatry, 2015

Speaker's notes to the previous slide:

- However, non-transitioned cases also show significant rates of psychopathology. The CHR states seem to represent general states of vulnerability to the development of different types of psychopathological outcomes.

- Results: At follow-up (2-14 years), 28% of the participants reported attenuated psychotic symptoms. Over the follow-up period, **68% experienced nonpsychotic disorders: mood disorder in 49%, anxiety disorder in 35%, and substance use disorder in 29%. For the majority (90%), nonpsychotic disorder was present at baseline, and it persisted for 52% of them**. During follow-up, 26% of the cohort had remission of a disorder, but 38% developed a new disorder. Only 7% did not experience any disorder at baseline or during follow-up. The incidence of nonpsychotic disorder was associated with more negative symptoms at baseline.

Preventing psychosis: when?

VIEWPOINT

Mental Disorders in Childhood
Shifting the Focus From Behavioral Symptoms to Neurodevelopmental Trajectories

Thomas R. Insel, MD
National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland.

Author Reading at jama.com

The recent Global Burden of Disease Study reported on morbidity and mortality for 291 disorders and injuries across 187 countries.[1] Expressed as "years lost to disability," mental and substance abuse disorders accounted for nearly 23% of global morbidity, more than any other group of disorders.[2] Although it may seem surprising that mental and substance abuse disorders would, by this measure, be more disabling than heart disease or cancer, at least part of the explanation velopment are extraordinary. In contrast to other organ systems, the brain develops, in part, through the exuberant overproduction of cells and connections, followed by a several-year sculpting of pathways by massive elimination of much of the neural architecture along with myelination of select fibers for rapid transmission of information. The human brain continues to develop into the third decade, with cortical maturation usually not completed until age 25.

Speaker's notes to the previous slide:

BEHAVIOURAL SYMPTOMS EXPRESSING PSYCHOSIS OF A VERY LATE PHASE OF NEURODEVELOPMENTAL DERAILMENT: Considering all these aspects, it is time to shift from an exclusive focus on behaviour- and symptom-based diagnosis to incorporate a deeper understanding of neurodevelopmental trajectories with interventions that can support the **healthy development of brain and behaviour.** Whether interventions are called preventive or preemptive,by identifying individuals at high risk or at very early stages of illness, early treatments can alter morbidity and mortality. But when **a group of disorders is defined as behavioural, knowing that behavioural symptoms are the final stage of a long-term pathological process, the opportunity** for early detection and early intervention **may be missed**.

Early developmental trajectories are inherently unpredictable, influenced by complex psychosocial factors, so the accuracy of a biological or cognitive predictor may be inherently less in childhood. There may be concerns that a label of "at risk" would do more harm than good for an early adolescent, especially if individuals who are false-positive are exposed to treatments with serious adverse effects. Both a scientific and ethical dilemma is created: improving the outcomes for psychotic disorders may require detection and intervention before psychosis, but the psychosocial consequences of early detection and intervention may render this approach unacceptable. Science may help resolve this dilemma. During the psychological and neurobiological journey of adolescence, most young people struggle with mood or cognitive changes that are transient and should not be labeled as risk factors. For those who seek help for specific features of the prodrome, including select cognitive changes and social withdrawal, especially for those with familial risk, there is a high probability of psychosis. Genetics and neuroimaging may soon define this risk more accurately.

What can be offered to a 15-year-old adolescent who is at high risk? It is important not to confuse a need for intervention with a call for pharmacological treatment. Novel approaches rely on emerging understanding of brain development, specifically the deficits in cortical circuits important for executive functions. **Targeted cognitive training using video games or other devices to build these circuits so that they are returned to a more normative developmental trajectory is an exciting new area of research for adolescents at risk. If a 15-year-old adolescent with prodromal features has been incorrectly labeled at risk, an intervention that improves cortical efficiency may still be useful for his or her intellectual and social development.**

Differential Neurodevelopmental Trajectories in Patients With Early-Onset Bipolar and Schizophrenia Disorders

Celso Arango*[,1,2], David Fraguas[1], and Mara Parellada[1]

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*To whom correspondence should be addressed; Hospital General Universitario Gregorio Marañón, Ibiza 43, 28009 Madrid, Spain; tel: 34-914265006; fax: 34-91426004, e-mail: carango@mprc.umaryland.edu

Schizophrenia and bipolar disorders share not only clinical features but also some risk factors such as genetic markers and childhood adversity, while other risk factors such as urbanicity and obstetric complications seem to be specific to schizophrenia. An intriguing question is whether the well-established abnormal neurodevelopment present in many children and adolescents who eventually develop schizo-

that the consequences of genetic predisposition and early adverse events, such as insults during gestation, would be latent throughout the first 2 decades of life and would only manifest as psychosis in early adulthood when normative maturational changes "unmask" an earlier insult. This hypothesis had been postulated some years earlier by John Strauss and William

Schizophrenia Bulletin vol. 40 suppl. no. 2 pp. S138–S146, 2014

The trajectory to schizophrenia

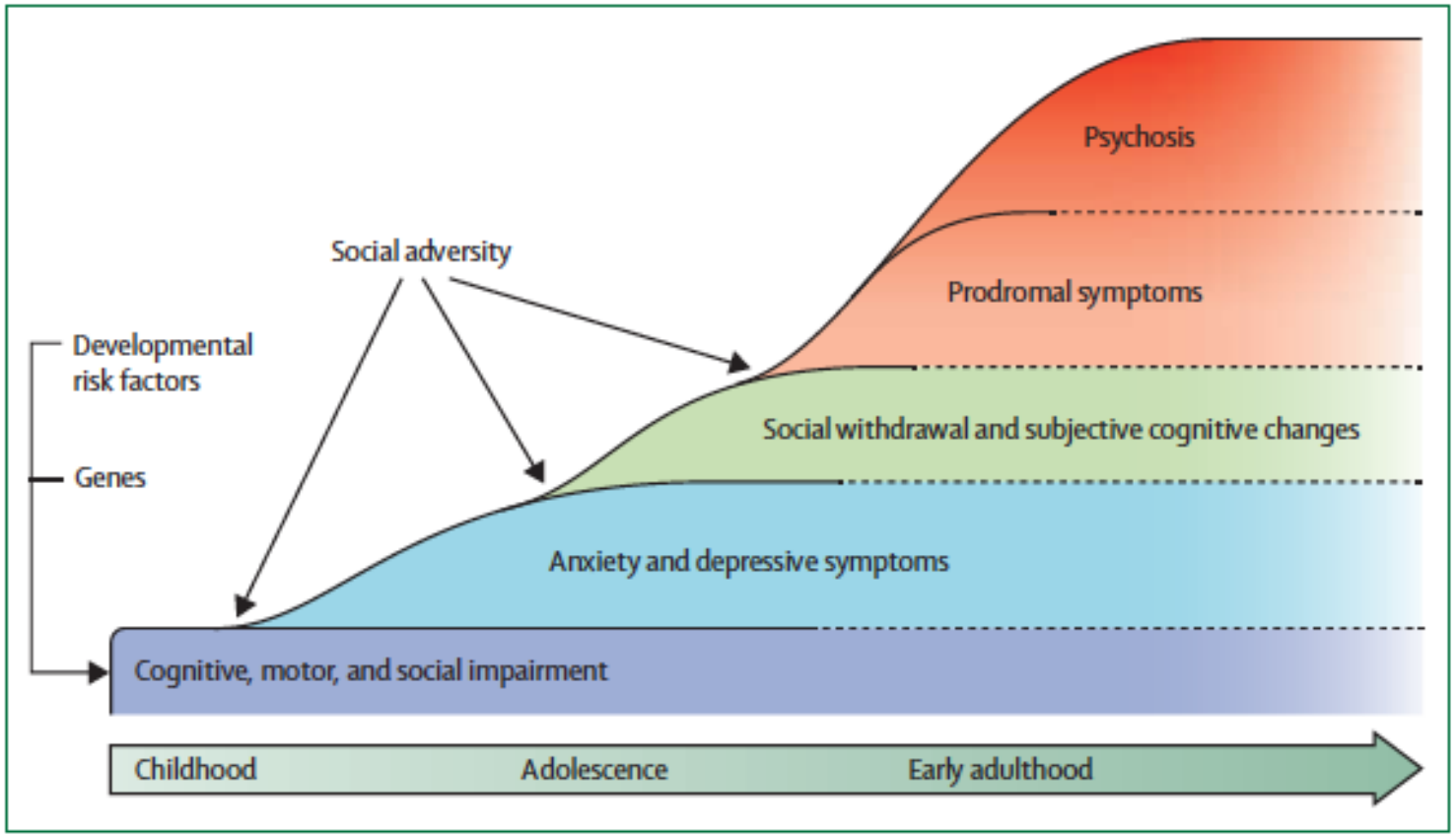


Figure 1: **The trajectory to schizophrenia showing the evolution of symptoms and the main risk factors**

Oliver D Howes, Robin M Murray

Lancet 2014; 383: 1677–87

Brain changes predate the onset of psychosis

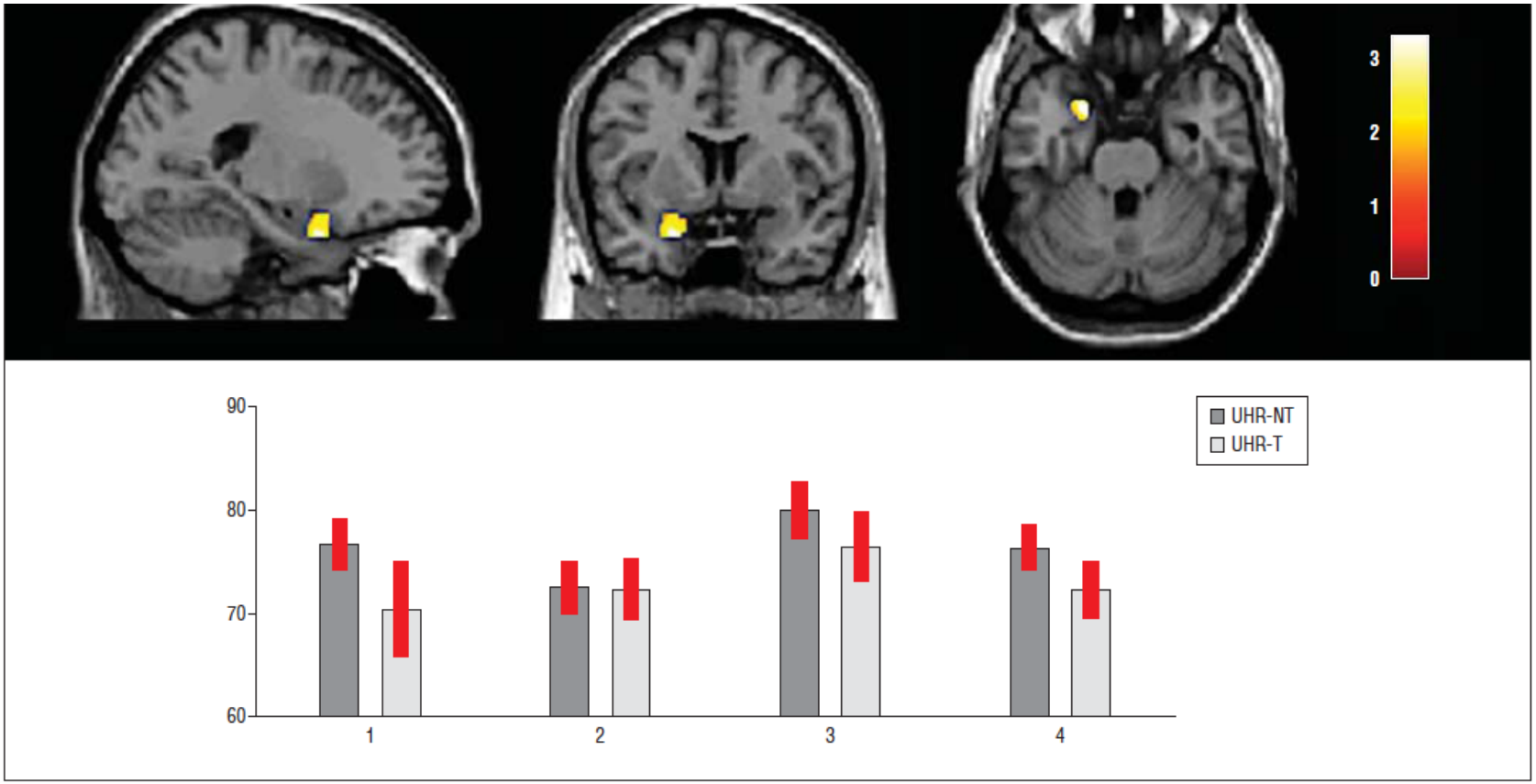


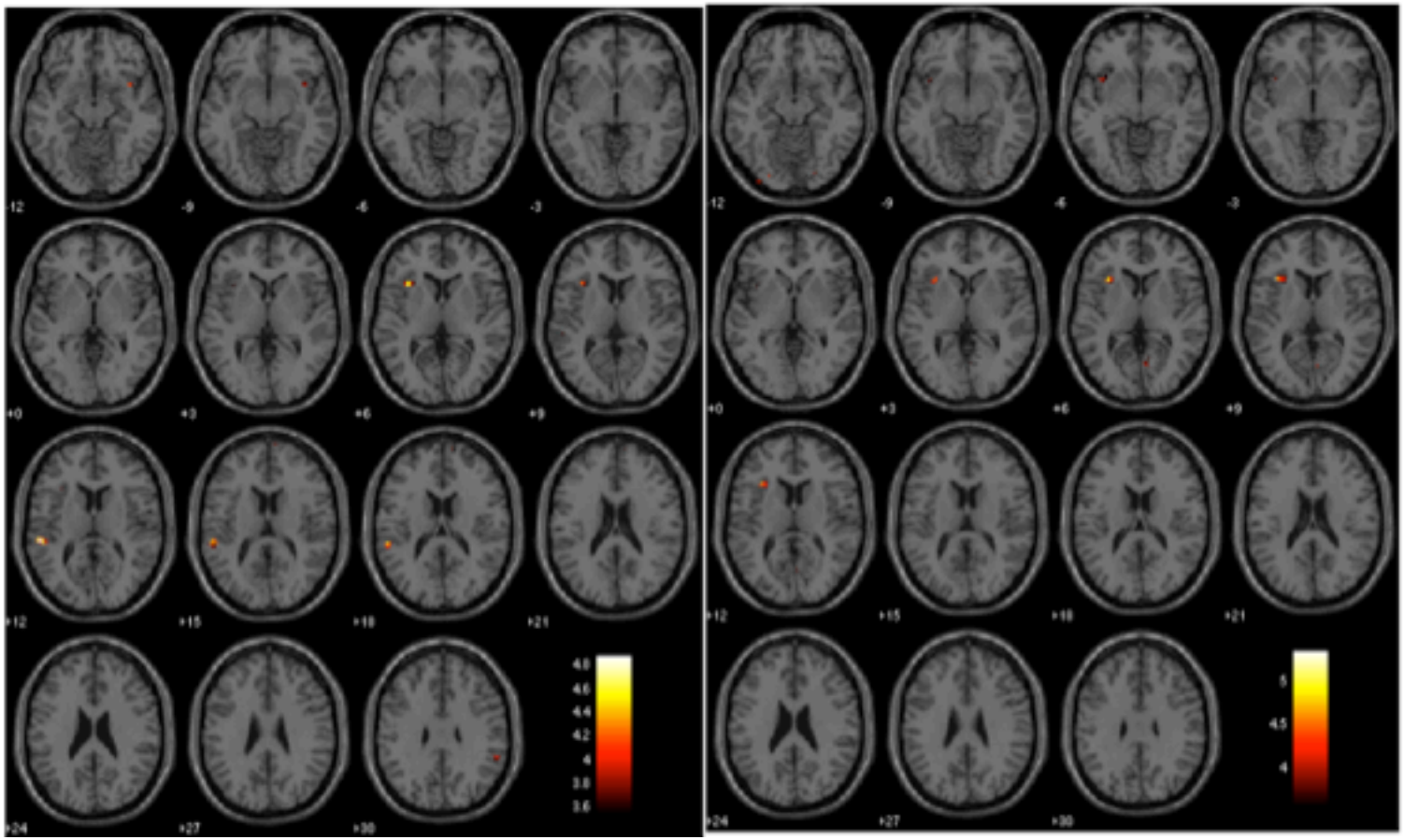
Figure 2. Differences between ultra-high-risk (UHR) individuals who did (UHR-T) and did not (UHR-NT) develop psychosis. The UHR-T individuals had less gray matter volume than did the UHR-NT individuals in the left parahippocampal gyrus, bordering the uncus (MNI [Montreal Neurological Institute] coordinates x, y, and z: –21, 6, and –27, respectively). For visualization purposes, effects are displayed at $P < .05$ uncorrected. The plot shows mean gray matter volumes for the 2

Mechelli et al.

ARCH GEN PSYCHIATRY/VOL 68 (NO. 5), MAY 2011

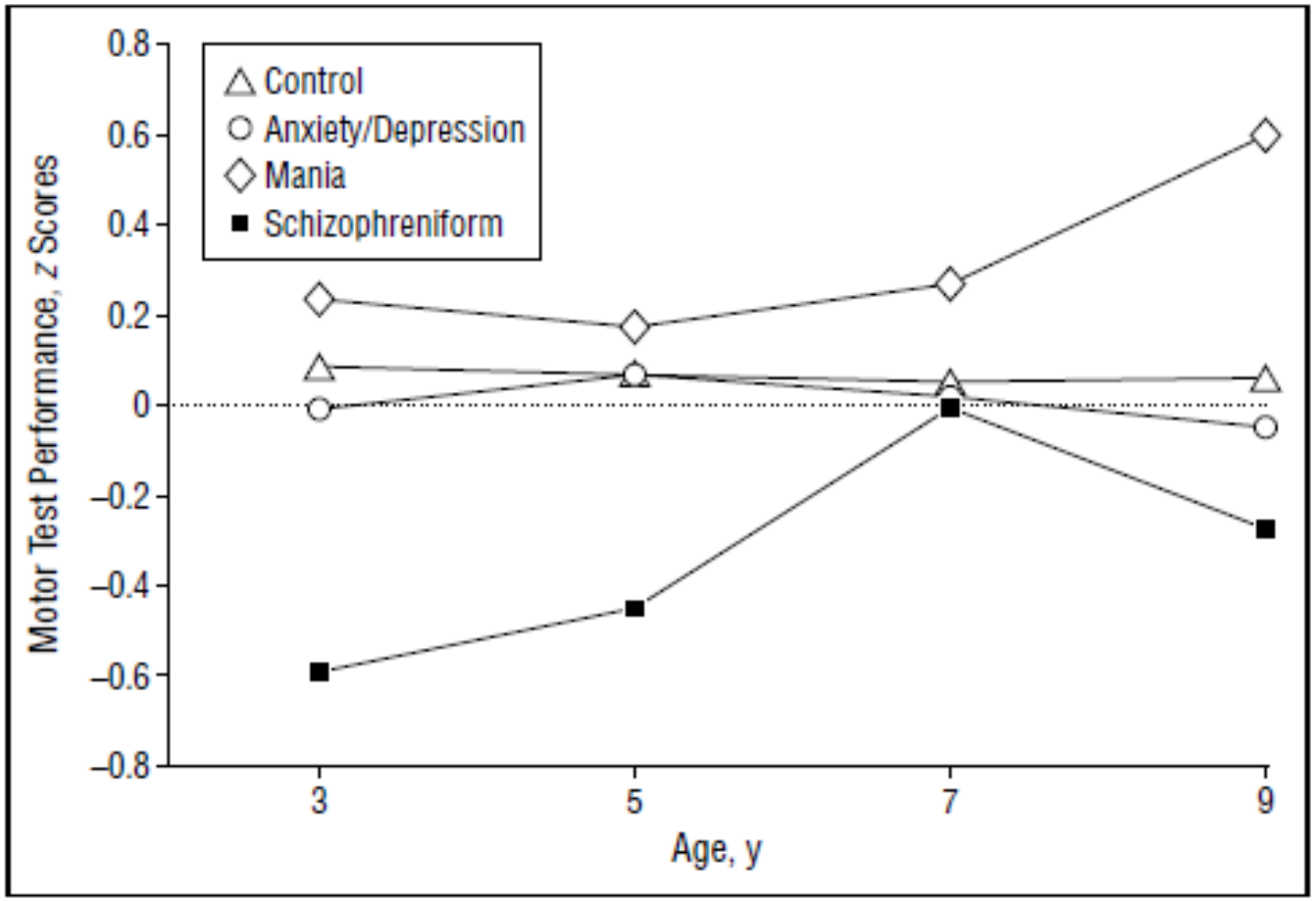
Brain changes are also present in child offspring of individuals with bipolar disorder or schizophrenia

Fig1. Significant clusters of relatively decreased gray matter volume in SzO relative to CcO and in SzO relative to BpO



Sugranyes et al., JAACAP. In press

Abnormalities in early motor development in psychosis



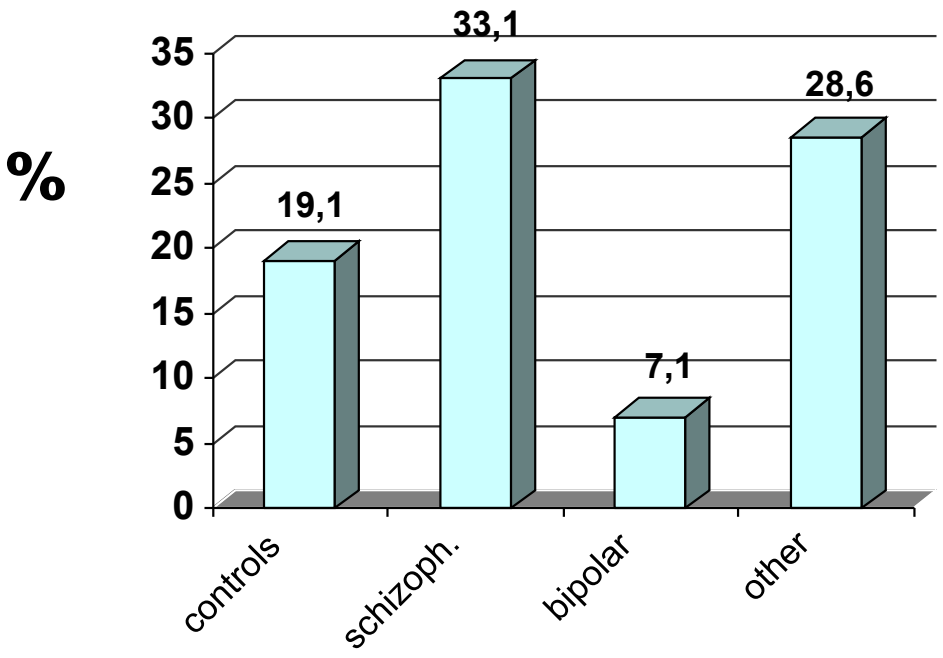
Cannon, Caspi et al., Arch Gen Psychiatry 2002

Speaker's notes to the previous slide:

Motor development in children who later (at age 26) develop BD, schizophrenia, anxiety disorders and controls between the ages of 3 and 9 (The Dunedin cohort). There seems to be a specific pattern of abnormal cognitive development for patients who later develop schizophreniform disorder or schizophrenia. Emotional problems and interpersonal difficulties were noted in children who later met diagnostic criteria for any of the adult psychiatric outcomes assessed. However, significant impairments in neuromotor, receptive language, and cognitive development were additionally present only among children later diagnosed as having schizophreniform disorder. Developmental impairments also predicted self-reported psychotic symptoms at age 11 years. These impairments were independent of the effects of socioeconomic, obstetric, and maternal factors.

Abnormalities in early motor development in early-onset psychosis

At least one psychomotor developmental deviance.



At least 2 Neurological Signs	Controls: 71.1%	EOP 95.9%	p<0.01

Parellada et al 2006, Mayoral 2009

Premorbid adjustment difficulties in EOP

Schizophrenia Research 146 (2013) 103–110

Contents lists available at SciVerse ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Premorbid impairments in early-onset psychosis: Differences between patients with schizophrenia and bipolar disorder

Beatriz Payá [a,*], Jose Manuel Rodríguez-Sánchez [a], Soraya Otero [a], Pedro Muñoz [b], Josefina Castro-Fornieles [c], Mara Parellada [d], Ana Gonzalez-Pinto [e], Cesar Soutullo [f], Inmaculada Baeza [c], Marta Rapado-Castro [d], Margarita Sáenz-Herrero [e], Dolores Moreno [d], Celso Arango [d]

Table 3
Childhood PAS scores in schizophrenia and bipolar disorder compared with healthy control group.

	SZ (N = 46)		BP (N = 23)		Controls (N = 91)		Statistic		Comparisons[a]
	χ	SD	χ	SD	χ	SD	F[b]	p	
Total PAS-C	0.36	0.21	0.28	0.16	0.12	0.10	**18.554**	**<0.001**	Controls<SZ***; Controls<BP***
PAS Acad-C	0.36	0.21	0.35	0.20	0.16	0.13	**5.784**	**0.004**	Controls<SZ**; Controls<BP*
PAS Social-C	0.36	0.28	0.21	0.21	0.08	0.13	**20.787**	**<0.001**	Controls<SZ***; controls<BP**
PAS1-C	2.24	1.93	1.13	1.52	0.53	0.87	**16.078**	**<0.001**	Controls<SZ***; BP<SZ*
PAS2-C	2.07	1.74	1.39	1.20	0.45	0.79	**20.280**	**<0.001**	Controls<SZ***; controls<BP***
PAS3-C	3.04	1.55	3.09	1.31	1.82	1.30	1.389	0.253	
PAS4-C	1.33	1.38	1.09	1.28	0.15	0.58	**11.003**	**<0.001**	Controls<SZ***; controls<BP**

Outline

- Prevention in psychiatry
- Psychosis (psychiatric disorders) as the reflection of abnormal developmental trajectories
- Shifting the focus towards prevention and early intervention in developmentally sensitive periods
- Implications and priorities for the future

Schizophrenia Bulletin vol. 41 no. 4 pp. 795–800, 2015
doi:10.1093/schbul/sbv050
Advance Access publication April 29, 2015

New Targets for Prevention of Schizophrenia: Is It Time for Interventions in the Premorbid Phase?

Absolutely!

Larry J. Seidman*[,1,2] and Merete Nordentoft[3,4]

- Evidence of premorbid developmental vulnerabilities to psychosis
- Promising results emerging from early, pre-emptive interventions during CHR phase
- Recognisition that the CHR is a relatively late phase of developmental derailment
- The staging perspective provides a framework for research and conceptualization of earlier premorbid interventions, perhaps beginning with pregnancy

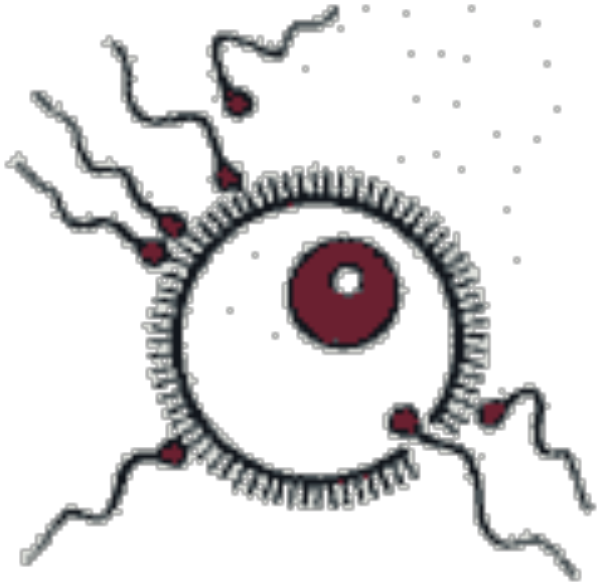
Clinical staging model framework for prevention and early intervention in psychotic and severe mood disorders

CLINICAL STAGE	DEFINITION	TARGET POPULATIONS	POTENTIAL INTERVENTIONS	INDICATIVE BIOLOGICAL AND ENDOPHENOTYPIC MARKERS
0	Increased risk of psychotic or severe mood disorder. No symptoms currently	1st degree teenage relatives of probands	Improved mental health literacy, family education, drug education, brief cognitive skills training	Trait marker candidates and endophenotypes, e.g. Smooth Pursuit Eye Movements, P50, niacin sensitivity, binocular rivalry, prepulse inhibition, Mismatch Negativity, olfactory deficits...
1a	Mild or non-specific symptoms, including neurocognitive deficits, of psychosis or severe mood disorder. Mild functional change or decline	Screening of teenage populations, referral by primary care physicians, referral by school counsellors	Formal mental health literacy, family psychoeducation, formal CBT, active substance abuse reduction	Trait and state candidates where feasible according to sample size
1b	Ultra high risk: moderate but subthreshold symptoms, with moderate neurocognitive changes and functional decline to caseness (GAF <70)	Referral by educational agencies, primary care physicians, emergency departments, welfare agencies.	Family psychoeducation, formal CBT, active substance abuse reduction, atypical antipsychotic agents for episode, antidepressant agents or mood stabilizers	Niacin sensitivity, folate status, MRI and MRS changes, HPA axis dysregulation
2	First episode of psychotic or severe mood disorder. Full threshold disorder with moderate-severe symptoms, neurocognitive deficits and functional decline (GAF 30–50).	Referral by primary care physicians, emergency departments, welfare agencies, specialist care agencies, drug and alcohol services	Family psychoeducation, formal CBT, active substance abuse, reduction, atypical antipsychotic agents for episode, antidepressant agents or mood stabilizers, vocational rehabilitation	Continue with markers of illness state, trait and progression
3a	Incomplete remission from FE of care. Could be linked or fast-tracked to Stage 4	Primary and specialist care services	As for '2' with additional emphasis on medical and psychosocial strategies to achieve full remission	Continue with markers of illness state, trait and progression
3b	Recurrence or relapse of psychotic or mood disorder which stabilizes with treatment at a level of GAF, residual symptoms, or neurocognition below the best level achieved following remission from first episode	Primary and specialist care services	As for '3a' with additional emphasis on relapse prevention and 'early warning signs' strategies	Continue with markers of illness state, trait and progression
3c	Multiple relapses, provided worsening in clinical extent and impact of illness is objectively present	Specialist care services	As for '3b' with emphasis on long-term stabilization	Continue with markers of illness state, trait and progression
4	Severe, persistent or unremitting illness as judged on symptoms, neurocognition and disability criteria. Note: could fast track to this stage at first presentation through specific clinical and functional criteria (from stage 2) or alternatively by failure to respond to treatment (from stage 3a)	Specialized care services	As for '3c' but with emphasis on clozapine, other tertiary treatments, social participation despite ongoing disability	Continue with markers of illness state, trait and progression

Cory et al.

Australian and New Zealand Journal of Psychiatry 2006; 40:616–622

Before conception



Maternal stress and delayed parenthood

Parental age

Table 2. Incidence Rate Ratios (IRRs) for Schizophrenia Associated With Parental Age

Age, y	IRR (95% Confidence Interval)				
	Unadjusted Model (Model 1)*	Adjusted for Age of Both Parents (Model 2)	Adjusted for Age and Psychiatric History of Both Parents (Model 3)	Full Model Adjusted for Family Psychiatric History and Socioeconomic Factors (Model 4)†	Full Model, Family History Negative Only (Model 5)
Paternal age					
<20	1.18 (1.01-1.39)	1.14 (0.97-1.35)	1.01 (0.93-1.30)	1.04 (0.88-1.23)	1.05 (0.85-1.29)
20-24	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
25-29	0.96 (0.90-1.03)	0.97 (0.90-1.04)	0.98 (0.91-1.05)	0.99 (0.92-1.07)	1.01 (0.93-1.11)
30-34	1.02 (0.95-1.10)	1.01 (0.93-1.10)	1.02 (0.93-1.11)	1.04 (0.95-1.13)	1.03 (0.93-1.14)
35-39	1.04 (0.95-1.13)	1.01 (0.91-1.12)	1.00 (0.90-1.11)	1.02 (0.91-1.13)	1.06 (0.93-1.20)
40-44	1.20 (1.08-1.34)	1.16 (1.02-1.32)	1.14 (1.00-1.30)	1.15 (1.00-1.31)	1.21 (1.03-1.42)
45-49	1.20 (1.02-1.41)	1.14 (0.95-1.37)	1.10 (0.92-1.32)	1.09 (0.90-1.31)	1.22 (0.98-1.51)
≥50	1.75 (1.41-2.16)‡	1.65 (1.32-2.08)	1.64 (1.30-2.06)	1.51 (1.19-1.92)	1.61 (1.21-2.13)
50-54	1.42 (1.09-1.84)	1.32 (1.00-1.74)	1.29 (0.98-1.71)	1.22 (0.92-1.62)	1.33 (0.95-1.86)
≥55	2.90 (2.05-4.11)	2.71 (1.89-3.88)	2.76 (1.92-3.96)	2.45 (1.69-3.54)	2.42 (1.56-3.77)
Maternal age					
<20	1.13 (1.04-1.23)	1.07 (0.98-1.18)	1.04 (0.95-1.14)	1.03 (0.94-1.13)	1.04 (0.93-1.16)
20-24	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
25-29	1.02 (0.96-1.08)	1.03 (0.96-1.09)	1.04 (0.98-1.11)	1.02 (0.96-1.09)	1.05 (0.97-1.13)
30-34	1.09 (1.02-1.17)	1.06 (0.98-1.15)	1.09 (1.00-1.18)	1.05 (0.97-1.14)	1.08 (0.98-1.20)
35-39	1.15 (1.05-1.26)	1.05 (0.94-1.18)	1.11 (0.99-1.24)	1.07 (0.95-1.20)	1.08 (0.94-1.24)
≥40	1.39 (1.20-1.62)‡	1.15 (0.97-1.37)	1.23 (1.03-1.46)	1.18 (0.98-1.41)	1.21 (0.99-1.49)
40-44	1.34 (1.14-1.58)	1.12 (0.94-1.34)	1.20 (1.00-1.44)	1.16 (0.96-1.39)	1.20 (0.97-1.48)
≥45	1.92 (1.26-2.94)	1.45 (0.93-2.26)	1.55 (0.99-2.42)	1.41 (0.90-2.24)	1.43 (0.86-2.39)

*Two separate models were conducted: model 1a for paternal age and model 1b for maternal age.

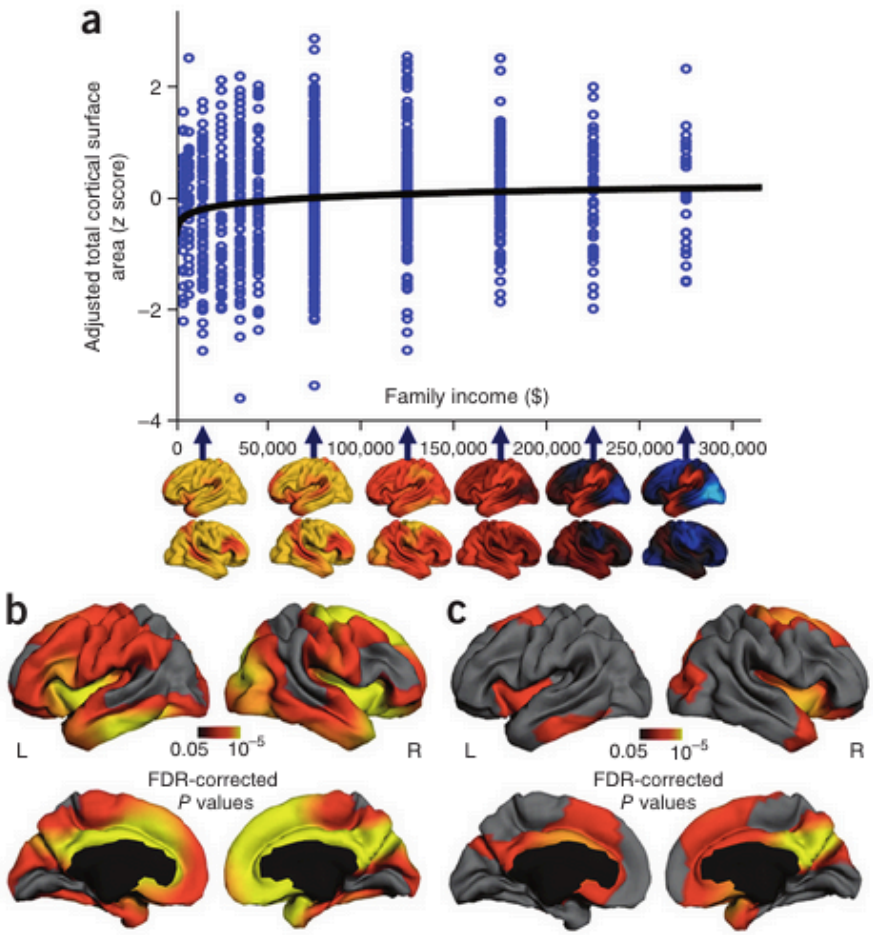
†Model adjusted for parental education, wealth, marital status, death before case admission not by suicide, family psychiatric history, history of suicide in parent or sibling, reference to father, place of birth, and sibship size.

‡Includes older age groups.

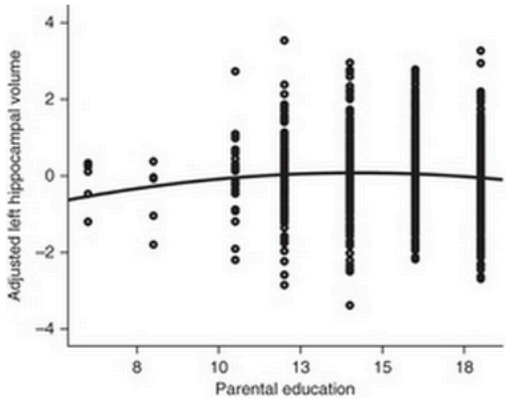
Byrne et al., Archives of General Psychiatry. July 1, 2003, Vol. 60, No. 7

Family income, parental education and brain structure in children and adolescents

Kimberly G Noble[1,2,32], Suzanne M Houston[3–5,32], Natalie H Brito[6], Hauke Bartsch[7], Eric Kan[4,5], Joshua M Kuperman[8–10], Natacha Akshoomoff[10–12], David G Amaral[10,13], Cinnamon S Bloss[10,14], Ondrej Libiger[15], Nicholas J Schork[16], Sarah S Murray[10,17], B J Casey[10,18], Linda Chang[10,19], Thomas M Ernst[10,19], Jean A Frazier[10,20], Jeffrey R Gruen[10,21–23], David N Kennedy[10,20], Peter Van Zijl[10,24,25], Stewart Mostofsky[10,25], Walter E Kaufmann[10,26,27], Tal Kenet[10,27,28], Anders M Dale[8–10,29–31], Terry L Jernigan[10–12,29] & Elizabeth R Sowell[4,5,10]



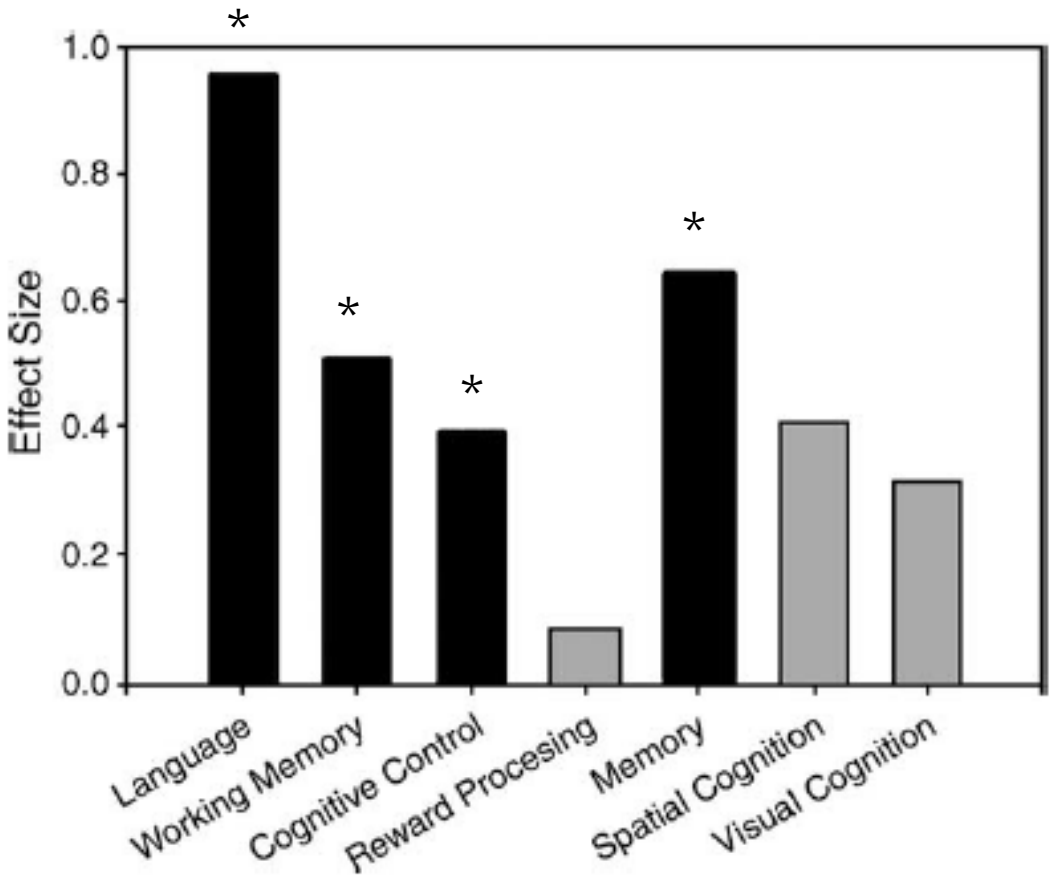
Family income is logarithmically associated with cortical surface area



Parental education is quadratically associated with left hippocampal volume

Childhood poverty: Specific associations with neurocognitive development

Martha J. Farah[a,], David M. Shera[b], Jessica H. Savage[a], Laura Betancourt[a], Joan M. Giannetta[c], Nancy L. Brodsky[c], Elsa K. Malmud[c], Hallam Hurt[c]*



* p<0.05 low vs. middle SES

Effect sizes of separation between low and middle SES

BRAIN RESEARCH 1110 (2006) 166–174

Speaker's notes to the previous slide:

Fig. 1 – Effect sizes, measured in standard deviations of separation between low and middle SES group performance, on the composite measures of the seven different neurocognitive systems assessed in this study. **Black bars represent effect sizes for statistically significant effects**; grey bars represent effect sizes for nonsignificant effects.

Role of cash in conditional cash transfer programmes for child health, growth, and development: an analysis of Mexico's *Oportunidades*

Lia C H Fernald, Paul J Gertler, Lynnette M Neufeld

Lancet 2008; 371: 828–37

See Comment page 789

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Summary

Background Many governments have implemented conditional cash transfer (CCT) programmes with the goal of improving options for poor families through interventions in health, nutrition, and education. Families enrolled in CCT programmes receive cash in exchange for complying with certain conditions: preventive health requirements and nutrition supplementation, education, and monitoring designed to improve health outcomes and promote positive behaviour change. Our aim was to disaggregate the effects of cash transfer from those of other programme components.

Methods In an intervention that began in 1998 in Mexico, low-income communities (n=506) were randomly assigned to be enrolled in a CCT programme (*Oportunidades*, formerly *Progresa*) immediately or 18 months later. In 2003, children (n=2449) aged 24–68 months who had been enrolled in the programme their entire lives were assessed for a wide variety of outcomes. We used linear and logistic regression to determine the effect size for each outcome that is associated with a doubling of cash transfers while controlling for a wide range of covariates, including measures of household socioeconomic status.

Findings A doubling of cash transfers was associated with higher height-for-age *Z* score (β 0·20, 95% CI 0·09–0·30; p<0·0001), lower prevalence of stunting (–0·10, –0·16 to –0·05; p<0·0001), lower body-mass index for age percentile (–2·85, –5·54 to –0·15; p=0·04), and lower prevalence of being overweight (–0·08, –0·13 to –0·03; p=0·001). A doubling of cash transfers was also associated with children doing better on a scale of motor development, three scales of cognitive development, and with receptive language.

Interpretation Our results suggest that the cash transfer component of *Oportunidades* is associated with better outcomes in child health, growth, and development.

Pregnancy

Substance use during pregnancy and risk of psychosis

BJPsych | The British Journal of Psychiatry (2009) 195, 294–300. doi: 10.1192/bjp.bp.108.062471

Maternal tobacco, cannabis and alcohol use during pregnancy and risk of adolescent psychotic symptoms in offspring

Stanley Zammit, Kate Thomas, Andrew Thompson, Jeremy Horwood, Paulo Menezes, David Gunnell, Chris Hollis, Dieter Wolke, Glyn Lewis and Glynn Harrison

Table 2 Crude and adjusted[a] odds ratios (OR) and 95% CI for psychosis-like symptoms (PLIKS) by maternal substance use during pregnancy

	n	Suspected or definite PLIKS Crude OR (95% CI)	Suspected or definite PLIKS Adjusted OR (95% CI)	Definite PLIKS Crude OR (95% CI)	Definite PLIKS Adjusted OR (95% CI)
Tobacco					
None	3579	1	1	1	1
1–9 cigarettes/day	295	1.15 (0.79–1.66)	0.92 (0.63–1.36)	1.53 (0.92–2.53)	1.25 (0.73–2.14)
10–19 cigarettes/day	266	1.88 (1.35–2.61)	1.47 (1.02–2.12)	2.33 (1.48–3.66)	1.65 (0.99–2.75)
⩾20 cigarettes/day	113	2.30 (1.45–3.65)	1.84 (1.12–3.03)	2.03 (1.01–4.10)	1.54 (0.73–3.25)
Linear trend	4253	1.33 (1.18–1.49), $P<0.001$	1.20 (1.05–1.37), $P=0.007$	1.39 (1.18–1.63), $P<0.001$	1.21 (1.01–1.47), $P=0.047$
Cannabis					
None	4175	1	1	1	1
<1/week	37	0.95 (0.34–2.70)	0.58 (0.20–1.70)	0.57 (0.08–4.20)	0.34 (0.04–2.56)
⩾1/week	41	1.62 (0.71–3.66)	1.04 (0.45–2.43)	1.63 (0.50–5.32)	1.12 (0.33–3.84)
Linear trend	4253	1.22 (0.83–1.79), $P=0.317$	0.94 (0.62–1.41), $P=0.755$	1.16 (0.65–2.09), $P=0.616$	0.91 (0.49–1.71), $P=0.776$
Alcohol					
None	2522	1	1	1	1
⩽7 units/week	1293	0.92 (0.74–1.14)	0.92 (0.74–1.15)	0.67 (0.48–0.94)	0.68 (0.48–0.96)
8–21 units/week	410	1.05 (0.77–1.48)	1.00 (0.71–1.39)	0.58 (0.33–1.04)	0.56 (0.31–1.02)
⩾22 units/week	28	2.58 (1.09–6.11)	2.40 (0.99–5.83)	2.14 (0.64–7.17)	1.86 (0.54–6.42)
Linear (per 10 units)[b]	4253	0.80 (0.51–1.25)	0.75 (0.47–1.19)	0.77 (0.48–1.25)	0.73 (0.45–1.18)
Quadratic (linear^2)[b]	4253	1.21 (1.00–1.47)	1.22 (1.00–1.49)	1.04 (0.97–1.12)	1.04 (0.97–1.12)
Likelihood ratio (for overall alcohol)[b]	4253	$\chi^2=9.8$, d.f. $=2$, $P=0.008$	$\chi^2=8.3$, d.f. $=2$, $P=0.016$	$\chi^2=1.3$, d.f. $=2$, $P=0.522$	$\chi^2=1.8$, d.f. $=2$, $P=0.415$

a. Adjusted for other substances used, and all variables in Table 1; data-set with no missing data for confounders 4253.
b. Results for linear and quadratic terms for alcohol use are with both included in same model.

Speaker's notes to the previous slide:

- Method: A longitudinal study of 6356 adolescents, age 12, who completed a semi-structured interview for psychotic symptoms in the Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort.

- **Results: Frequency of maternal tobacco use during pregnancy was associated with increased risk of suspected or definite psychotic symptoms (adjusted odds ratio 1.20, 95% CI 1.05– 1.37, P = 0.007). Maternal alcohol use showed a non-linear association with psychotic symptoms, with this effect almost exclusively in the offspring of women drinking >21 units weekly. Maternal cannabis use was not associated with psychotic symptoms. Results for paternal smoking during pregnancy and maternal smoking post-pregnancy lend some support for a causal effect of tobacco exposure in utero on development of psychotic experiences**.

Vitamin deficiency during pregnancy and risk of schizophrenia in offspring

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Prenatal Nutritional Deficiency and Risk of Adult Schizophrenia

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Converging evidence suggests that a neurodevelopmental disruption plays a role in the vulnerability to schizophrenia. The authors review evidence supporting in utero exposure to nutritional deficiency as a determinant of schizophrenia. We first describe studies demonstrating that early gestational exposure to the Dutch Hunger Winter of 1944–1945 and to a severe famine in China are each associated with an increased risk of schizophrenia in offspring. The plausibility of several candidate micronutrients as potential risk factors for schizophrenia and the biological mechanisms that may underlie these associations are then reviewed. These nutrients include folate, essential fatty acids, retinoids, vitamin D, and iron. Following this discussion, we describe the methodology and results of an epidemiologic study based on a large birth cohort that has tested the association between prenatal homocysteine, an indicator of serum folate, and schizophrenia risk. The study capitalized on the use of archived prenatal serum specimens that make it possible to obtain direct, prospective biomarkers of prenatal insults, including levels of various nutrients during pregnancy. Finally, we discuss several strategies for subjecting the prenatal nutritional hypothesis of schizophrenia to further testing. These approaches include direct assessment of additional prenatal nutritional biomarkers in relation to schizophrenia in large birth cohorts, studies of epigenetic effects of prenatal starvation, association studies of genes relevant to folate and other micronutrient deficiencies, and animal models. Given the relatively high prevalence of nutritional deficiencies during pregnancy, this work has the potential to offer substantial benefits for the prevention of schizophrenia in the population.

a vulnerability to schizophrenia in adolescence or adulthood. Accumulating data have implicated the in utero environment in the etiology of this disorder.[1] In this article, we review and discuss the sources of evidence for testing hypotheses about the relation of prenatal nutritional deficiency to offspring risk of schizophrenia. The long interval between an exposure in the prenatal period and the risk of schizophrenia in adulthood and the difficulty of obtaining precise data on prenatal nutritional intake are among the considerable challenges faced by researchers in this field. Nonetheless, successful studies have been built around historic events, a design sometimes referred to as a "natural experiment."

We first describe studies linking prenatal exposure to the Dutch Hunger Winter of 1944–1945 with offspring schizophrenia and a recent worthy replication of this finding. We also discuss some of the candidate nutritional deficiencies that might explain the results from these studies. Next we describe how the intriguing findings from these studies can be pursued in birth cohorts followed up for schizophrenia, making use of archived biological specimens to measure prenatal nutritional status. Finally, we discuss the approaches being developed for more powerful tests of these hypotheses, focusing for illustrative purposes on the folate/homocysteine (hcy) pathway.

Natural Experiments

The strongest evidence linking prenatal starvation to schizophrenia derives from natural experiments. Natural experiments are perhaps best known in the context of genetic epidemiology where twin and adoption studies are classic examples. However, natural experiments of a different kind can be built around circumscribed historical events. Sometimes these are tragic events such as famines, as in the examples described below, but a beneficial event

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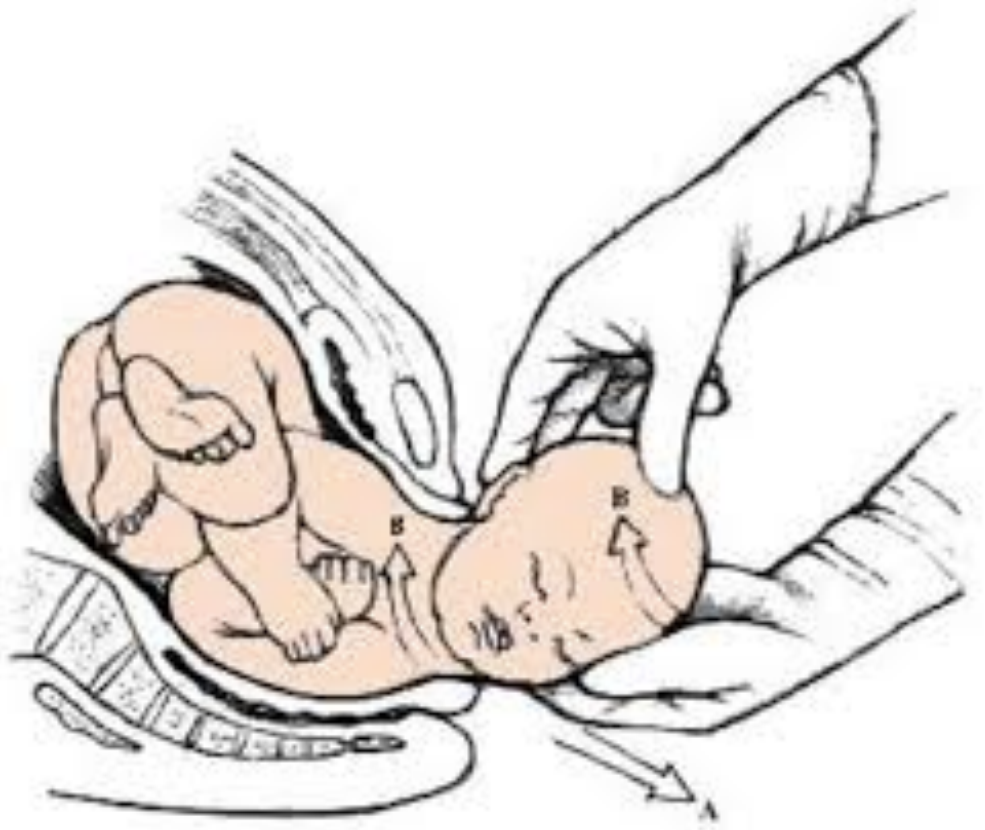
Vitamin D supplementation during the first year of life and risk of schizophrenia: a Finnish birth cohort study

John McGrath[a,b,*], Kaisa Saari[c,d], Helinä Hakko[c,d], Jari Jokelainen[c,e,f], Peter Jones[g], Marjo-Riitta Järvelin[e,h], David Chant[a], Matti Isohanni[c]

Table 2
Male cohort members only (n=4616)

		Time at risk (years)	Incidence per 100000 years at risk	RR (95% CI)	Adjusted RR (95% CI)*
Schizophrenia					
Frequency of vitamin D supplements					
None	1	411	243	1 (reference)	1 (reference)
Irregularly	4	17,034	23	0.10 (0.01–0.82)	0.08 (0.01–0.95)
Regularly	46	123,686	38	0.15 (0.02–1.02)	0.12 (0.02–0.90)
Dose of vitamin D					
Less than 2000 IU/day	2	1474	136	1 (reference)	1 (reference)
At least 2000 IU/day	49	139,657	35	0.26 (0.06–1.02)	0.23 (0.06–0.95)

Birth and perinatal period



Low birth weight and risk of mental disorders

Table 4. ORs Restricted to Birth at 37 Weeks or Later: Any Psychiatric Diagnoses vs the General Population (Sweden Only)[a,b]

	Any Psychiatric Diagnosis		
Birth Weight, g	n1	n2	Adjusted OR (95% CI)
500-1499	9	334	
1500-1999	63	1156	1.79 (1.39-2.31)
2000-2499	551	12 020	1.52 (1.39-1.66)
2500-2999	3818	100 352	1.27 (1.22-1.32)
3000-3499	11 198	341 944	1.10 (1.08-1.14)
3500-3999	10 578	362 020	1 [Reference]
4000-4499	4081	145 635	0.97 (0.94-1.01)
≥4500	819	30 730	0.94 (0.87-1.01)

Kathryn M. Abel, MD, PhD; Susanne Wicks, MSc; Ezra S. Susser, MD, PhD; Christina Dalman, MD, PhD; Marianne G. Pedersen, MSc; Preben Bo Mortensen, DrMedSc; Roger T. Webb, MSc, PhD

ARCH GEN PSYCHIATRY/VOL 67 (NO. 9), SEP 2010

Speaker's notes to the previous slide:

- Schizophrenia was associated with birth weight less than 2500 g, but this association was not restricted to birth weight less than 2500 g and there was a significant linear trend of increasing odds ratios with decreasing birth weight across the birth weight range. ***This was mirrored for any psychiatric diagnosis and for each of the categories of psychiatric disorder (schizophrenia, alcohol-drug use disorders, affective disorders, neurotic, stress-related and somatoform disorders).*** **Table 4 shows the effect of birth weight on the prevalence of adult mental health disorders controlling for the potential effect of prematurity.**
- **Conclusions:** Findings suggest there is an association between birth weight and adult mental disorder, but there is no indication this effect is specific to birth weight less than 2500 g or to schizophrenia. Future research should explore common disorder-specific mechanisms that may link birth weight to development of psychiatric disorder in adulthood.

Obstetric complications and psychosis

Eur Child Adolesc Psychiatry (2009)
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BRIEF REPORT

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Obstetric complications as a risk factor for first psychotic episodes in childhood and adolescence

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Abstract There are reports of significant association between obstetric complications (OC) and childhood psychosis. Authors conducted a case-control study of 102 children and adolescents with a first episode psychosis (FEP) and 94 healthy controls (HC), using the obstetric complications scale (OCS) and their medical records, to examine the risk of FPE. Patients were recruited from child and adolescent psychiatry units at six university hospitals and controls from publicly-funded schools of similar characteristics and from the same geographic areas. A logistic regression was performed to quantify the risk of psychosis in childhood and adolescence, based on OC, adjusting for potential confounding factors like socio economic status (SES) and family psychiatric history (FPH). OC appeared more frequently in the records of patients. Significant differences between patients and controls were found in Prenatal OC (15.7% vs. 5.3%, $P < 0.05$) and among them, *bleeding in pregnancy* showed the greatest difference between groups (12.7% vs. 2.1%, $P < 0.01$). In the logistic regression, bleeding in pregnancy showed a crude odds ratio (OR) of 6.7 (95%CI = 1.4–30.6) and 5.1 (CI 95% = 1.0–24.9) adjusted for SES and FPH. Therefore, bleeding in pregnancy is a likely risk factor for early-onset psychosis.

Key words early psychosis – first onset – case-control – OCS

Risk of psychosis in pre-term children

Table 3. Crude and Adjusted HRs ("Relative Risks") for Incidence of First Hospitalization With a Selected Psychiatric Diagnosis After an Individual's 16th Birthday in Relation to Pregnancy Outcomes

	HR (95% CI)					
	Nonaffective Psychosis		Depressive Disorder		Bipolar Affective Disorder	
Exposure	Crude	Fully Adjusted[a]	Crude	Fully Adjusted[a]	Crude	Fully Adjusted[a]
Gestational age, wk						
<32	2.8 (1.2-6.7)	2.5 (1.0-6.0)	3.0 (1.9-4.7)	2.9 (1.8-4.6)	7.2 (2.7-19.6)	7.4 (2.7-20.6)
32-36	1.8 (1.2-2.5)	1.6 (1.1-2.3)	1.4 (1.1-1.7)	1.3 (1.1-1.7)	2.6 (1.6-4.4)	2.7 (1.6-4.5)
37-41	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
≥42	1.0 (0.8-1.2)	1.0 (0.8-1.3)	1.1 (1.0-1.3)	1.1 (1.0-1.2)	1.0 (0.7-1.5)	1.0 (0.7-1.5)
Birth weight for gestational age, SDS						
≤2	1.1 (0.7-1.6)	1.0 (0.7-1.5)	1.1 (0.8-1.3)	1.1 (0.9-1.4)	1.0 (0.5-2.1)	1.0 (0.5-2.0)
−1.99 to 1.99	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
≥2	0.9 (0.5-1.6)	0.9 (0.5-1.5)	0.8 (0.6-1.1)	0.7 (0.5-1.0)	0.9 (0.3-2.4)	0.8 (0.3-2.1)
Apgar score at 5 min						
0-3	0.8 (0.1-5.8)	0.7 (0.1-4.8)	2.4 (1.3-4.4)	2.2 (1.2-4.0)	5.3 (1.3-21.2)	3.8 (0.9-15.5)
4-6	1.6 (0.8-3.4)	1.3 (0.6-2.8)	1.2 (0.8-2.0)	1.1 (0.7-1.7)	0.7 (0.1-5.2)	0.5 (0.1-3.6)
7-10	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]

	HR (95% CI)					
	Eating Disorders		Drug Dependency		Alcohol Dependency	
Exposure	Crude	Fully Adjusted[a]	Crude	Fully Adjusted[a]	Crude	Fully Adjusted[a]
Gestational age, wk						
<32	3.7 (1.4-10.0)	3.5 (1.3-9.6)	1.2 (0.7-2.3)	1.2 (0.6-2.2)	1.5 (0.9-2.3)	1.3 (0.8-2.3)
32-36	1.4 (0.8-2.3)	1.4 (0.9-2.4)	1.3 (1.1-1.6)	1.2 (1.0-1.4)	1.4 (1.2-1.7)	1.3 (1.1-1.5)
37-41	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
≥42	1.2 (0.9-1.5)	1.1 (0.9-1.5)	1.0 (0.9-1.1)	1.0 (0.9-1.1)	1.1 (1.0-1.2)	1.1 (1.0-1.2)
Birth weight for gestational age, SDS						
≤2	0.7 (0.4-1.4)	0.7 (0.4-1.3)	1.5 (1.3-1.8)	1.4 (1.2-1.6)	1.3 (1.1-1.5)	1.2 (1.0-1.4)
−1.99 to 1.99	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
≥2	0.7 (0.3-1.6)	0.7 (0.3-1.5)	0.8 (0.6-1.0)	0.8 (0.6-1.1)	0.9 (0.7-1.1)	0.9 (0.7-1.1)
Apgar score at 5 min						
0-3	3.1 (0.8-12.5)	3.0 (0.8-12.3)	1.1 (0.5-2.4)	1.0 (0.4-2.2)	1.5 (0.8-2.9)	1.3 (0.7-2.6)
4-6	1.6 (0.6-4.4)	1.6 (0.6-4.4)	0.8 (0.5-1.3)	0.7 (0.4-1.0)	1.3 (0.9-1.9)	1.1 (0.8-1.6)
7-10	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]

Abbreviations: HR, hazard ratio; SDS, standard deviation score.
[a]The HRs are adjusted for the other variables in the table and for sex, parity, maternal age at delivery, maternal education, and maternal psychiatric family history.

Nosarti et al., JAMA Psychiatry 2012

Prevention of adverse obstetric outcomes in at-risk populations: women with severe mental illness

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Schizophrenia Research

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Adverse obstetric and neonatal outcomes in women with severe mental illness: To what extent can they be prevented?

Fiona Judd [a,b,*], Angela Komiti [a,b], Penny Sheehan [c], Louise Newman [d], David Castle [a,e], Ian Everall [a,f,g]

Table 1
Antenatal care: Comparing study and control groups.

	Study (n = 112)	Control (n = 19,755)	χ^2/t-test	p
Mean age (SD)	31.7 (6.1)	30.4 (5.3)	−2.3	.02
Alcohol use (%)	20.6	0.6	625	<.001
Smoking—<20 weeks (%)	38.3	6.6	171	<.001
Illicit drug use (%)	17.9	2.6	95.5	<.001
Mean gestation at 1st AN appt. (SD)	18.8 (7.8)	15.1 (6.6)	−5.0	<.001

Note: AN = antenatal.

Table 3
Neonatal outcomes: comparing study and control groups.

	Study (n = 112)	Control (n = 19,755)	χ^2/t-test	p
Apgar score 8–10 at 1 min (%)	69.6	79.8	7.08	.008
Apgar score <4 at 1 min (%)	5.4	5.7	0.02	.88
Apgar score 8–10 at 5 min (%)	86.6	92.5	5.43	.02
Mean infant weight, grams (SD)	3172 (680)	3247 (719)	1.10	.27
- Excluding smokers	3262 (711)	3275 (699)	0.15	.88
Mean gestation at birth, weeks (SD)	38.4 (2.7)	38.5 (3.0)	0.46	.64
Pre-term births (<37 weeks) (%)	17.9	10.9	5.52	.02
NISC admission (%)	27.7	12.5	23.38	<.001

Note: NISC = neonatal intensive special care.

Speaker's notes to the previous slide:

- Women with schizophrenia and bipolar disorder presented later for their first antenatal visit and had higher rates of smoking and illicit drug use than the control group. They also had higher rates of pre-eclampsia and gestational diabetes. Their infants were less likely to have Apgar scores 8–10 at both 1 and 5 minutes and were more likely to be admitted to special care/neonatal intensive care nursery than the infants of controls. The rate of pre-term birth was significantly higher in the women with schizophrenia and bipolar disorder. **Pre-term birth and admission to special care/neonatal intensive care were predicted by smoking and illicit drug use.**
- Conclusion: These data point to potentially modifiable factors as significant contributors to the high rate of adverse obstetric and neonatal outcomes in women with mental illness. **Comprehensive management of women with mental illness before and during pregnancy and in the postnatal period may have long-term benefits for their offspring.**

Toddlerhood and pre-school age

Primary Care Services Promoting Optimal Child Development From Birth to Age 3 Years

Review of the Literature FREE

Michael Regalado, MD; Neal Halfon, MD, MPH

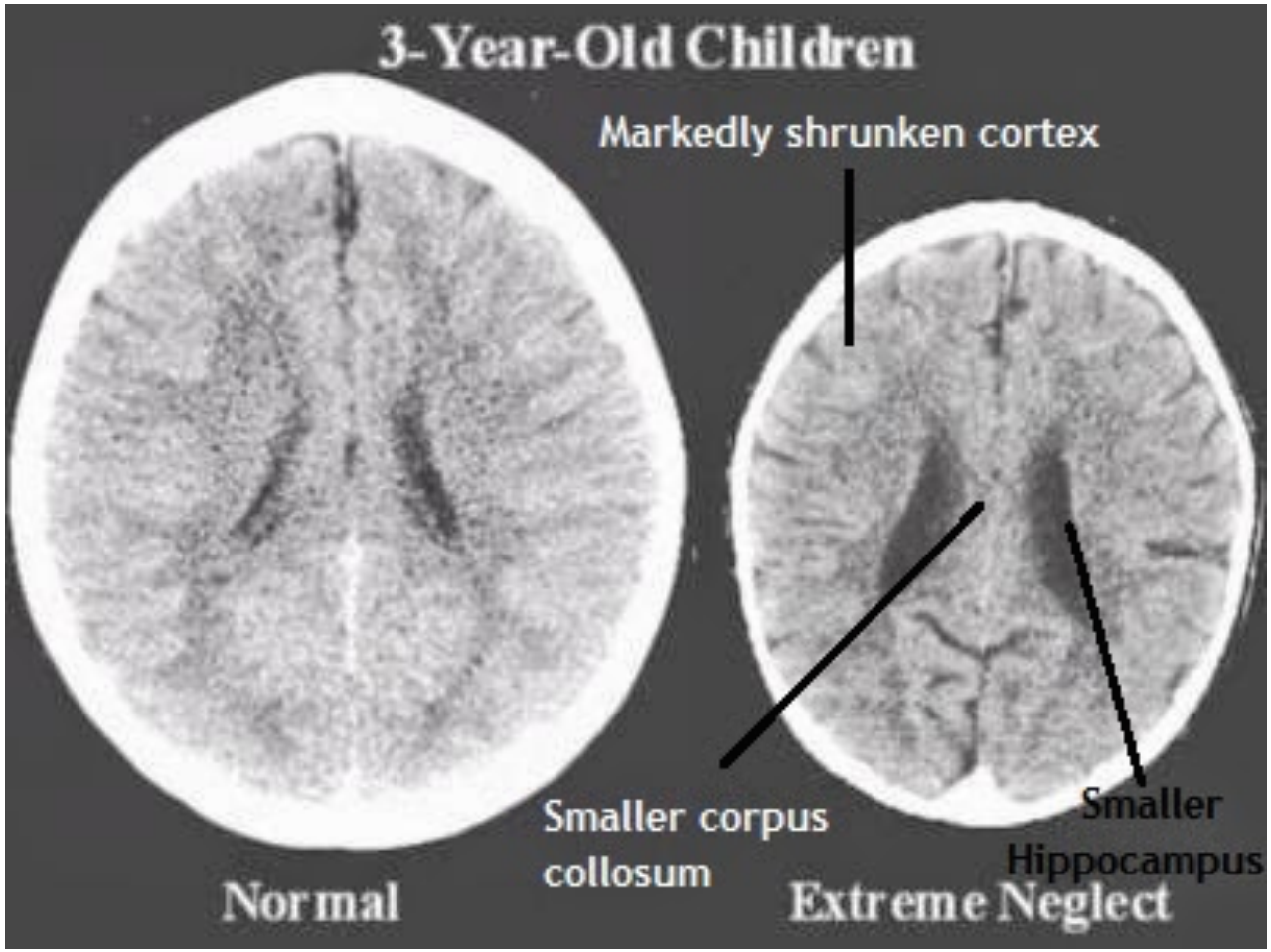
The literature suggests that many primary care activities promoting the optimal development of children are efficacious. Study results support the efficacy of:

1. Primary care educational efforts towards promoting optima parent-child interaction, parents' understanding of child temperament, book-sharing activities, and approaches to healthy sleep habits

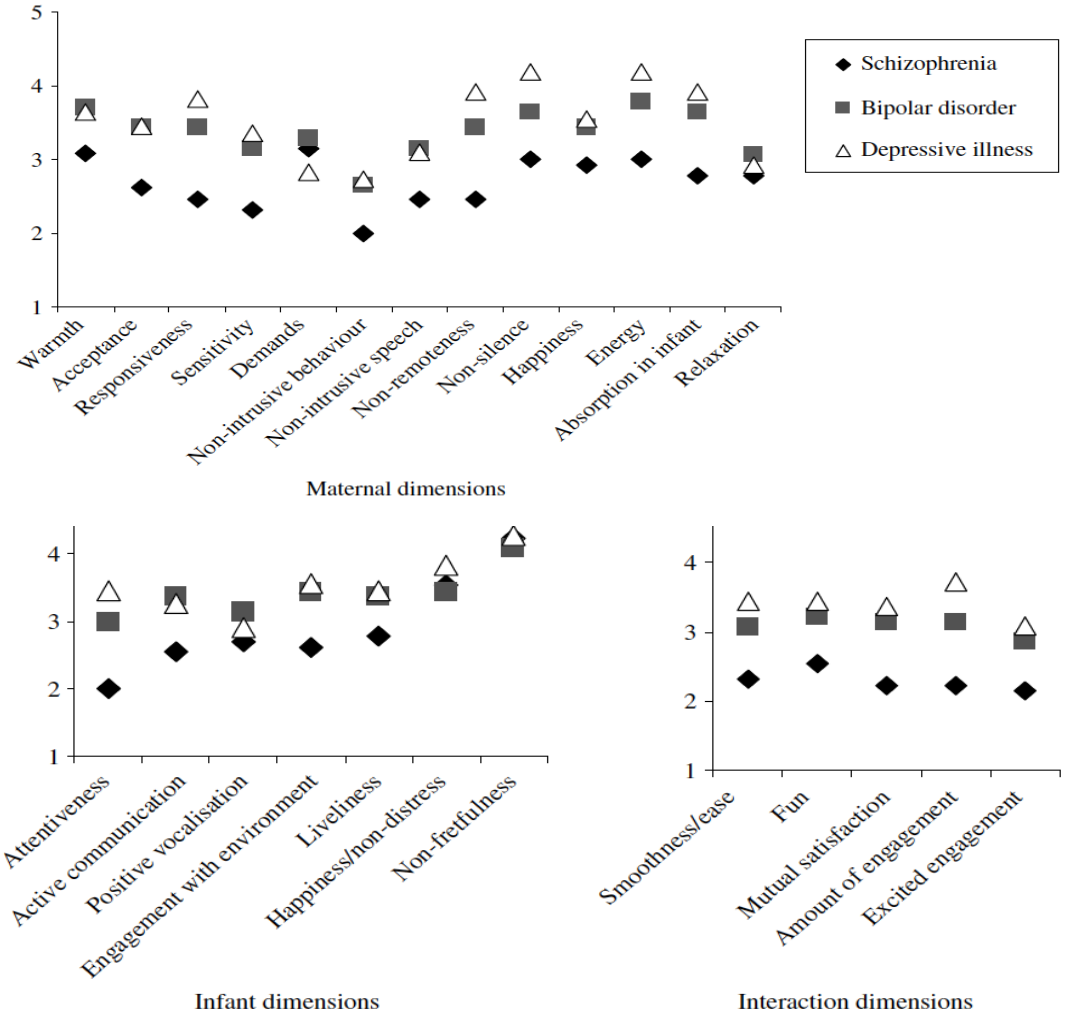
2. Office interventions such as counselling for the management of excessive infant crying and sleep problems.

Arch Pediatr Adolesc Med. 2001;155(12):1311-1322.

Effects of neglect on brain development



Poorer infant-mother interaction in schizophrenia



M. W. Wan et al.

Psychological Medicine, 2007, **37**, 537–546.

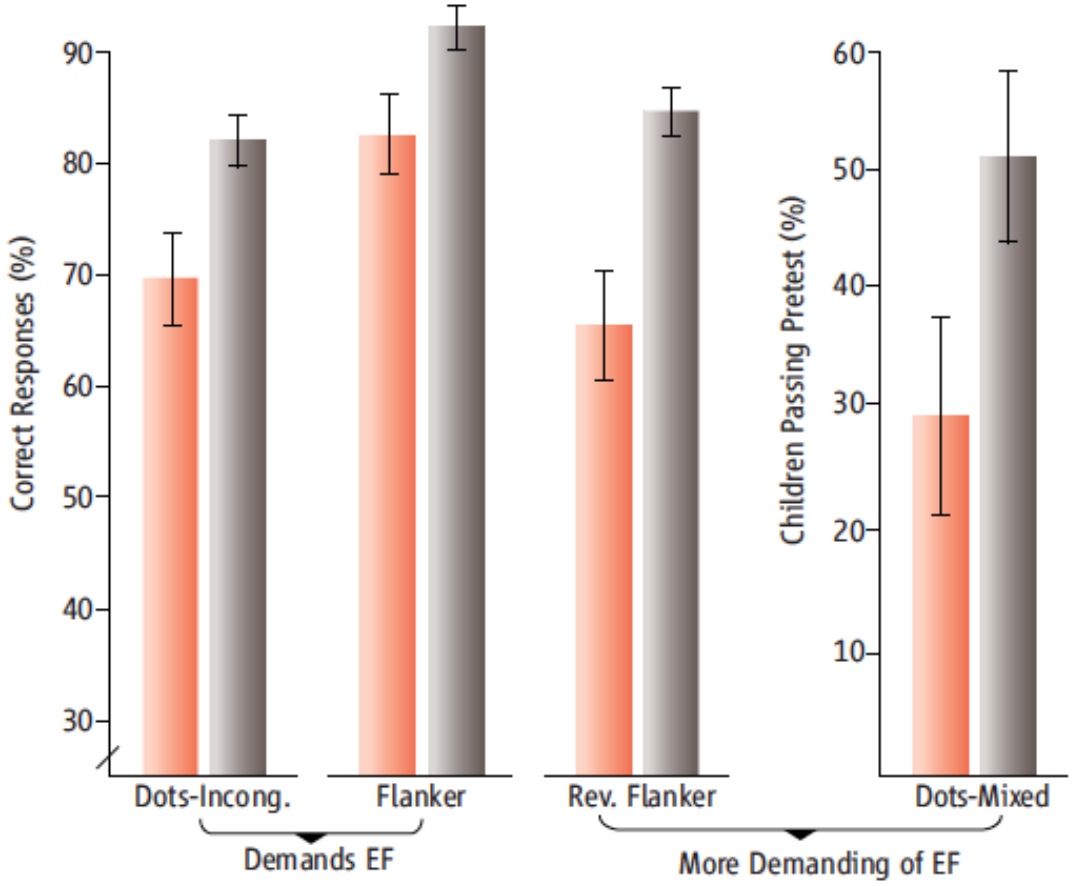
Speaker's notes to the previous slide:

The results replicate and extend previous findings showing poor interactive behaviours in mothers with schizophrenia, their infants, and in the dyad, in a range of areas following clinical recovery. The findings suggest that factors other than illness duration, dose of medication, marital status and occupational status are explanatory for the interactive deficits associated with maternal schizophrenia. **Parenting interventions that aim to improve maternal sensitivity need to be developed specifically for this group.**

Preschool Program Improves Cognitive Control

Cognitive control skills important for success in school and life are amenable to improvement in at-risk preschoolers without costly interventions.

Adele Diamond,[1]* W. Steven Barnett,[2] Jessica Thomas,[2] Sarah Munro[1]



Speaker's notes to the previous slide:

- Children participating in a programme aimed at improving EF showed significantly better performance in EF tasks of differing difficulty.

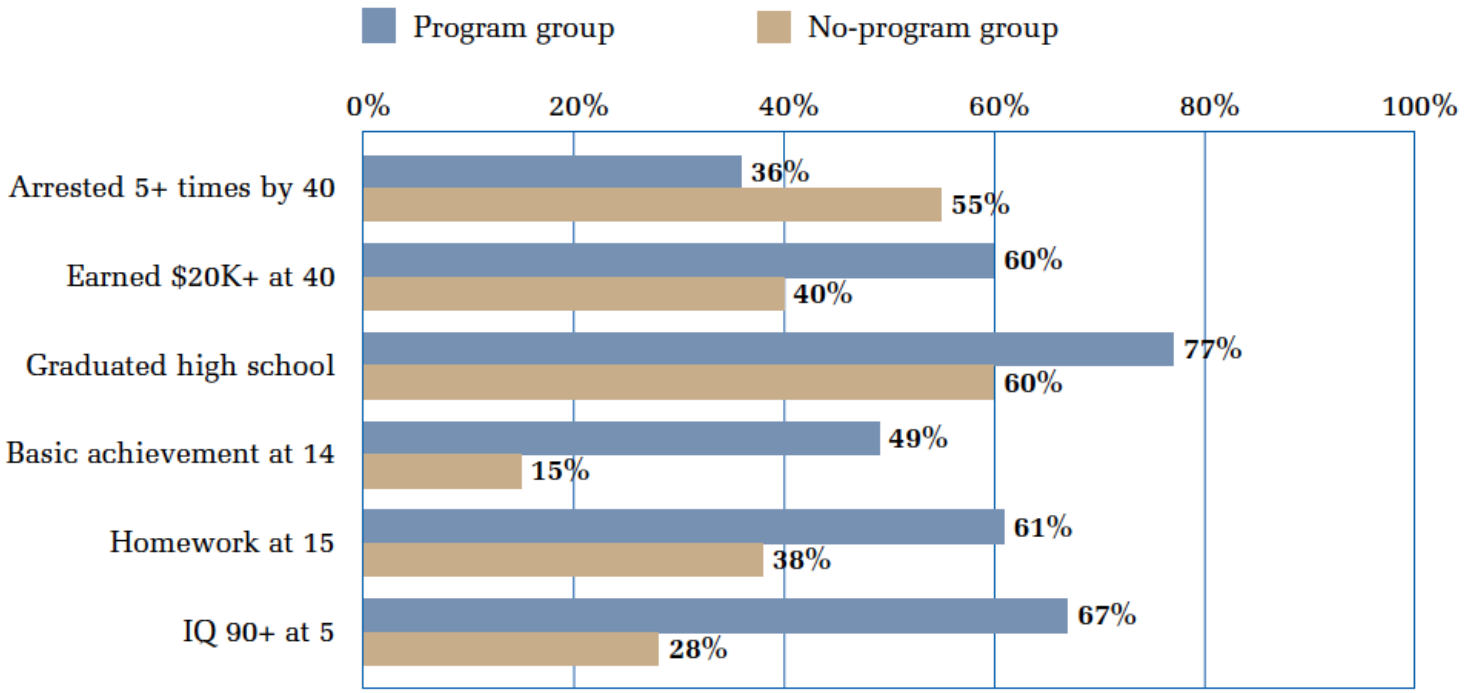
- EF-training curriculum: Tools. The Tools curriculum (16) is based on Vygotsky's insights into EF and its development. Its core is 40 EF-promoting activities, including telling oneself out loud what one should do ("self-regulatory private speech") (17), dramatic play (18), and aids to facilitate memory and attention (19). Tools teachers spent ~80% of each day promoting EF skills. Tools has been refined through 12 years of research in preschools and kindergartens. Only when EFs were challenged and supported by activities throughout the day did gains generalize to new contexts (2).

Effective preventive interventions in preschool age children

The High/Scope Perry Preschool Study Through Age 40

Figure 1

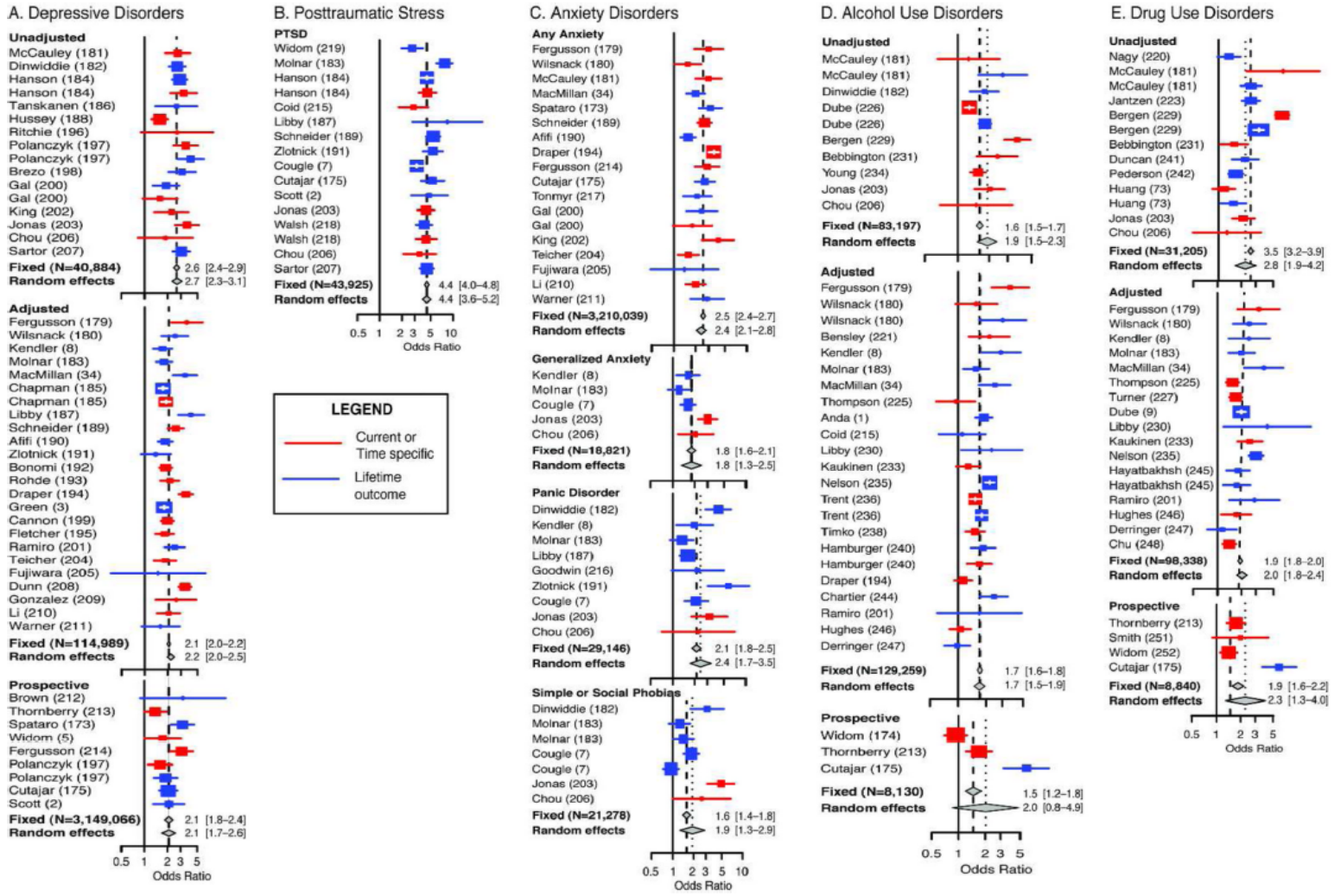
Major Findings: High/Scope Perry Preschool Study at 40



Schweinhart et al.

Primary school

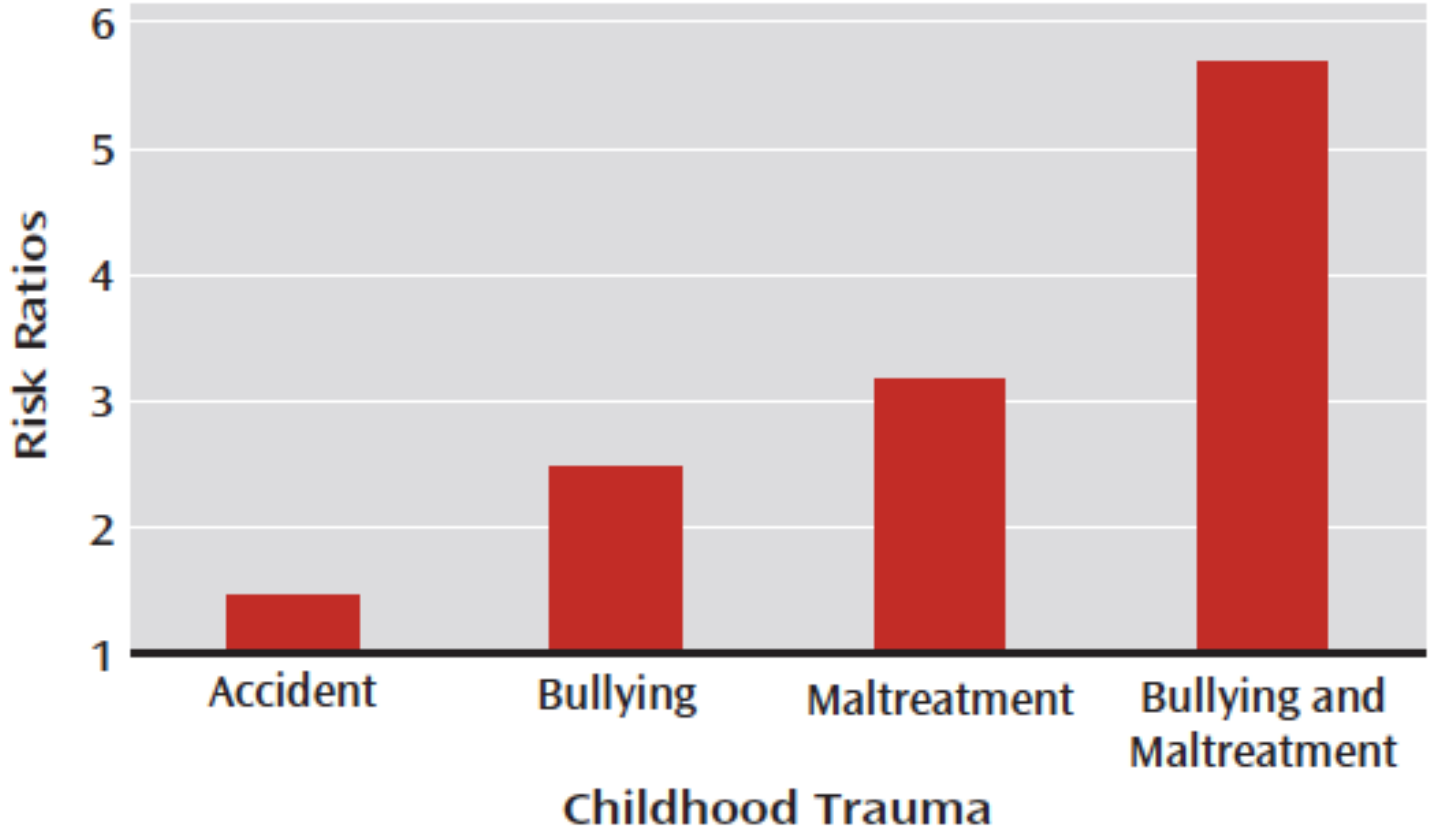
Child abuse is associated with increased risk for most mental health disorders



Teicher and Samson, Am J Psychiatry 2013

Child abuse and risk for psychosis

FIGURE 1. Risk of Psychotic Symptoms at Age 12 Associated With Cumulative Childhood Trauma



ARSENEAULT, CANNON, FISHER, ET AL.

Am J Psychiatry 168:1, January 2011

Prevention of child abuse

Preventing Child Abuse: A Meta-Analysis of Parent Training Programs

Brad W. Lundahl
Janelle Nimer
Bruce Parsons
University of Utah

Objective: A meta-analysis was conducted to evaluate the ability of parent training programs to reduce parents' risk of abusing a child. Method: A total of 23 studies were submitted to a meta-analysis. Outcomes of interest included parents' attitudes toward abuse, emotional adjustment, child-rearing skills, and actual abuse. Conclusions: Immediately following treatment and prior to moderator analyses, effect sizes for all outcomes were in the moderate range (d = 0.45-0.60). Moderator analyses suggest inclusion of home visitors and conducting parent training in both a home and office setting significantly enhanced the effectiveness. In addition, inclusion of a behavioral component and delivering some of the parent training in an individual setting, as opposed to group only, enhanced outcomes significantly.

Keywords: *child abuse; prevention; parent training; meta-analysis*

Research on Social Work Practice 2006; 16; 251

Speaker's notes to the previous slide:

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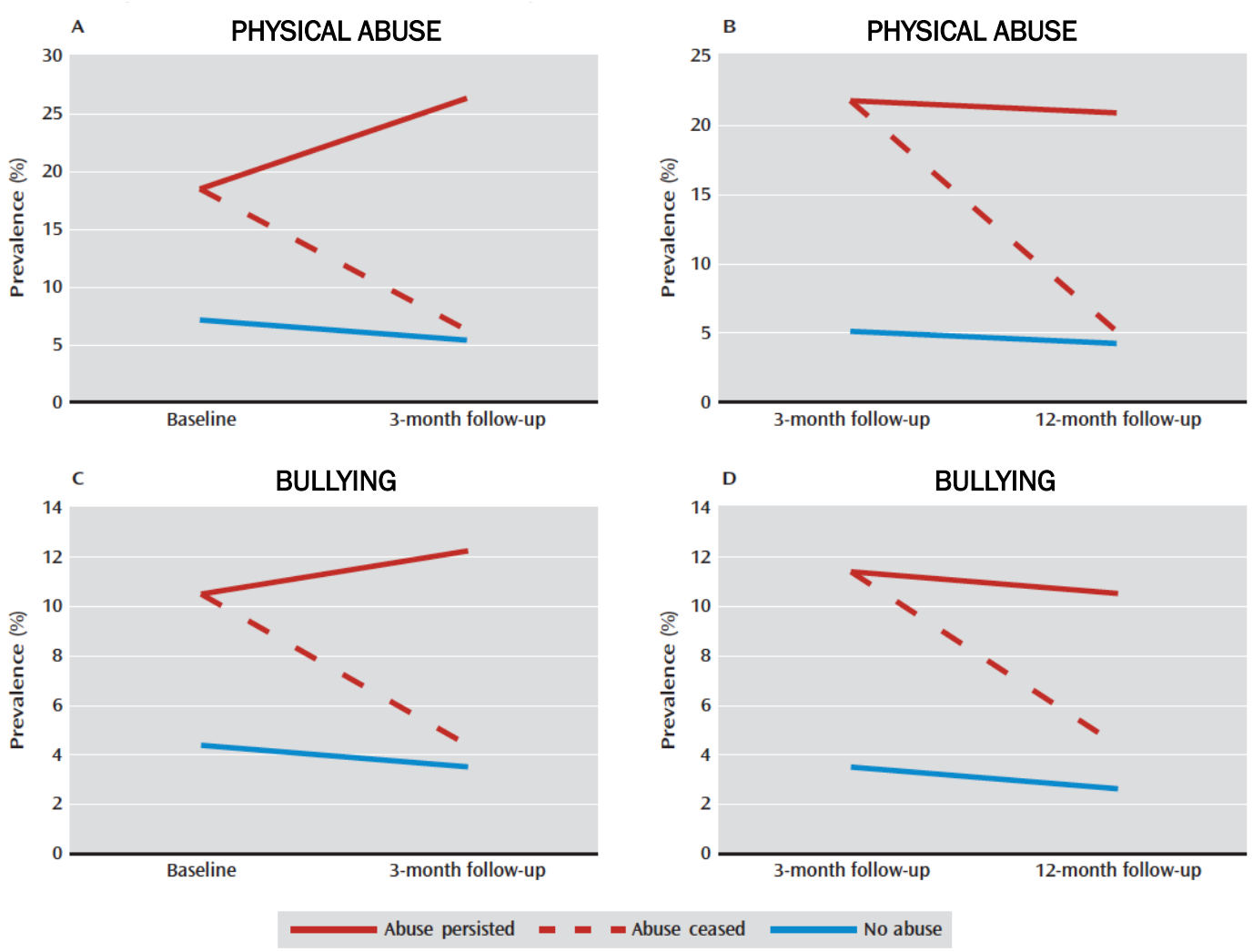
- *some of the parent training in an individual setting, as opposed to group only, enhanced outcomes significantly.*

Effects on psychotic experiences of ceasing maltreatment and bullying



Speaker's notes to the previous slide:

- The effects of bullying and maltreatment on psychotic experiences could be reversed during childhood if they cease.

- **FIGURE 1.:** Point Prevalence of Psychotic Experiences in Individuals for Whom Abuse Ceased or Persisted Across Two Time Points, Compared With Individuals Who Did Not Report Abuse at Either Time Point[a]
- [a] Panel A shows the point prevalence of psychotic experiences in individuals whose physical abuse ceased from baseline to 3-month follow-up compared with individuals whose physical abuse persisted. Panel B shows the point prevalence of psychotic experiences in individuals whose physical abuse ceased from 3-month to 12-month follow-up compared with individuals whose physical abuse persisted. Panel C shows the point prevalence of psychotic experiences in individuals whose bullying ceased from baseline to 3-month follow-up compared with individuals whose bullying persisted. Panel D shows the point prevalence of psychotic experiences in individuals whose bullying ceased from 3-month to 12-month follow-up compared with individuals whose bullying persisted.

Children with low IQ are at risk of psychosis and other mental disorders

Table 2. Crude and Adjusted ORs and 95% CIs for Developing Psychiatric Disorders According to Premorbid IQ (scored 1–9; 1 = highest)

	OR (95% CI)	
	Crude	Adjusted[a]
Psychoses	1.28 (1.09, 1.51)	1.29 (1.09, 1.52)
Neuroses		
Depression	1.08 (1.04, 1.12)	1.06 (1.02, 1.11)
Other	1.15 (1.13, 1.17)	1.14 (1.12, 1.17)
All	1.13 (1.11, 1.15)	1.13 (1.10, 1.15)
Personality disorder	1.29 (1.25, 1.33)	1.26 (1.22, 1.30)
Alcoholism	1.53 (1.42, 1.64)	1.49 (1.38, 1.62)
Drug dependence	1.16 (1.10, 1.23)	1.08 (1.02, 1.15)[b]
Other diagnoses	1.28 (1.24, 1.32)	1.27 (1.23, 1.31)

Note: OR, odds ratio; CI, confidence interval. All crude and all adjusted results are $P < 0.001$.
[a]Adjusted for drug use, smoking, disturbed behavior, and place of upbringing.
[b]Not adjusted for drug use.

A. S. David *et al.*

Schizophrenia Bulletin vol. 34 no. 6 pp. 1035–1041, 2008

Speaker's notes to the previous slide:

It was found that reduced intellectual functioning was found in association with psychosis and neurotic disorders including depression, personality disorders, alcoholism, and drug dependence.The effectwas particularly strong for alcoholism. This presumably represents a combination of premorbid deficits (as demonstrated in those who developed schizophrenia some years later) plus coincident impairments.

Children with low IQ and disabilities are also at risk of experiencing bullying and maltreatment

Prevalence and risk of violence against children with disabilities: a systematic review and meta-analysis of observational studies

Lisa Jones, Mark A Bellis, Sara Wood, Karen Hughes, Ellie McCoy, Lindsay Eckley, Geoff Bates, Christopher Mikton, Tom Shakespeare, Alana Officer

	Any disability			Mental or intellectual disability		
	Studies	Odds ratio (95% CI)	Heterogeneity	Studies	Odds ratio (95% CI)	Heterogeneity
Any maltreatment	4	3·68 (2·56–5·29)	91·8% (87·7–94·1)	3	4·28 (2·12–8·62)	94·0% (90·2–95·9)
Physical violence	6	3·56 (2·80–4·52)	50·6% (0–73·0)	4	3·08 (2·08–4·57)	50·8% (0–77·2)
Sexual violence	9	2·88 (2·24–3·69)	86·9% (78·8–90·9)	4	4·62 (2·08–10·23)	84·7% (64·4–91·2)
Emotional abuse	4	4·36 (2·42–7·87)	94·4% (91·4–96·0)	3	4·31 (1·37–13·56)	96·2% (94·2–97·3)
Neglect	3	4·56 (3·23–6·43)	73·8% (27·7–86·0)	2	..	..

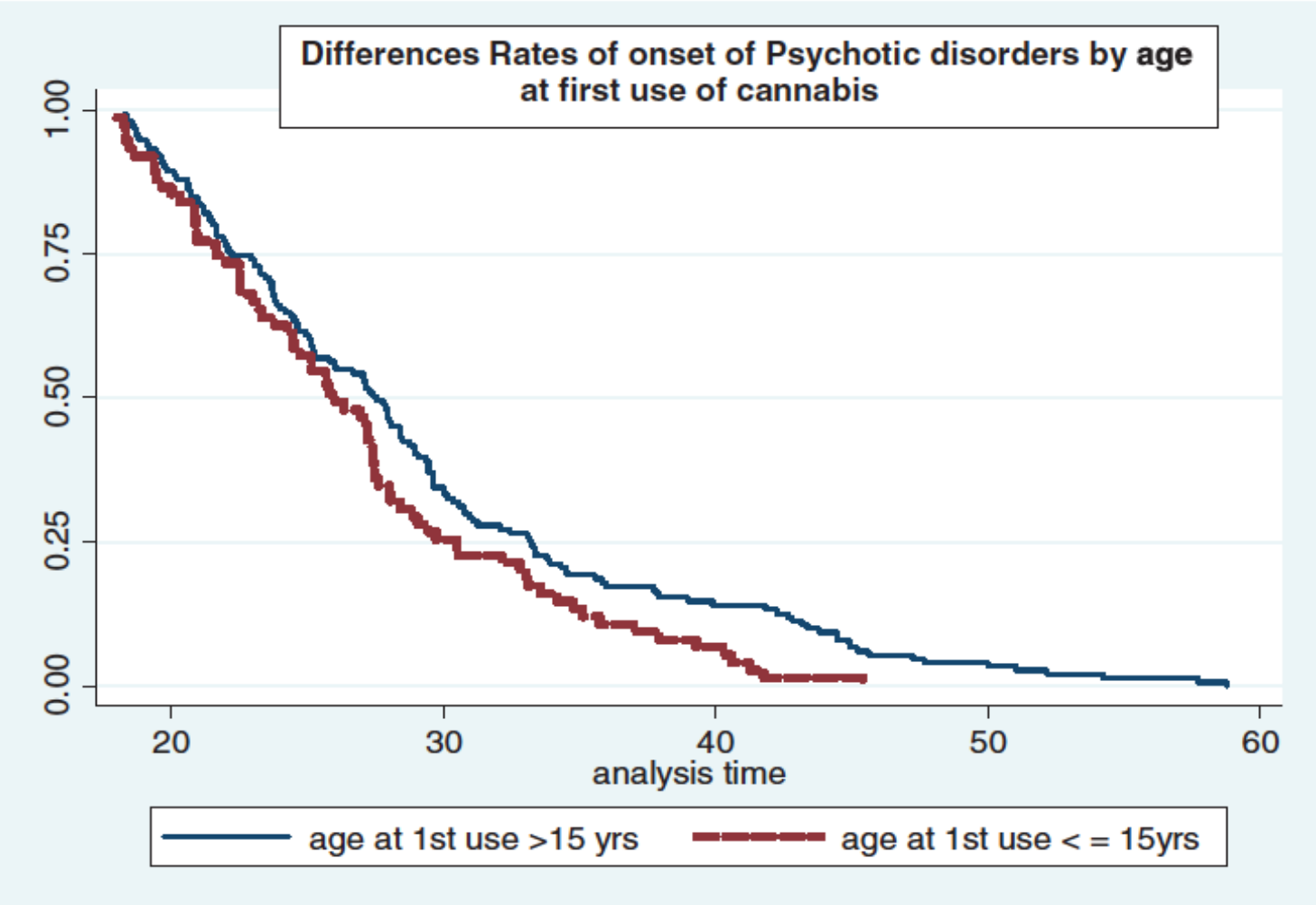
We used the I^2 statistic (95% CI) to estimate heterogeneity between pooled studies. .. = insufficient sample.

Table 3: Random-effects pooled odds ratios for risk of violence

Lancet 2012; 380: 899–907

Adolescence

Earlier onset of cannabis use associated with earlier onset of psychosis



Di Forti et al., Schizophr Bull (2014) 40 (6): 1509-1517.

OPEN ACCESS Freely available online

PLOS | ONE

Primary Prevention of Cannabis Use: A Systematic Review of Randomized Controlled Trials

Melissa M. Norberg*, Sarah Kezelman, Nicholas Lim-Howe

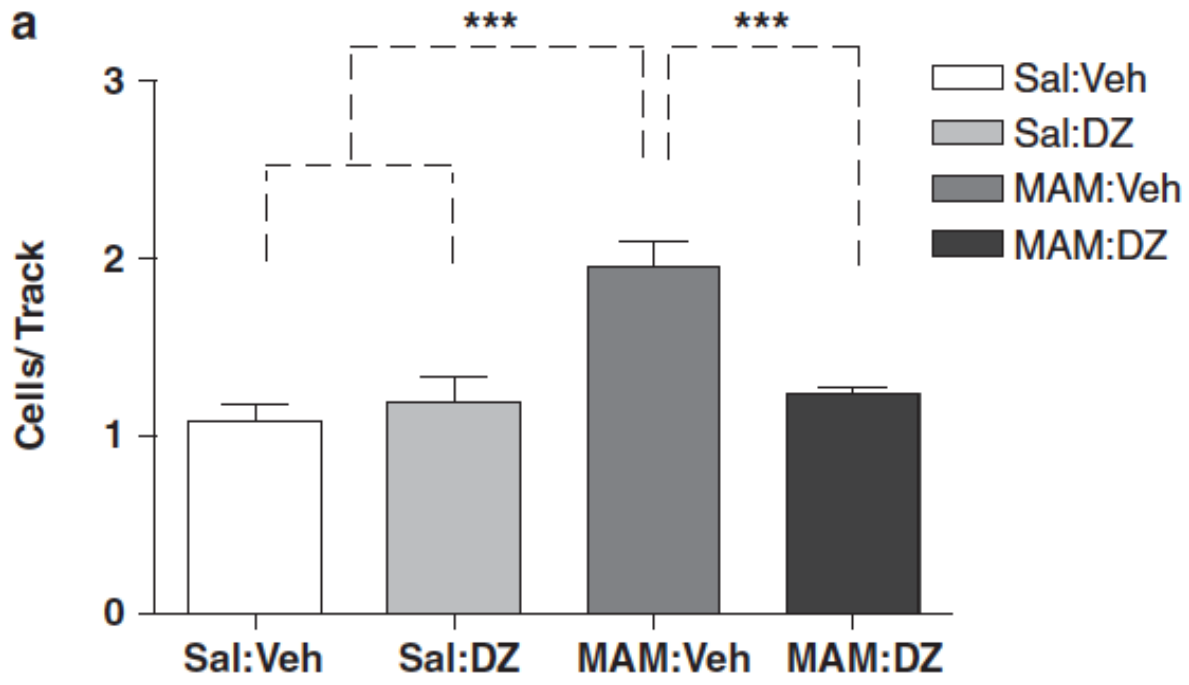
National Cannabis Prevention and Information Centre, University of New South Wales, Randwick, New South Wales, Australia

Abstract

A systematic review of primary prevention was conducted for cannabis use outcomes in youth and young adults. The aim of the review was to develop a comprehensive understanding of prevention programming by assessing universal, targeted, uni-modal, and multi-modal approaches as well as individual program characteristics. Twenty-eight articles, representing 25 unique studies, identified from eight electronic databases (EMBASE, MEDLINE, CINAHL, ERIC, PsycINFO, DRUG, EBM Reviews, and Project CORK), were eligible for inclusion. Results indicated that primary prevention programs can be effective in reducing cannabis use in youth populations, with statistically significant effect sizes ranging from trivial (0.07) to extremely large (5.26), with the majority of significant effect sizes being trivial to small. Given that the preponderance of significant effect sizes were trivial to small and that percentages of statistically significant and non-statistically significant findings were often equivalent across program type and individual components, the effectiveness of primary prevention for cannabis use should be interpreted with caution. Universal multi-modal programs appeared to outperform other program types (i.e, universal uni-modal, targeted multi-modal, targeted unimodal). Specifically, universal multi-modal programs that targeted early adolescents (10–13 year olds), utilised non-teacher or multiple facilitators, were short in duration (10 sessions or less), and implemented boosters sessions were associated with large median effect sizes. While there were studies in these areas that contradicted these results, the results highlight the importance of assessing the interdependent relationship of program components and program types. Finally, results indicated that the overall quality of included studies was poor, with an average quality rating of 4.64 out of 9. Thus, further quality research and reporting and the development of new innovative programs are required.

Targeting increased stress sensitivity during adolescence

Peripubertal Diazepam Administration Prevents the Emergence of Dopamine System Hyperresponsivity in the MAM Developmental Disruption Model of Schizophrenia



Y Du and AA Grace

Neuropsychopharmacology (2013) 38, 1881–1888

Speaker's notes to the previous slide:

Increased stress sensitivity during adolescence has been linked to schizophrenia in humans and could be a target of early intervention, especially through psychosocial interventions. In a developmental model of schizophrenia in mice, the administration of diazepam during adolescence prevented the pathological increase in the number of spontaneously active dopamine (DA) neurons (presented as cells/track). (a) MAM:Veh (n.7) rats had a significantly higher number of DA neurons firing per electrode track compared with MAM:DZ (n.7), Sal:Veh (n.7), and Sal:DZ rats (n.7; Bonferroni post hoc test). In contrast, diazepam treatment did not significantly affect the number of DA neurons firing in saline rats (Sal:Veh vs Sal:DZ rats, p40.05). Peripubertal administration of diazepam to this animal model of schizophrenia was also associated with an attenuation of the aberrant enhancement of the locomotor response to D-amphetamine

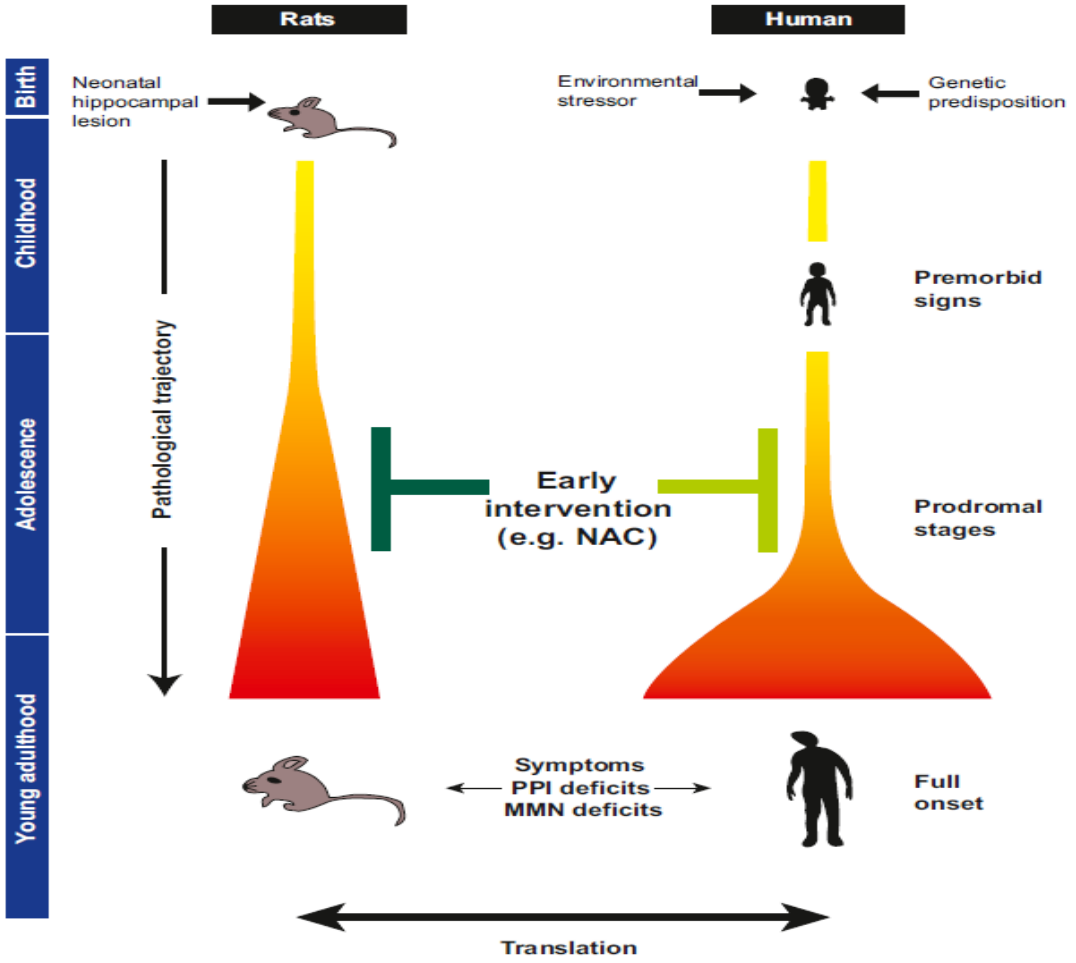
Oxidative stress in EOP

- Reduced antioxidant defense in early-onset first-episode psychosis (Micó et al 2011)

- Decreased glutathione levels predict loss of brain volume in EOP (Fraguas et al 2012).

- Inflammatory and oxidative markers in childhood predict psychosis in adolescence/ early adulthood (Khandaker et al 2014, Leza et al in press).

Preventive interventions in adolescent oxidative stress



Akira Sawa[1,*] and Larry J. Seidman[2]

Outline

- Prevention in psychiatry
- Psychosis (psychiatric disorders) as the reflection of abnormal developmental trajectories
- Shifting the focus towards prevention and early intervention in developmentally sensitive periods
- Implications and priorities for the future

ROAMER
A Roadmap for Mental Health Research in Europe

High Level Priorities

ROAMER's 6 Mental Health Research Priorities

1. Research into mental disorder prevention, mental health promotion and interventions in children, adolescents and young people
2. Focus on the development and causal mechanisms of mental health symptoms, syndromes and well-being across the lifespan (including older populations)
3. Developing and maintaining international and interdisciplinary research networks and shared databases
4. Developing and implementing better interventions using new scientific and technological advances
5. Reducing stigma, empowering service users and carers in decisions about mental health care, research
6. Health and social systems research that addresses quality of care and takes account of socio-cultural and socio-economic contexts and approaches

Speaker's notes to the previous slide:

- Preventive interventions are a priority for research in mental health in the coming years, as has been recognised by the ROAMER project. Such preventive interventions should especially target children, adolescents and young people.
- **These are the six high-level priorities arising from the ROAMER survey**
- **These provide a fairly comprehensive overview of the material generated by ROAMER**
- **But they also identify the most important, effective, and feasible research to conduct next in Europe**
- **These priorities reflect the multidisciplinary input of researchers and stakeholders in society**

Prevention and very early intervention in the context of a developmental perspective

Putting science into practice for early child development

UNICEF/NYHQ2011-0721/Asselin

Published Online
September 20, 2014
http://dx.doi.org/10.1016/
S0140-6736(14)61680-9

The debate between nature and nurture as determinants of early child development is over. Today, we understand that the two are inextricably linked. The degree of their interdependence—and the impact of this interplay on the developing brains of children—is even greater than we previously imagined.[1] This knowledge has tremendous implications for how we design and deliver early child development interventions.

During the past 24 years, the united efforts and shared goals of the global community have achieved substantial progress in child survival, and child mortality worldwide has declined by 49%.[2] We can build on those gains by focusing new effort and attention not only on saving

violent conflicts and other catastrophes. Toxic stress increases the production of cortisol, a hormone that can disrupt the healthy development of the brain, affecting health, learning, and behaviour. Toxic stress also undermines the ability of the body to absorb nutrients, so potentially exacerbating malnutrition.[5]

We are just beginning to understand how environmental factors—including the quality of parenting—might modify the expression of genes, and possibly affect not just one, but multiple, generations.[6,7] This growing area of inquiry is beginning to change the way we think about development in early childhood and early childhood development interventions. As separate

Recommendations:

1) Early interventions should start with prenatal care, even before conception.
2) Policies and interventions should be interdisciplinary involving health, education, nutrition, high-quality caregiving and protection
3) Effective programmes should take into account brain development, with special focus on critical periods such as early childhood and adolescence.

Anthony Lake, *Margaret Chan

Speaker's notes to the previous slide:

They outline recommendations including:

- Focusing on early interventions that start with prenatal care;
- Ensuring that policies and interventions involve health, nutrition, high-quality caregiving and protection;
- Including brain development in efforts to design effective programmes.

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doi:10.1093/schbul/sbv053
Advance Access publication April 22, 2015

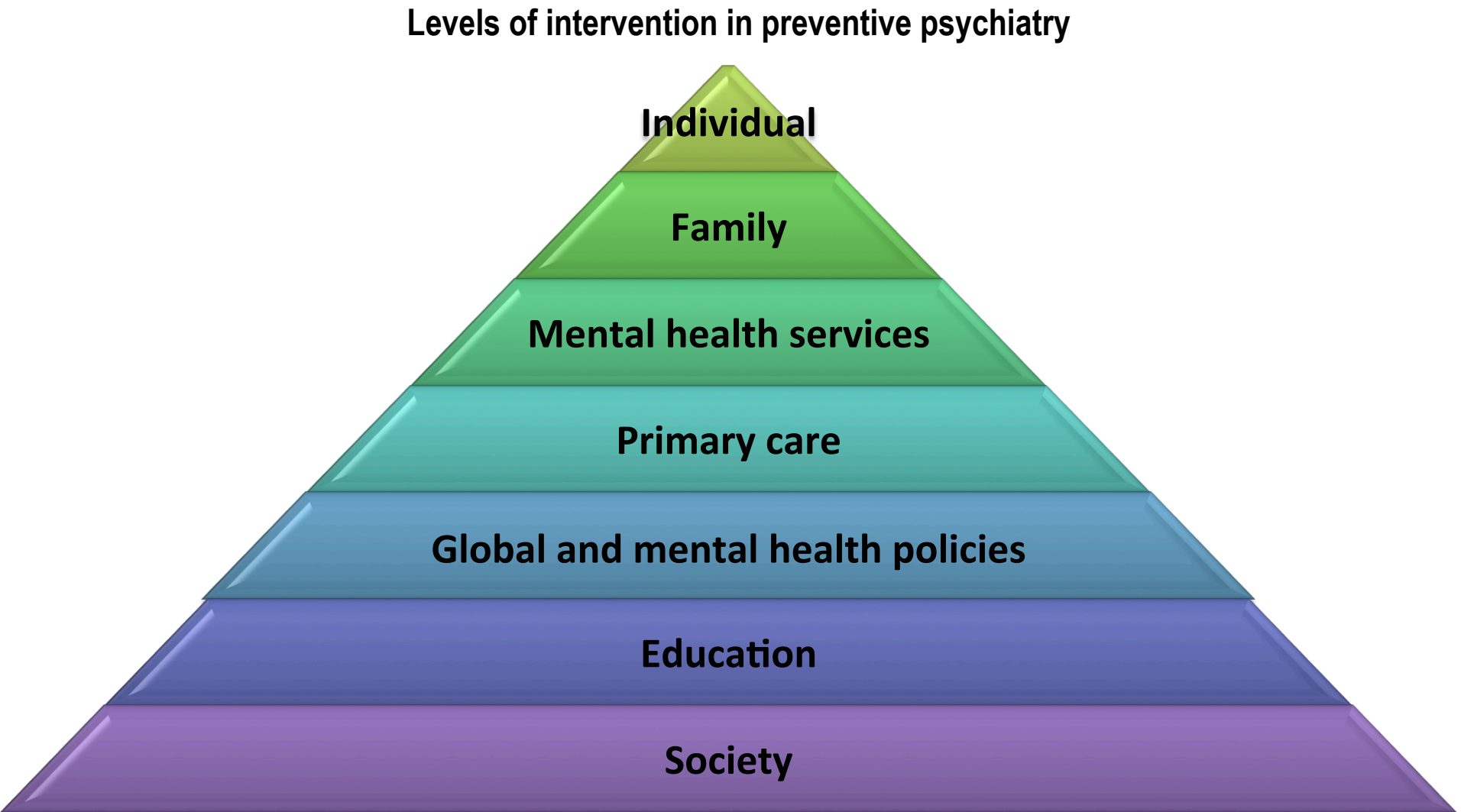
EDITORIAL

Ethical Challenges in the Primary Prevention of Schizophrenia

Challenges:

- How to identify the target population earlier than the emergence of prodromal symptoms.
- How to manage information given to the patient on the label as “high risk” and its potential stigmatising consequences.
- What the real conversion rates are.
- Balancing the risk-benefit ratio of interventions: focus on interventions that can provide other benefits besides reducing psychosis risk such as improved social adjustment, better parent-child interactions and enhanced cognitive function and not associated with side effects.

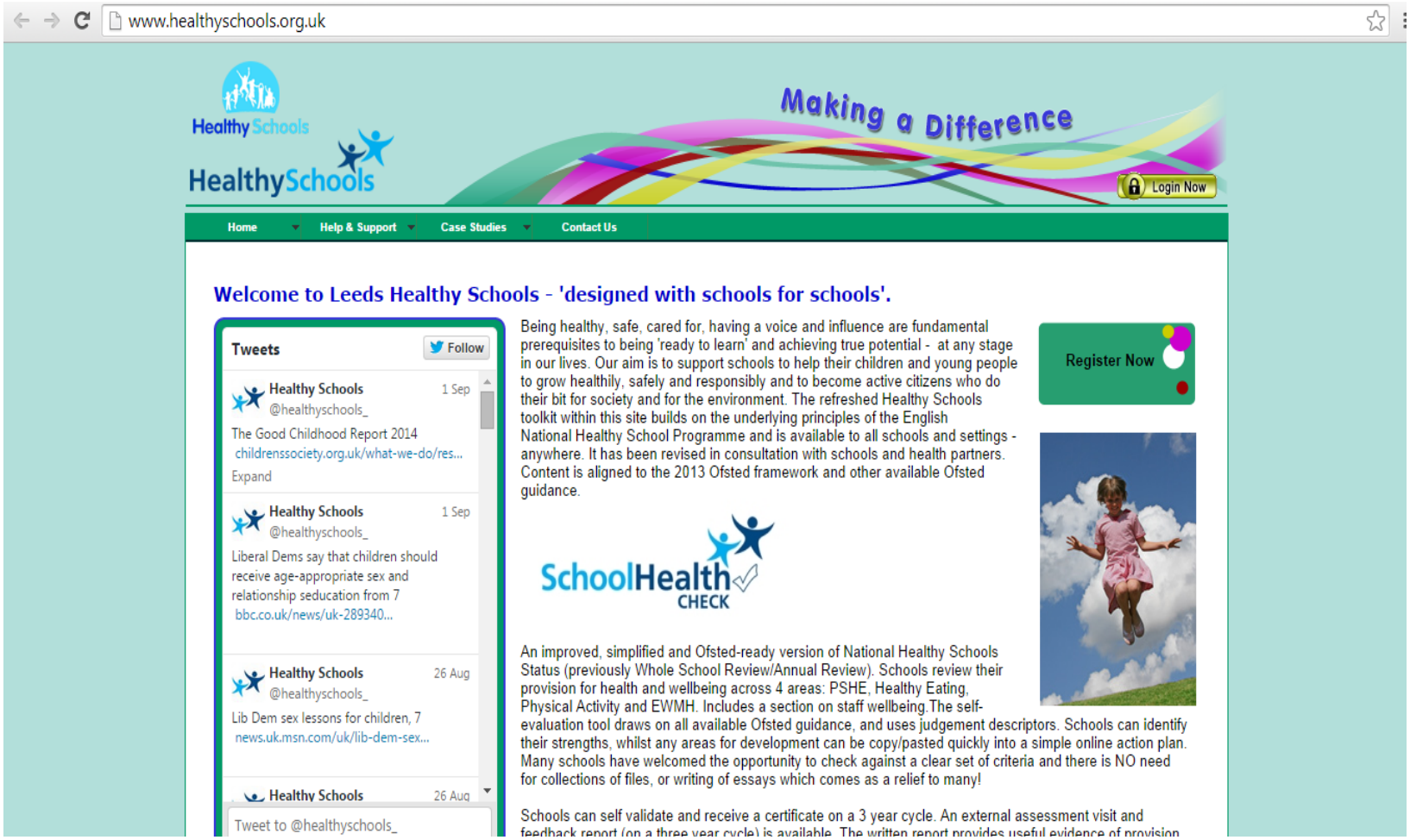
Challenges for the future: What should be done?



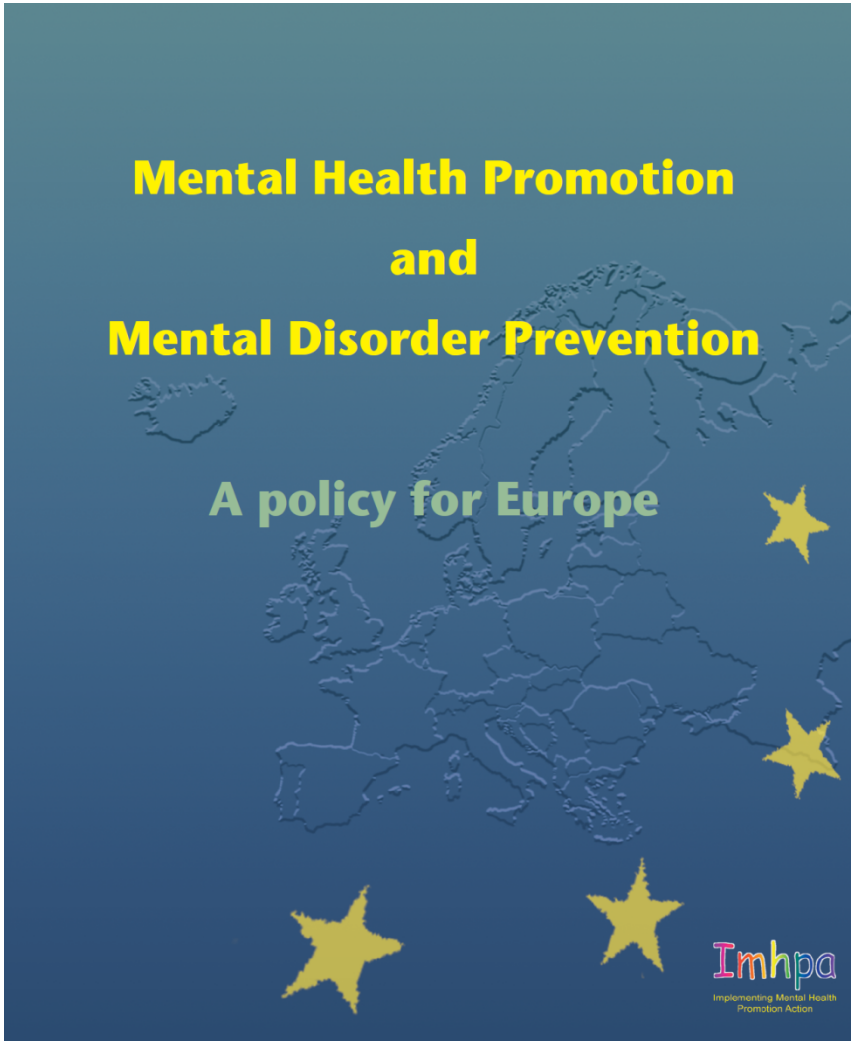
SOCIETY

Increase awareness of risk factors and implement preventive interventions

EDUCATIONAL LEVEL
Training in healthy mental styles



HEALTH POLICY LEVEL



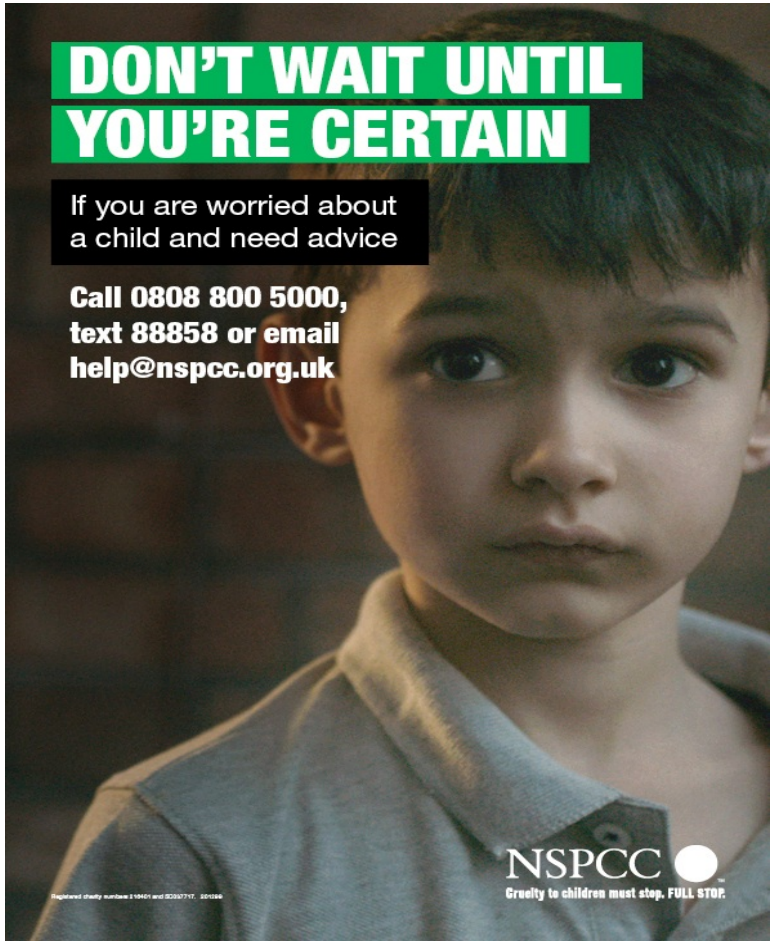
Ten action areas

1 Support parenting and the early years of life
2 Promote mental health in schools
3 Promote workplace mental health
4 Support mentally healthy ageing
5 Address groups at risk for mental disorders
6 Prevent depression and suicide
7 Prevent violence and harmful substance use
8 Involve primary and secondary health care
9 Reduce disadvantage and prevent stigma
10 Link with other sectors

Five common principles

1 Expand the knowledge base for mental health
2 Support effective implementation
3 Build capacity and train the workforce
4 Engage different actors
5 Evaluate policy and programme impact

Early detection and intervention in high-risk situations



- Increase social awareness of child abuse and neglect.
- Specific education of professionals in contact with children: teachers, pediatricians, doctors working in emergency services, social workers.
- Early detection at schools.
- Create safe environments facilitating the reporting of child abuse and avoiding re-victimisation.
- Close monitoring of cases of child abuse for early detection of development of mental disorders.
- Avoid service fragmentation.

Early intervention strategies in patients at ultra-high risk of psychosis

Early interventions to prevent psychosis: systematic review and meta-analysis

Table 2| **Summary of effects for transition to psychosis**

Comparison	Time point (months of treatment)	No (%) of trials in analysis	No (%) of participants in analysis	Risk ratio (95% CI), random effects	Heterogeneity (I^2 (%), χ^2 (P))	Quality of evidence (GRADE)
CBT *v* supportive counseling[23-25, 28, 29]	0-6	4 (80)	591 (88)	0.62 (0.29 to 1.31)	17, 3.6 (P=0.31)	Low*‡
	6-12	5 (100)	645 (71)	0.54 (0.34 to 0.86)	0, 2.51 (P=0.64) =0.P2)	Moderate*
	12+	4 (80)	570 (85)	0.63 (0.40 to 0.99)	0, 2.50(P=0.48)	Low*‡
CBT and risperidone *v* supportive counselling[24, 30]	0-6	2 (100)	130 (100)	0.35 (0.13 to 0.95)	0, 0.59 (P=0.44)	Very low*‡§
	6-12	2 (100)	130 (100)	0.63 (0.33 to 1.21)	0, 0.25 (P=0.61)	Very low*‡§
	12+	1 (50)	41 (32)	0.59 (0.34 to 1.04)	NA	Very low*‡§
Integrated psychotherapy *v* supportive counselling[37]	6-12	1 (100)	125 (100)	0.19 (0.04 to 0.81)	NA	Very low*‡¶
	12+	1 (100)	125 (100)	0.32 (0.11 to 0.92)	NA	Very low*‡¶
Integrated psychotherapy *v* standard care[35]	6-12	1 (100)	67 (85)	0.24 (0.07 to 0.81)	NA	Low*‡
	12+	1 (100)	65 (82)	0.52 (0.26 to 1.02)	NA	Low*‡
CBT and risperidone *v* CBT and placebo[24]	0-6	1 (100)	87 (100)	1.02 (0.15 to 6.94)	NA	Very low*‡§
	6-12	1 (100)	87 (100)	1.02 (0.39 to 2.67)	NA	Very low*‡§
Olanzapine *v* placebo[27]	6-12	1 (100)	60 (100)	0.43 (0.17 to 1.08)	NA	Very low*‡§
Omega 3 fatty acids *v* placebo[26]	0-6	1 (100)	76 (94)	0.13 (0.02 to 0.95)	NA	Low*§
	6-12	1 (100)	81 (100)	0.18 (0.04 to 0.75)	NA	Low*§

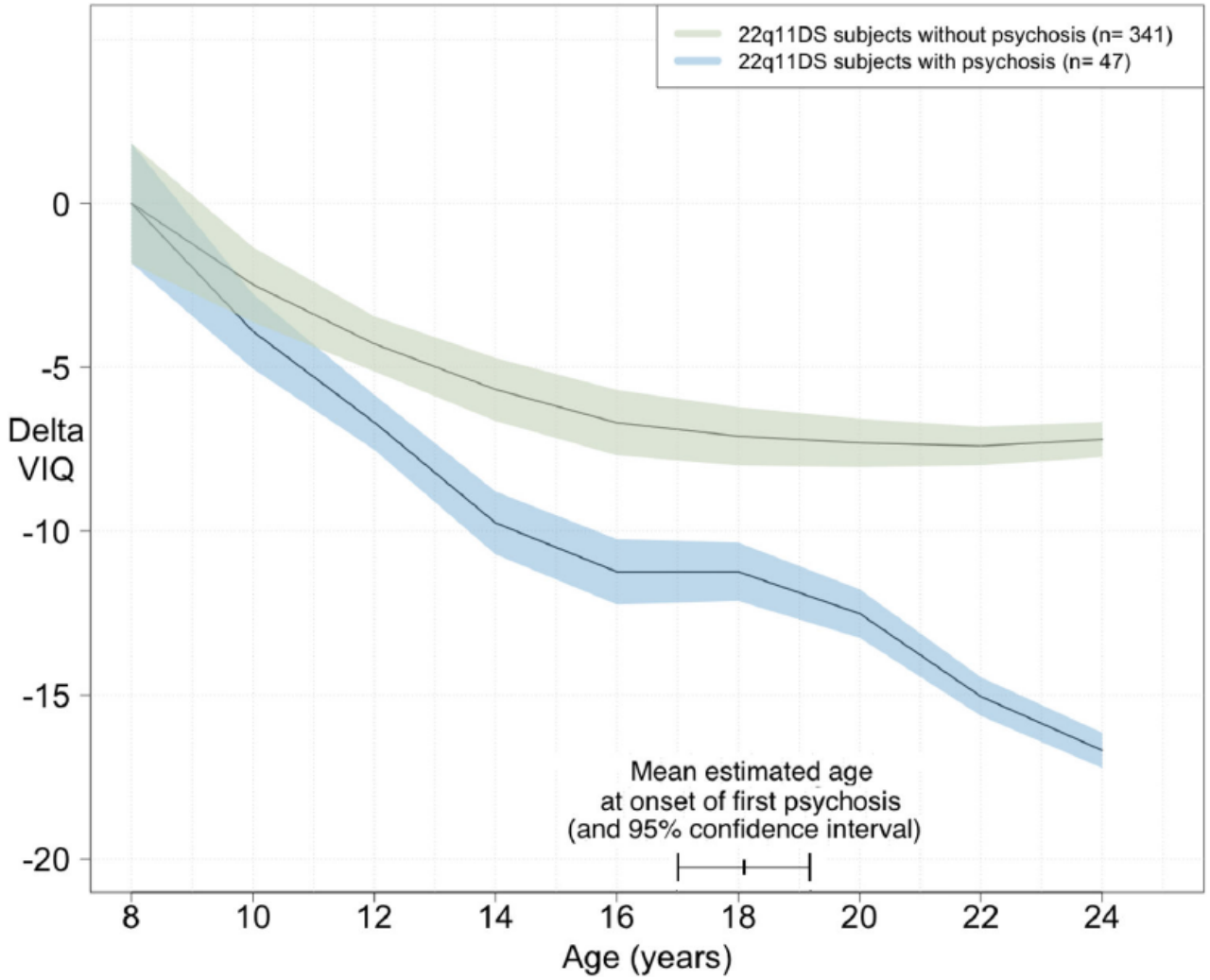
Stafford et al.,

BMJ 2013;346:f185

Speaker's notes to the previous slide:

- **Results** 11 trials including 1246 participants and eight comparisons were included. Median sample size of included trials was 81 (range 51-288). Meta-analyses were performed for transition to psychosis, symptoms of psychosis, depression, and mania; quality of life; weight; and discontinuation of treatment. **Evidence of moderate quality showed an effect for cognitive behavioural therapy on reducing transition to psychosis at 12 months** (risk ratio 0.54 (95% confidence interval 0.34 to 0.86); risk difference −0.07 (−0.14 to −0.01). *Very low quality evidence for omega-3 fatty acids and low to very low quality evidence for integrated psychotherapy also indicated that these interventions were associated with reductions in transition to psychosis at 12 months.*
- **Conclusions** Although evidence of benefits for any specific intervention is not conclusive, these findings suggest that it might be possible to delay or prevent transition to psychosis. Further research should be undertaken to establish conclusively the potential for benefit of psychological interventions in the treatment of people at high risk of psychosis.

Cognitive decline preceding psychosis in 22q11 deletion syndrome



Vorstman et al.

JAMA Psychiatry. 2015 April 1; 72(4): 377–385

Effect of a supportive environment on cognitive and behavioural development in 22q11 deletion syndrome

Journal of Intellectual Disability Research doi: 10.1111/jir.12054

VOLUME 58 PART 1 pp 31–47 JANUARY 2014

Association of the family environment with behavioural and cognitive outcomes in children with chromosome 22q11.2 deletion syndrome

T. M. Allen,[1] J. Hersh,[1] K. Schoch,[2] K. Curtiss[2], S. R. Hooper[3] & V. Shashi[2]

- Modest associations were found between aspects of the family social environment and parenting styles with social-behavioural and cognitive/ academic outcomes.

- Physical punishment, socioeconomic status, parental control and family organisation significantly predicted social-behavioural and cognitive outcomes in children with 22q11DS.

- Understanding the impact of environmental variables on developmental outcomes can be useful in determining more effective targets for intervention.

Supporting parenting in mothers with schizophrenia

INTERVENTIONS

- Diagnostic, neuropsychological and parenting assessments
- Outpatient, home outreach, crisis and inpatient treatment when needed
- Individual-, marital-, family- and group-treatment modalities
- Parent education
- Extensive linkages with schools, child protection and legal services
- Income supplementation
- Safe housing
- Respite and domestic aid
- Treatment accessibility for children
- Emphasis on prevention of negative impact of the mother's illness on the child (i.e. prenatal care, good obstetrics, postnatal psychiatric care, infant monitoring and early intervention with the child

Seeman et al., Primary Psychiatry 2002

Journal of the American Academy of
CHILD & ADOLESCENT
PSYCHIATRY

Effect of Preventive Interventions in Mentally Ill Parents on the Mental Health of the Offspring: Systematic Review and Meta-Analysis

Results

Thirteen trials including 1,490 children were analyzed. Interventions included cognitive, behavioral, or psychoeducational components. Seven trials assessed the incidence of mental disorders and seven trials assessed symptoms. In total 161 new diagnoses of mental illness were recorded, with interventions decreasing the risk by 40% (combined relative risk 0.60, 95% CI 0.45–0.79). Symptom scores were lower in the intervention groups: standardized mean differences were −0.22 (95% CI −0.37 to −0.08) for internalizing symptoms (p = .003) and −0.16 (95% confidence interval −0.36 to 0.04) for externalizing symptoms (p = .12).

Conclusions

Interventions to prevent mental disorders and psychological symptoms in the offspring of parents with mental disorders appear to be effective.

January 2012. Volume 51, Issue 1, Pages 8–17.e8

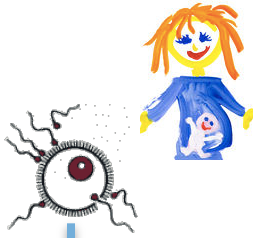
Developmentally sensitive interventions

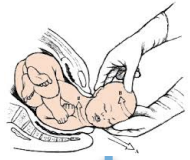
Clinical risk symptoms

Good prenatal care to improve nutrition, reduce maternal infection, substance misuse, stress, obstetric complications

- Screening for cognitive, social and motor deficits
- Prevention of trauma and bullying
- Participation in sports, art, music

- CBT, family therapy
- Medication
- Supported employment for clinical conditions







CONCEPTION | BIRTH | PRE-SCHOOL | PRIMARY SCHOOL | PUBERTY ADOLESCENCE | LATE TEENS AND 20s

Good perinatal support, good supportive parental care, early mother-child interaction support

- Support school function
- Support relationships
- Family psychoeducation
- Cognitive enhancement

- Prevention of substance use
- Management of risk taking
- Prosocial activities
- Forming identity

Familial risk for psychosis

Adapted from Seidman and Nortendoft. Schiz Bulletin, 2015

Speaker's notes to the previous slide:

Phase specific early intervention & prevention strategies for clinical and familial high risk. Clinical risk symptoms are contrasted with family risk for psychosis by depicting the greater likelihood of conversion to psychosis to occur in the clinical risk group by the larger reddish arrow. Interventions above the line for the clinical risk group begin around the end of elementary school reflecting the earliest period that prodromal symptoms are typically reported, whereas those below the line begin during pregnancy reflecting more of a primary prevention approach.

Eur Child Adolesc Psychiatry (2012) 21:475–476
DOI 10.1007/s00787-012-0313-6

EDITORIAL

Someone is not listening to the facts: there is little psychiatry outside (child and adolescent) psychiatry

preventive

Celso Arango

Published online: 2 August 2012
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Given these trying economic times, let us start with some economic evidence. We have recently learned from a study funded by the European College of Neuropsychopharmacology (ECNP) and the European Brain Council (EBC) that brain disorders, and mental disorders in particular, are not only one of the main causes of burden and suffering for European countries, but they cost the EU more than cardiovascular and oncologic disorders combined. The

could be one of the plausible explanations for this finding. Another article in this issue reflects that some environmental factors, such as sexual abuse, are far more common than expected. Using data from a longitudinal randomised controlled trial of a school-based intervention programme for reducing adolescent sexual assault and related risk behaviours, Brasmen et al. (in press) assessed the prevalence of adolescent peer-on-peer sexual victimisation over

Conclusions

- There is still little interest in preventative interventions in psychiatry, as compared with other medical specialties.

- Behavioural symptoms are late manifestations of the underlying brain process. Recent knowledge about developmental risks for psychosis has shaped a promising outlook for early intervention.

- Risk factors do not seem to be disorder-specific. In psychosis, even early intervention is most often secondary prevention.

Conclusions

- A priority for the next few years will be to focus towards “very early” interventions in which the aim is not prevention of psychosis. Eventually, specific interventions in developmentally sensitive periods, may reduce the incidence of psychosis or shift the evolution towards less severe presentations.

- In those at very increased risk of presenting psychosis, narrow monitoring, parent training and training in coping skills should be mandatory.

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