Schizophrenia spectrum disorders

Aetiology, staging, treatment and physical co-morbidities

Questions - etiology

- What is the estimated percentage explaining schizophrenia using the information of 108 genetic loci related to the disorder?

a. 10%

b. 20%

c. 30%

- These loci are related to

a. Serotonin

b. GABA

c. Immune system

Questions - etiologie

- The risk of schizophrenia is increased by childhoodtrauma with:

a. 2-4%

b. 4-6%

c. 6-10%

- A first degree family member has increased risk of schizophrenia:

a. 5-20%

b. 20-35%

c. 35-50%

Aetiology - Genes

Schizophrenia Bulletin vol. 41 no. 1 pp. 15–19, 2015
doi:10.1093/schbul/sbu162
Advance Access publication November 13, 2014

GE

Schizophrenia Genetics: Building the Foundations of the

Katherine E. Tansey*, Michael J. Owen, and Michael C. O'Donovan

MRC Centre for Neuropsychiatric Genetics and Genomics, Institute of Psycholo
Medicine, Cardiff University, Cardiff, UK

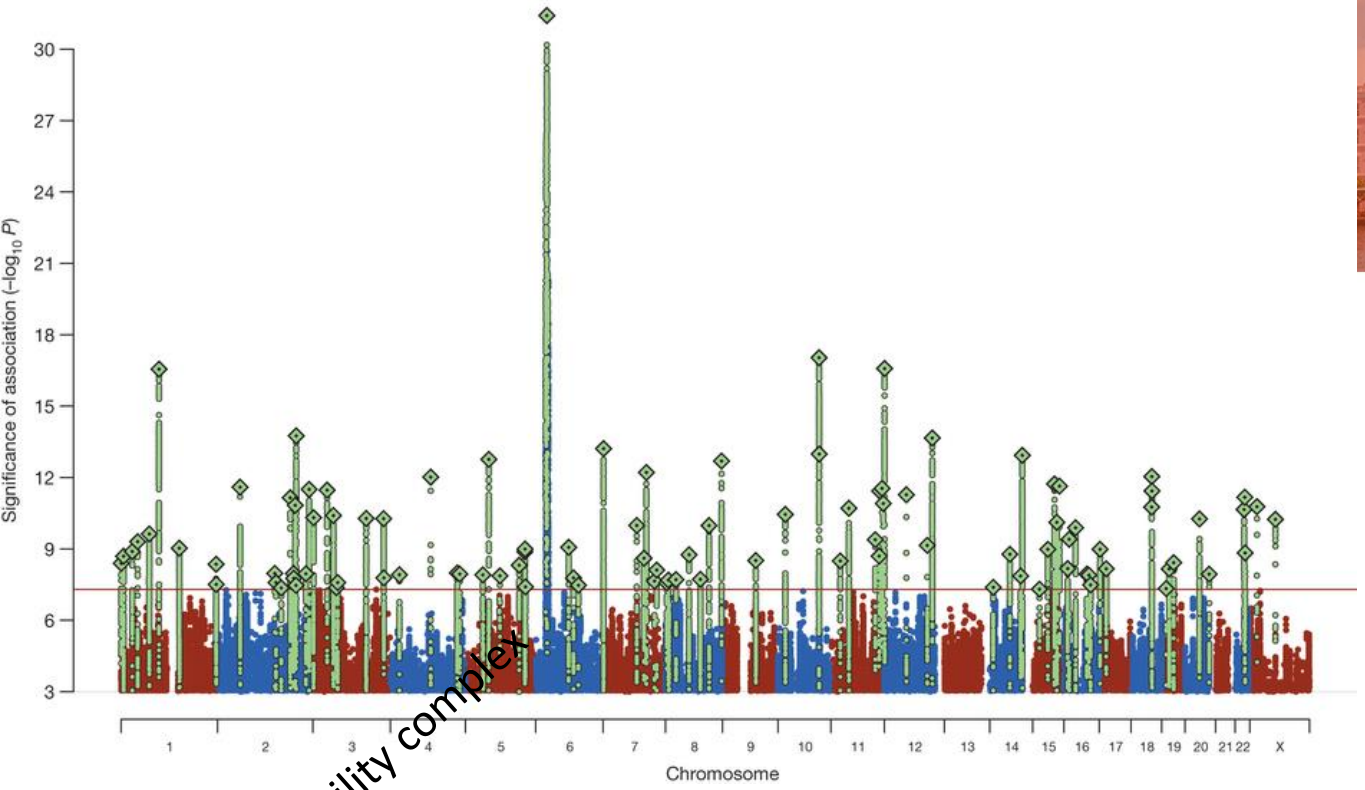
*To whom correspondence should be addressed; MRC Centre for Neuropsych
Medicine and Clinical Neurosciences, School of Medicine, Cardiff Universit
fax: +44-029-20-687-068, e-mail: tanseyk@cardiff.ac.uk

Biological insights from 108 schizophrenia–associated genetic loci

Schizophrenia Working Group of the Psychiatric Genomics Consortium*

Schizophrenia is a highly heritable disorder. Genetic risk is conferred by a large number of alleles, including common alleles of small effect that might be detected by genome-wide association studies. Here we report a multi-stage schizophrenia genome-wide association study of up to 36,989 cases and 113,075 controls. We identify 128 independent associations spanning 108 conservatively defined loci that meet genome-wide significance, 83 of which have not been previously reported. Associations were enriched among genes expressed in brain, providing biological plausibility for the findings. Many findings have the potential to provide entirely new insights into aetiology, but associations at *DRD2* and several genes involved in glutamatergic neurotransmission highlight molecules of known and potential therapeutic relevance to schizophrenia, and are consistent with leading pathophysiological hypotheses. Independent of genes expressed in brain, associations were enriched among genes expressed in tissues that have important roles in immunity, providing support for the speculated link between the immune system and schizophrenia.

The latest example comes from the Schizophrenia Working Group of the Psychiatric Genomics Consortium (PGC-SCZ) which, at the time of publication, included contributions from around 37 000 individuals with schizophrenia, 302 investigators, 35 countries, and 4 continents.[1] In their recent paper, published in *Nature* in July 2014, the PGC-SCZ group report 128 statistically independent genetic associations, implicating a minimum of 108 conservatively defined schizophrenia-associated genetic loci.[1]



Major histocompatibility complex
MHC

Characterization of associated loci

Of the 108 loci, 75% include protein-coding genes (40%, a single gene) and a further 8% are within 20 kb of a gene (Supplementary Table 3). Notable associations relevant to major hypotheses of the aetiology and treatment of schizophrenia include *DRD2* (the target of all effective antipsychotic drugs) and many genes (for example, *GRM3*, *GRIN2A*, *SRR*, *GRIA1*) involved in glutamatergic neurotransmission and synaptic plasticity. In addition, associations at *CACNA1C*, *CACNB2* and *CACNA1I*, which encode voltage-gated calcium channel subunits, extend previous findings implicating members of this family of proteins in schizophrenia and other psychiatric disorders[11,13,31,32]. Genes encoding calcium channels, and proteins involved in glutamatergic neurotransmission and synaptic plasticity have been independently implicated in schizophrenia by studies of rare genetic variation[33–35], suggesting convergence at a broad functional level between studies of common and rare genetic variation.

The genetic overlap between schizophrenia and other non-psychiatric disorders

Improved Detection of Common Variants Associated with Schizophrenia by Leveraging Pleiotropy with Cardiovascular-Disease Risk Factors

Ole A. Andreassen,[1,2,3,*] Srdjan Djurovic,[1,2] Wesley K. Thompson,[3] Andrew J. Schork,[4,5,6] Kenneth S. Kendler,[7] Michael C. O'Donovan,[8] Dan Rujescu,[9] Thomas Werge,[10] Martijn van de Bunt,[11] Andrew P. Morris,[11] Mark I. McCarthy,[11] International Consortium for Blood Pressure GWAS, Diabetes Genetics Replication and Meta-analysis Consortium, Psychiatric Genomics Consortium Schizophrenia Working Group, J. Cooper Roddey,[4,13] Linda K. McEvoy,[4,12] Rahul S. Desikan,[4,12] and Anders M. Dale[3,4,12,13,*]

Several lines of evidence suggest that genome-wide association studies (GWASs) have the potential to explain more of the "missing heritability" of common complex phenotypes. However, reliable methods for identifying a larger proportion of SNPs are currently lacking. Here, we present a genetic-pleiotropy-informed method for improving gene discovery with the use of GWAS summary-statistics data. We applied this methodology to identify additional loci associated with schizophrenia (SCZ), a highly heritable disorder with significant missing heritability. Epidemiological and clinical studies suggest comorbidity between SCZ and cardiovascular-disease (CVD) risk factors, including systolic blood pressure, triglycerides, low- and high-density lipoprotein, body mass index, waist-to-hip ratio, and type 2 diabetes. Using stratified quantile-quantile plots, we show enrichment of SNPs associated with SCZ as a function of the association with several CVD risk factors and a corresponding reduction in false discovery rate (FDR). We validate this "pleiotropic enrichment" by demonstrating increased replication rate across independent SCZ substudies. Applying the stratified FDR method, we identified 25 loci associated with SCZ at a conditional FDR level of 0.01. Of these, ten loci are associated with both SCZ and CVD risk factors, mainly triglycerides and low- and high-density lipoproteins but also waist-to-hip ratio, systolic blood pressure, and body mass index. Together, these findings suggest the feasibility of using genetic-pleiotropy-informed methods for improving gene discovery in SCZ and identifying

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IEA

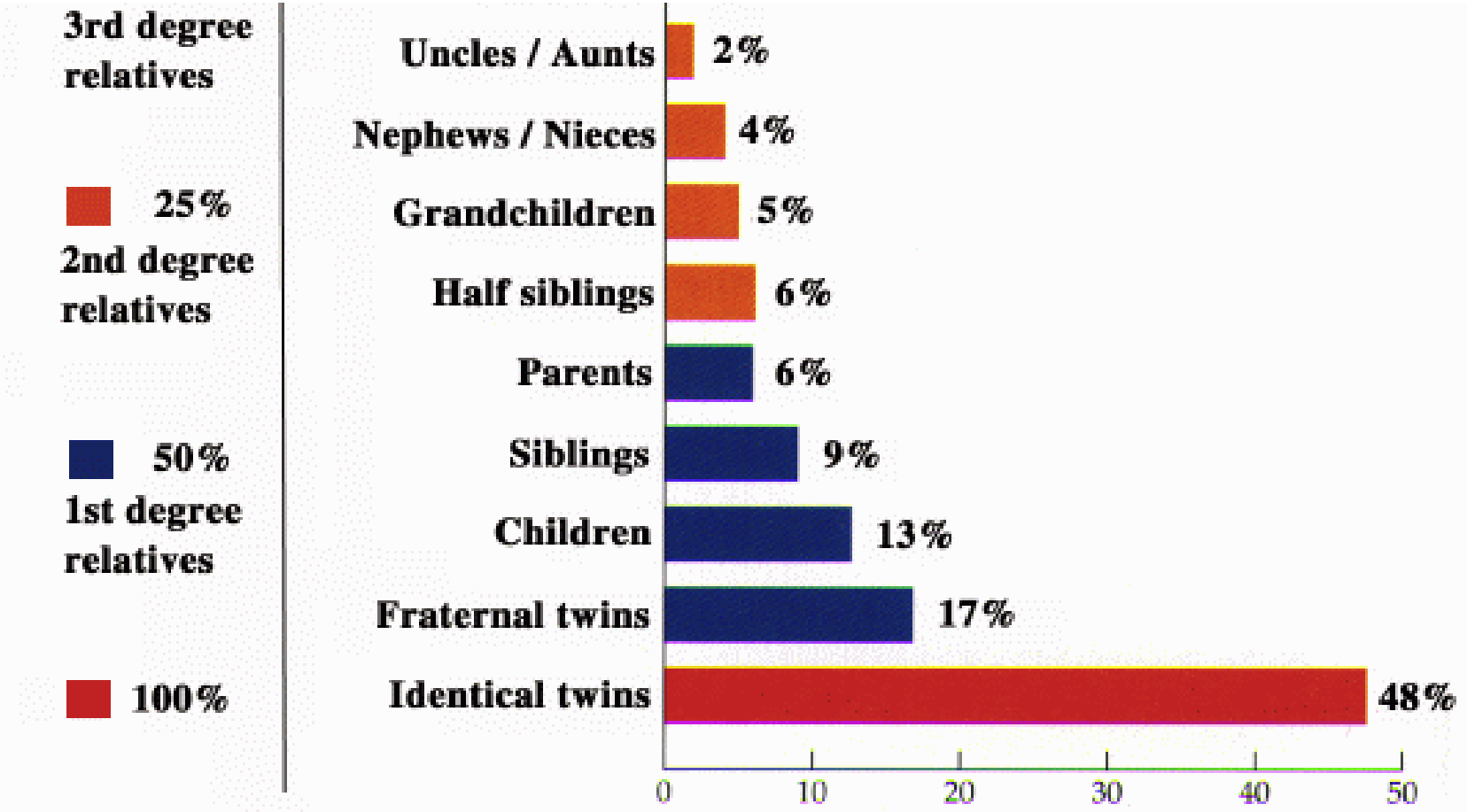
International Journal of Epidemiology, 2015, 1–16
doi: 10.1093/ije/dyv136
Original article

Original article

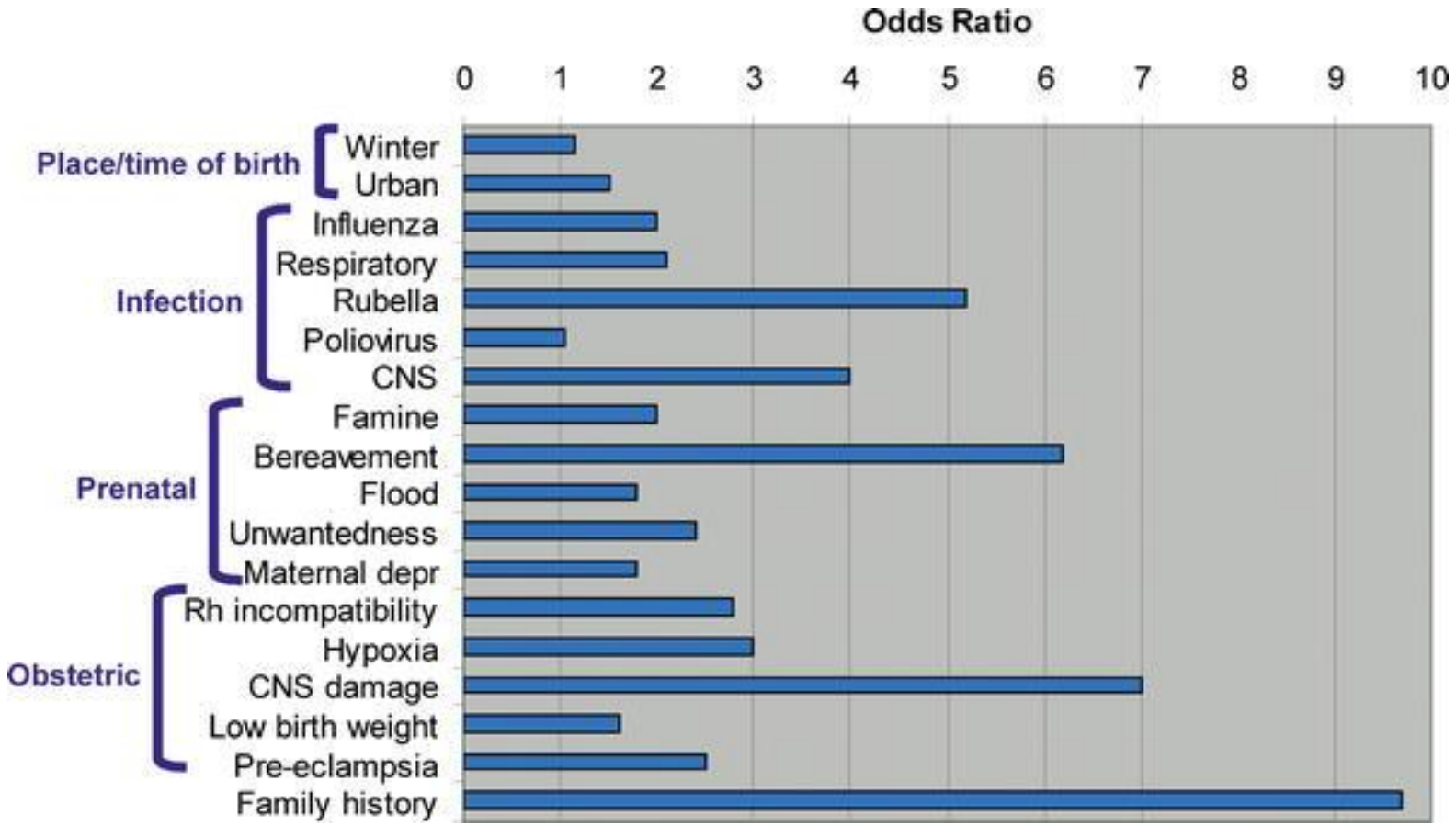
New data and an old puzzle: the negative association between schizophrenia and rheumatoid arthritis

S Hong Lee,[1,2] Enda M Byrne,[1] Christina M Hultman,[3] Anna Kähler,[3]

Family risk


3rd degree relatives
25%
2nd degree relatives
50%
1st degree relatives
100%
Uncles / Aunts
2%
Nephews / Nieces
4%
Grandchildren
5%
Half siblings
6%
Parents
6%
Siblings
9%
Children
13%
Fraternal twins
17%
Identical twins
48%
0
10
20
30
40
50

Environmental factors and schizophrenia



ONLINE FIRST

Family-Based Analysis of Genetic Variation Underlying Psychosis-Inducing Effects of Cannabis

Sibling Analysis and Proband Follow-up

Ruud van Winkel, MD, MSc, PhD; Genetic Risk and Outcome of Psychosis (GROUP) Investigators

Table 4. Lifetime Frequency of Cannabis Use and Relative Risks, Determined by Multinomial Logistic Regression Analysis, According to *AKT1* rs2494732 Genotype in 679 Patients[a] With a Psychotic Disorder

	CIDI Lifetime Use, %			RR		
	T/T (n=237)	C/T (n=313)	C/C (n=129)	T/T (n=237)	C/T (n=313)	C/C (n=129)
No use	48.1	44.7	35.7	b	b	b
Less than weekly use	9.7	6.4	6.2	1 [Reference]	0.71	0.86
Weekly use	9.3	11.8	12.4	1 [Reference]	1.31	1.72
Daily use	32.5	37.1	45.7	1 [Reference]	1.23	1.90[c]

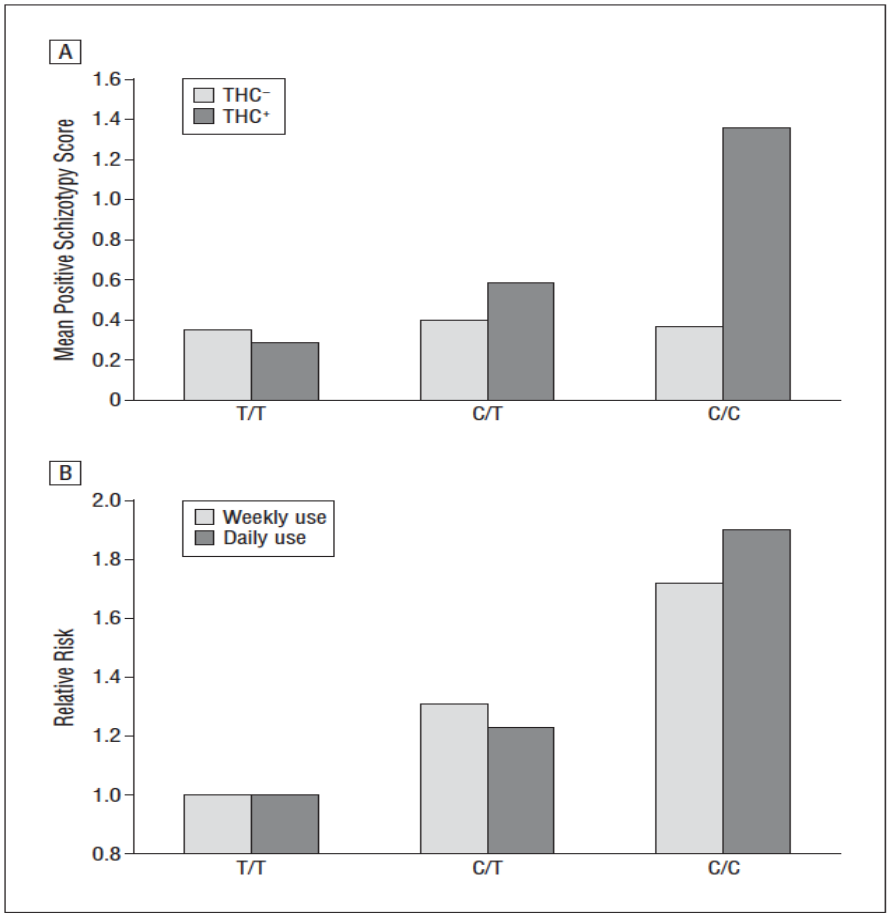


Figure. *AKT1* rs2494732 × cannabis interaction in the at-risk and case-only paradigm. A, Mean positive schizotypy scores according to *AKT1* rs2494732 genotype in 728 unaffected siblings with (n=55) and without (n=673) recent cannabis use. Genotyping was unsuccessful in 12 unaffected siblings. THC indicates tetrahydrocannabinol. B, Relative risks for weekly and daily lifetime cannabis use in the patients according to *AKT1* rs2494732 genotype.

Psychological Medicine (2013), **43**, 225–238. © Cambridge University Press 2012
doi:10.1017/S0033291712000785

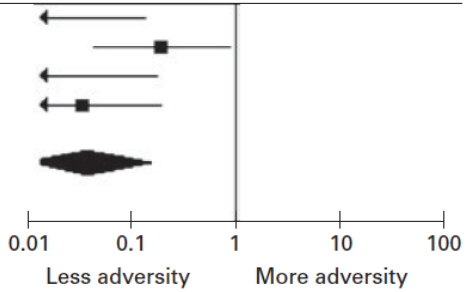
REVIEW ARTICLE

Childhood adversity in schizophrenia: a systematic meta-analysis

(*e*)

Study or subgroup	Schizophrenia Events	Schizophrenia Total	Dissociative / PTSD Events	Dissociative / PTSD Total	Weight	Odds ratio M-H, Random, 95% CI
Fink 1990	1	11	15	16	18.8%	0.01 (0.00–0.12)
Honig 1998	3	18	8	15	33.4%	0.17 (0.04–0.87)
Nurcombe 1996	0	10	22	25	17.5%	0.01 (0.00–0.16)
Ross 1989	2	20	16	20	30.3%	0.03 (0.00–0.17)
Total (95% CI)		59		76	100.0%	0.03 (0.01–0.15)
Total events	6		61			

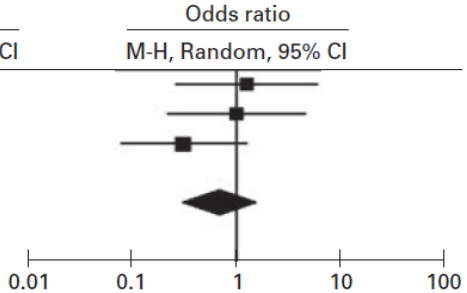
Heterogeneity: $\tau^2 = 1.28$; $\chi^2 = 6.06$, df = 3 ($p = 0.11$); $I^2 = 51\%$
Test for overall effect: $Z = 4.31$ ($p < 0.0001$)



(*f*)

Study or subgroup	Schizophrenia Events	Schizophrenia Total	Other psychoses Events	Other psychoses Total	Weight	Odds ratio M-H, Random, 95% CI
Craine 1989	21	43	3	7	30.4%	1.27 (0.25–6.38)
Goff 1991	11	33	3	9	32.3%	1.00 (0.21–4.78)
Hlastala 2005	17	27	17	20	37.2%	0.30 (0.07–1.29)
Total (95% CI)		103		36	100.0%	0.69 (0.28–1.68)
Total events	49		23			

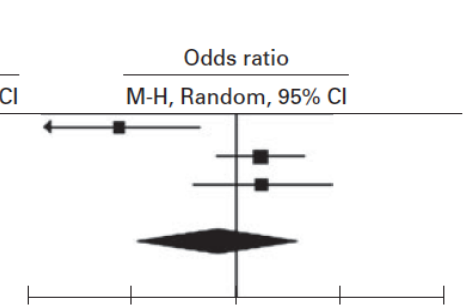
Heterogeneity: $\tau^2 = 0.01$; $\chi^2 = 2.03$, df = 2 ($p = 0.36$); $I^2 = 2\%$
Test for overall effect: $Z = 0.82$ ($p = 0.41$)



(*g*)

Study or subgroup	Schizophrenia Events	Schizophrenia Total	Personality disorders Events	Personality disorders Total	Weight	Odds ratio M-H, Random, 95% CI
Byrne 1990	4	14	13	15	30.3%	0.06 (0.01–0.41)
Craine 1988	21	43	8	23	37.4%	1.79 (0.63–5.09)
Kingdon 2010	56	59	30	33	32.3%	1.87 (0.35–9.82)
Total (95% CI)		116		71	100.0%	0.65 (0.09–4.71)
Total events	81		51			

Heterogeneity: $\tau^2 = 2.43$; $\chi^2 = 10.26$, df = 2 ($p = 0.006$); $I^2 = 80\%$
Test for overall effect: $Z = 0.42$ ($p = 0.67$)



Childhood adversity and risk of psychosis

Trauelsen AM et al. Childhood adversity specificity and dose-response effect in non-affective first-episode psychosis. Schizophr Res. 2015 Jun;165(1):52-9.

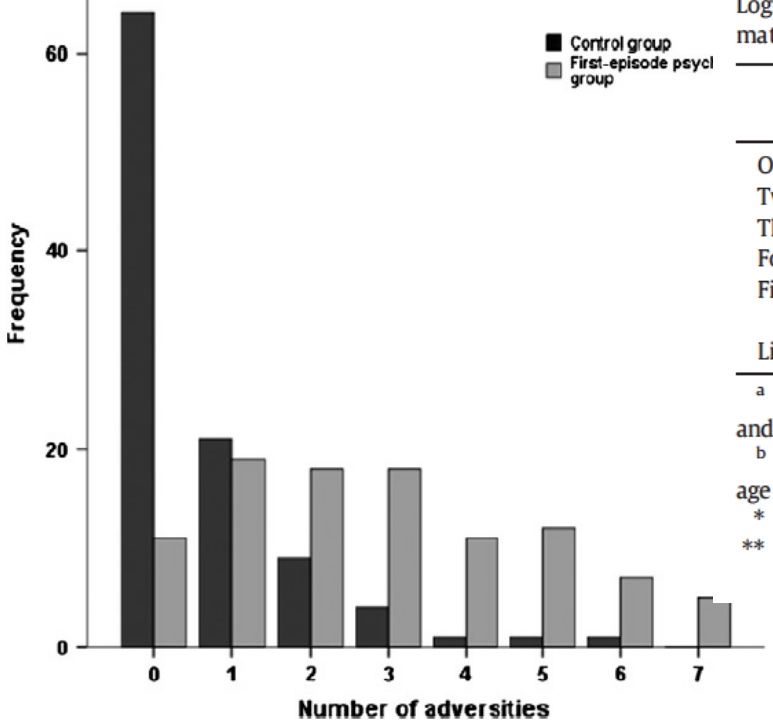


Fig. 1. Number of reported adversities including sexual, physical, emotional abuse, physical and emotional neglect, separation and institutionalization in persons with FEP (n = 101) and matched control persons (n = 101).

Table 2
Logistic regression analysis for number of adversities in persons with FEP (n = 101) and matched control persons (n = 101).

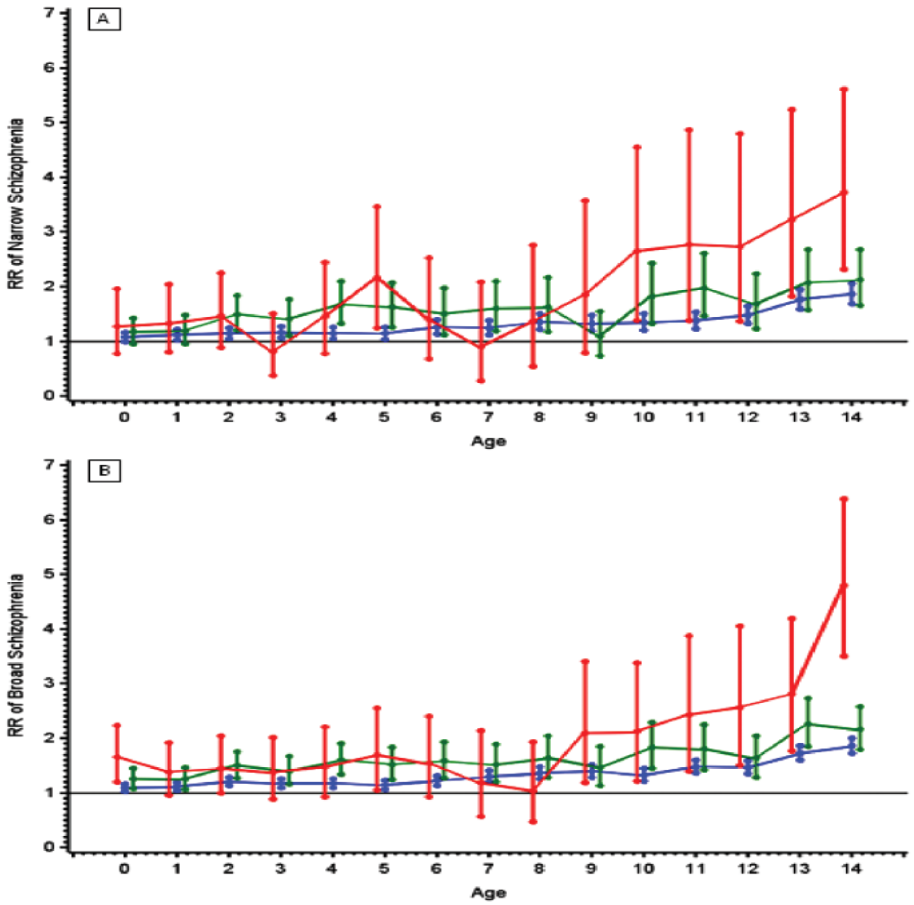
	Cases N (%)	Controls N (%)	OR[a]	95 CI	p-value	Wald
One adversity	19 (19)	21 (21)	0.95	0.45–1.98	0.88	7.41
Two adversities	18 (18)	9 (9)	1.84	0.82–4.87	0.13	2.29
Three adversities	18 (18)	4 (4)	5.06	1.59–16.17	0.01*	7.49
Four adversities	11 (11)	1 (1)	12.78	1,56–105	0.02*	5.62
Five or more adversities	24 (24)	2 (2)	12.95	2.84–59.00	0.001**	10.96
Linear trend[b]			2.55	1.91–3.40	<0.001**	39.97

[a] Logistic Regression model adjusted for gender, age, first degree psychiatric disorder and parent's socio-economic status.
[b] Adversities included are CTQ subcategories, separation and institutionalization before age 18.
* $P < 0.05$.
** $P < 0.01$.

Schizophrenia Bulletin vol. 41 no. 2 pp. 346–354, 2015
doi:10.1093/schbul/sbu074
Advance Access publication June 5, 2014

Childhood Residential Mobility, Schizophrenia, and Bipolar Disorder: A Population-based Study in Denmark

Diana Paksarian*[,1,5], William W. Eaton[1], Preben B. Mortensen[2–4], and Carsten B. Pedersen[2–4]

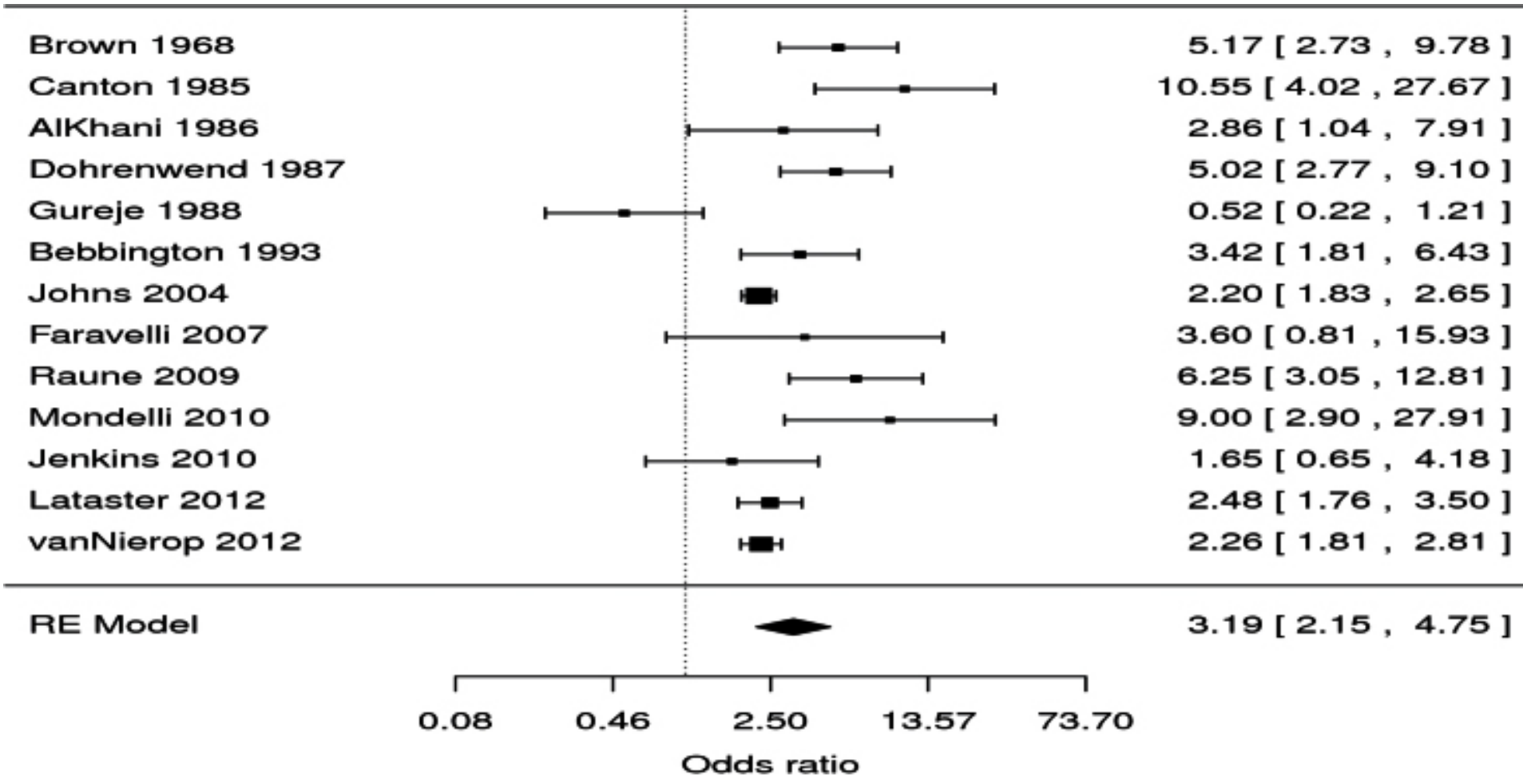


Relative risks and 95% confidence intervals. Blue lines represent RRs for 1 move. Green lines represent RRs for 2 moves. Red lines represent 3 or more moves. Estimates are adjusted for age, sex, calendar year, birth period, parental age, urbanicity level at birth, and history of mental disorder in a parent or sibling. For a color version, see this figure online.

Schizophrenia Bulletin vol. 39 no. 4 pp. 740–747, 2013
doi:10.1093/schbul/sbt065
Advance Access publication May 13, 2013

Life Events and Psychosis: A Review and Meta-analysis

Stephanie Beards*[,1], Charlotte Gayer-Anderson[1], Susana Borges[1], Michael E. Dewey[2], Helen L. Fisher[3,4], and Craig Morgan[1,4]



Questions - etiology

- What is the estimated percentage using the information from 108 genetic loci explaining schizophrenia?

a. 10%

b. 20%

c. 30%

- These loci are related to

a. Serotonin

b. GABA

c. Immune system

Questions - etiologie

The risk of schizophrenia is increased by childhood trauma with:

a. 2-4%

b. 4-6%

c. 6-10%

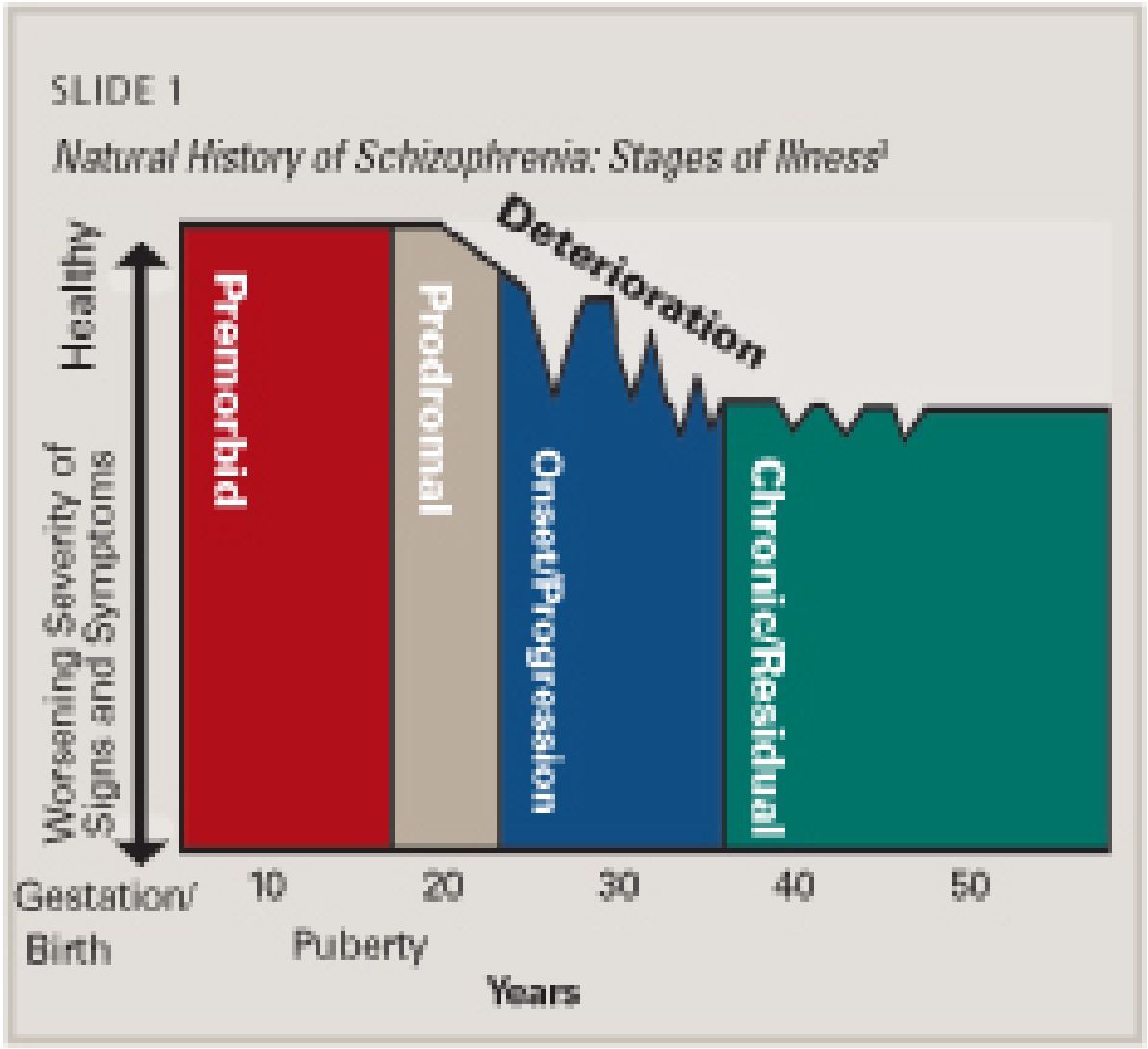
A first degree family member has increased risk of schizophrenia:

a. 5-20%

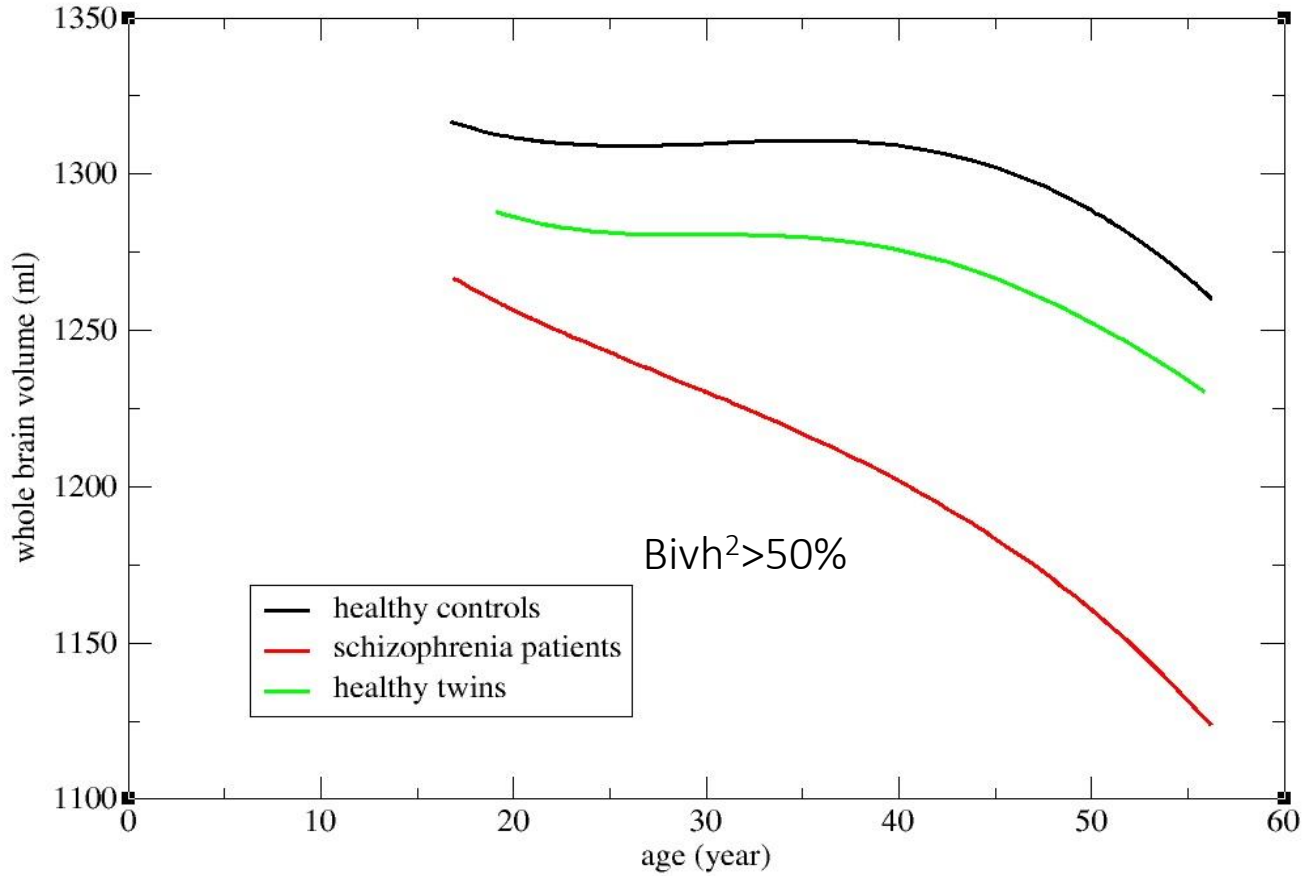
b. 20-35%

c. 35-50%

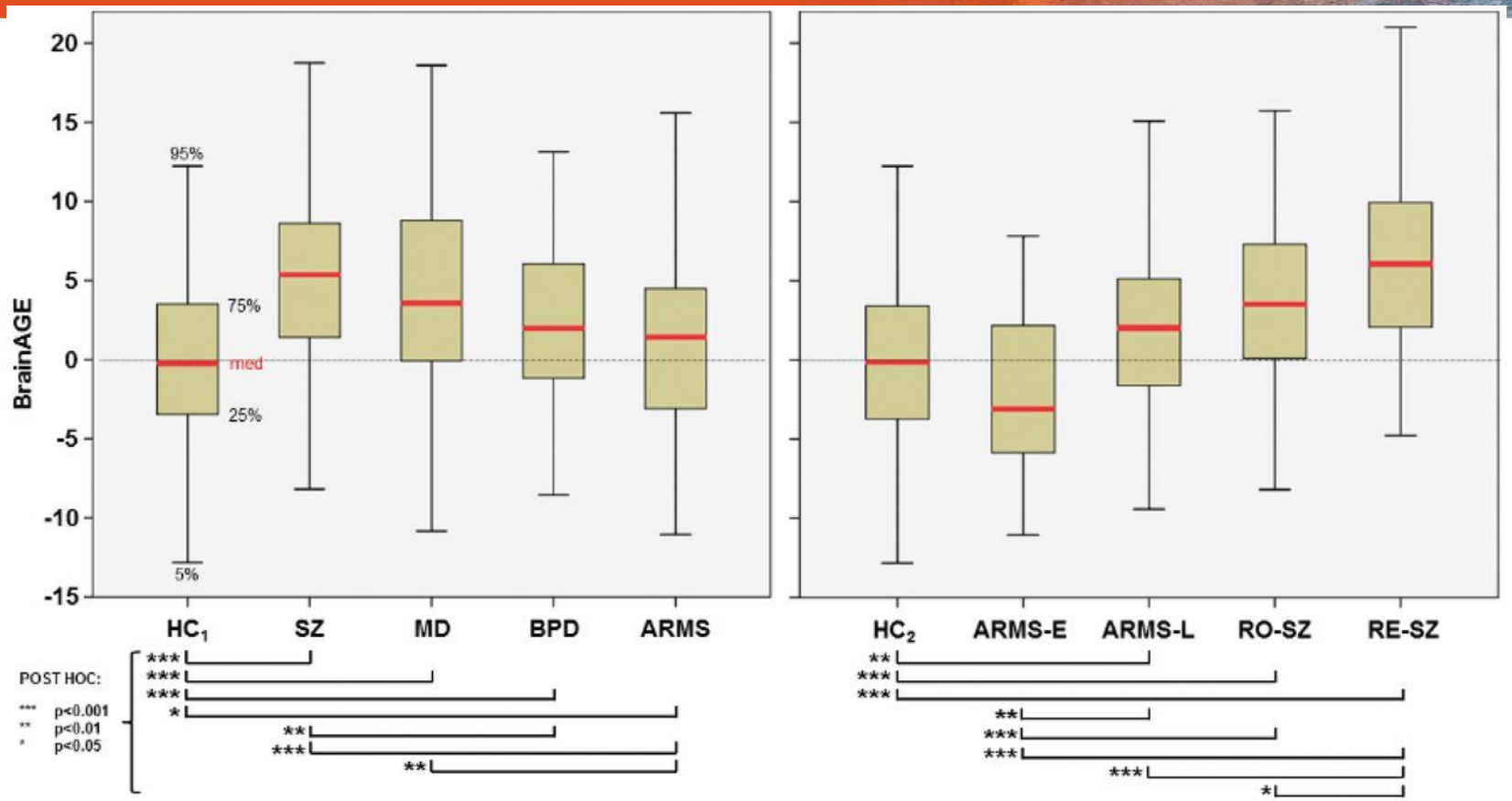
Staging schizophrenia



Brain volume changes with age



Accelerated brain aging



Koutsouleris N et al. Schizophr Bull 2014;40:1140-1153

Schizophrenia Bulletin

Questions staging

- To reduce the prevalence of psychotic disorders we should:

1. Set up pecialized clinics for subjects who have prodromal symptoms
2. Follow-up subjects seen in the child and adolescent psychiatry department
3. Screen the pre-adolescent population
4. Other

- Are we able to detect all subjects who will develop a psychotic disorder if we do all of the above?

1. Yes
2. No

Questions treatment

- What is the percentage of patients with a first episode psychosis receiving a diagnosis of schizophrenia spectrum disorder?

a. 60 %

b. 70%

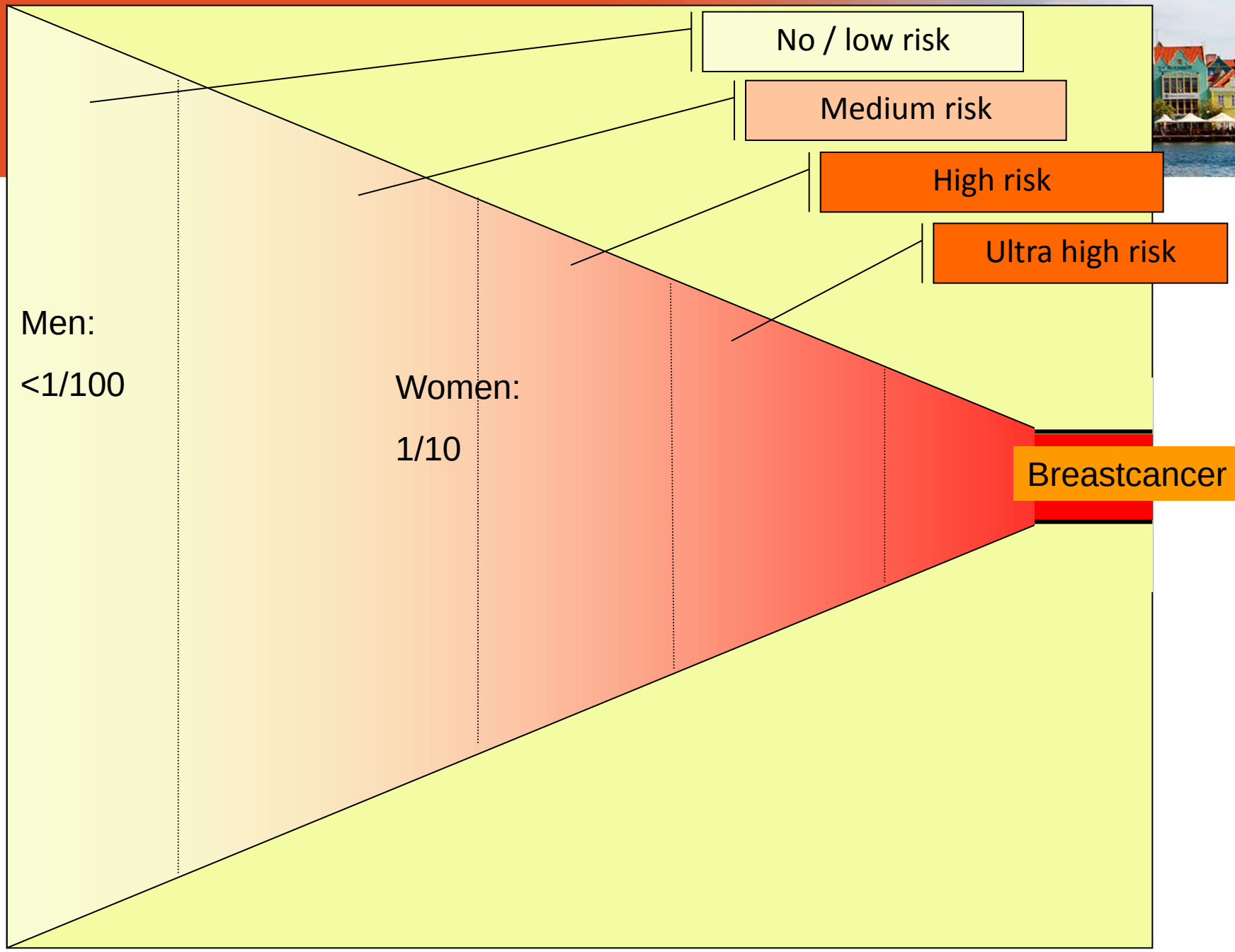
c. 80%

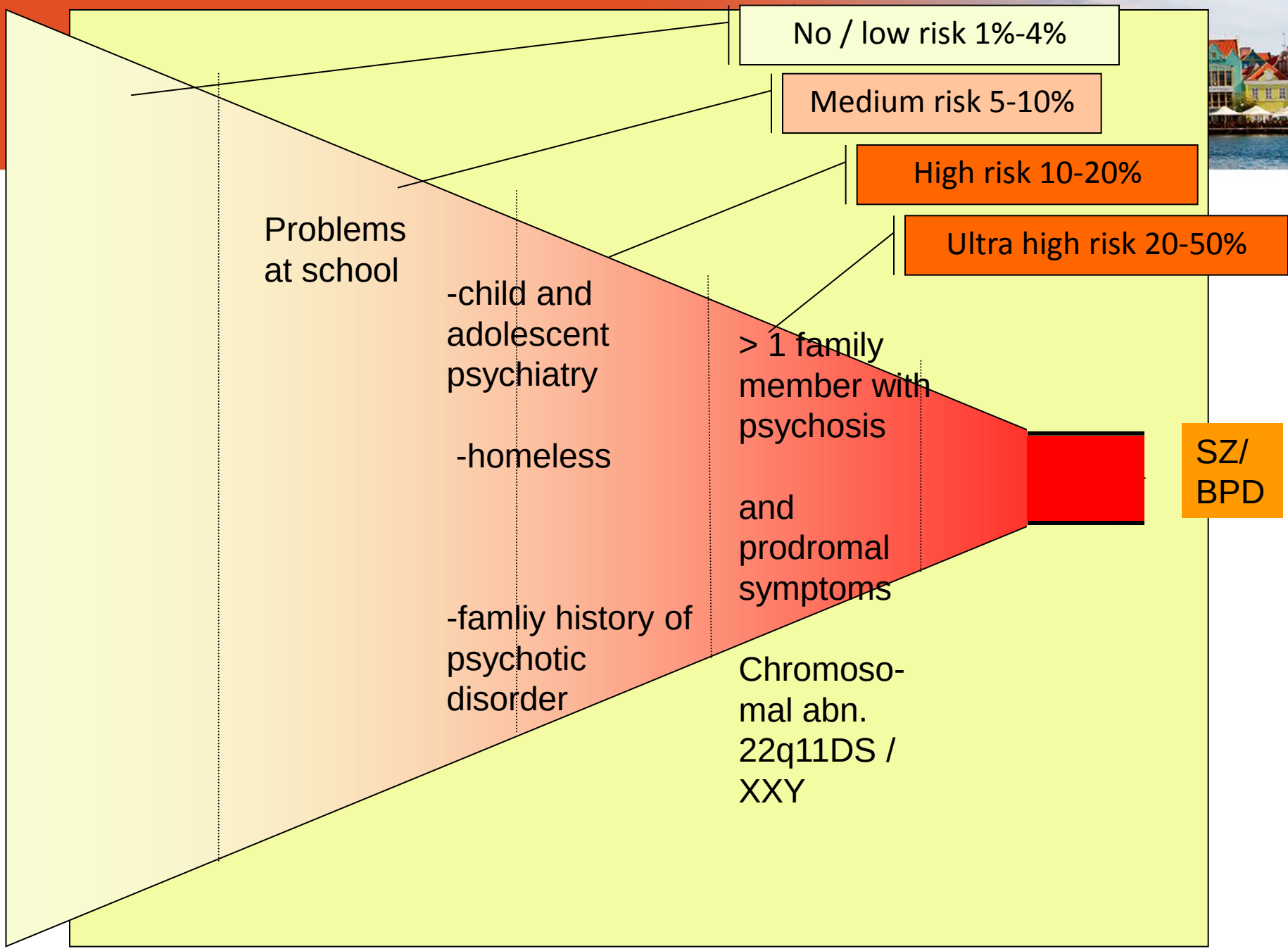
- Which treatment is not proven effective yet for patients with schizophrenia?

a. Cognitive behavioral treatment

b. EMDR

c. Psychoeducation


No / low risk
Medium risk
High risk
Ultra high risk
Men:
<1/100
Women:
1/10
Breastcancer


No / low risk 1%-4%
Medium risk 5-10%
High risk 10-20%
Ultra high risk 20-50%
Problems at school
-child and adolescent psychiatry
-homeless
-famliy history of psychotic disorder
> 1 family member with psychosis
and prodromal symptoms
Chromoso-mal abn. 22q11DS / XXY
SZ/ BPD

Ultra High Risk Criteria

PACE:

Ultra-high risk was defined by the presence of subthreshold and/or self-limiting psychotic symptoms and/or having a family history of psychotic disorder combined with functional Decline.

PRIME:

One or more of 3 criteria

1. new onset or recent worsening of subsyndromal ‘‘attenuated’’ positive psychotic symptoms
2. very brief periods of fully psychotic positive symptoms
3. deterioration in functioning within the last year and schizotypal personality disorder or a having first-degree relative with psychosis.

Transition rate of prodromal to psychosis

TABEL 2 *Onderzoeken bij jongeren met een ultrahoog risico voor schizofrenie (patiënten in de tweede lijn met een sterk verhoogd risico op een psychose binnen één jaar)*

UHR- centrum	Intakecriteria	Aantal patiënten	Aantal (%) psychotisch binnen 12 maanden
PACE (Australië) (Yung & McGorry 1996)	PACE	104	36 (34,6)
PRIME (VS) (McGlashan & Miller 2004)	PRIME	14	7 (50)
RAP (VS) (Cornblatt e.a. 2002)	CHR+	34	9 (26,5)
TOPP (Noorwegen) (Larsen 2002)	PRIME	14	6 (43)
EDIE (Manchester) (Morrison e.a. 2002)	PACE	23	5 (22)
PAS (Newcastle, Australië) (Carr e.a. 2000)	PACE	74	37 (50)
PIER (VS) (McFarlane e.a.2002)	PRIME of BLIPS	47	11 (23,4) : BLIPS
FETZ (CER) (Duitsland) (Klosterkötter e.a. 2001)	BSABS	51	5 (9,8)*
CARE (VS, San Diego) (Cadenhead e.a.)	PRIME	25	4 (16)
EPOS (Duitsland, Engeland, Finland, Nederland)	PRIME en BSABS	250	loopt

Deze tabel is mede totstandgekomen met behulp van gegevens uit Yung e.a. 2004 en Cornblatt e.a. 2003

* binnen 15 maanden

UHR = ultra high risk; PACE = Personal Assessment and Crisis Evaluation; PRIME = Prevention through Risk Identification, Management and Education; RAP = Recognition en Prevention Program; TOPP = early detection of pre psychose programma; EDIE = Early Identification and Intervention Evaluation; PAS = Psychological Assistenæ Service; PIER = Portland Identification and Early Referral; BLIPS = Brief Limited Intermittent Psychotic Symptoms; FETZ = FruhErkennungs- und Therapie Zentrum fur Psychischen Krisen; CER = Cologne Early Reagnition; CARE = Cognitive Assessment and Risk Evaluation; EPOS = European Prediction Of Psychosis Study; BSABS = Bonn Scale for the Assessment of Basic Symptoms

Evidence That Transition from Health to Psychotic Disorder Can Be Traced to Semi-Ubiquitous Environmental Effects Operating against Background Genetic Risk

Martine van Nierop[1☯], Mayke Janssens[1☯], Genetic Risk OUtcome of Psychosis (GROUP) Investigators ¶, Richard Bruggeman[2], Wiepke Cahn[3], Lieuwe de Haan[4], René S. Kahn[3], Carin J. Meijer[4], Inez Myin-Germeys[1], Jim van Os[1,5]*, Durk Wiersma[2]

Table 4. Transition as a function of proxy environmental and genetic exposures.

		Non-transition		Transition		Odds ratio$_{adj}$*	95% CI	PAF #
		n	%	n	%			
Minority position	Majority	1,117	88.5	7	63.6	3.8	1.2−12.8	28%
	Minority	145	11.5	4	36.4			
Urban birth	Non-urban	807	68.0	3	32.0	3.7	0.9−15.4	45%
	Urban	379	37.5	5	62.5			
Cannabis use	No use	798	63.2	3	27.3	4.1	1.1−15.4	57%
	Use	464	36.8	8	72.7			
Early trauma	No	921	78.9	1	11.1	34.4	4.4−267.4	86%
	Yes	247	21.2	8	88.9			
Any exposure	No	447	35.4	0	0.0	∞		
	Yes	815	64.6	11	100.0			
High risk group	Comparison subject	460	99.6	2	0.4	2.2	0.5−10.3	50%
	Sibling	802	98.9	9	1.1			

*Odd ratio's adjusted for age sex and high-risk sibling status.
PAF = population attributable fraction, or the reduction in incidence that would be observed if the population were entirely.
unexposed, compared with its current exposure pattern.
∞ = OR is infinity due to zero denominator.
doi:10.1371/journal.pone.0076690.t004

Review

Randomized-controlled trials in people at ultra high risk of psychosis: A review of treatment effectiveness

Antonio Preti [a,*], Matteo Cella [b,1]

[a] Centro Medico Gennerusi, Via Costantinopoli 42, 09129 Cagliari, Italy
[b] King's College London, Institute of Psychiatry, Department of Psychological Medicine, Weston Education Centre, Cutcombe Rd, London SE5 9RJ, United Kingdom

Table 1
RCT of focused treatment aimed at reducing the risk of transition to psychosis in people at high risk of psychosis.

Study	Criteria for diagnosis	Criteria for outcome	Focused treatment (FT)	Contrast group (C)	Transition to psychosis at 1 year*	Transition to psychosis at more than 1 year*
McGorry et al., 2002; Phillips et al., 2007	UHR criteria according to PACE criteria based on the CAARMS	Suprathreshold levels of psychosis	Risperidone 1–2 mg + CBT Duration = 6 months N = 31 Dropout = none	Needs-based intervention (?) Duration = 6 months N = 28 Dropout = none	FT = 6/31 (19.3%) C = 10/28 (35.7%)	Within 3/4 years FT = 10/31 (32.2%) C = 12/28 (42.8%) Dropout = 18 (7/11)
Morrison et al., 2004; Morrison et al., 2007	UHR criteria equivalent to PACE criteria based on PANSS	Transition to psychosis using cut-off points on PANSS	CT Duration = 6 months N = 35 Dropout = 9	Monitoring Duration = 6 months N = 23 Dropout = 7	FT = 2/35 (5.7%) C = 5/23 (21.7%)	Within 3 years FT = 7/35 (20.0%) C = 7/23 (30.4%) Dropout = 31 (18/13)
McGlashan et al. (2006)	UHR criteria based on the SIPS	Conversion to psychosis according to the Presence of Psychosis Scale	Olanzapine 5–15 mg Duration = 12 months N = 31 Dropout = 14	Placebo Duration = 12 months N = 29 Dropout = 19	FT = 5/31 (16.1%) C = 11/29 (37.9%)	Within 2 years FT = 8/31 (25.8%) C = 13/29 (44.8%) Dropout = none
Nordentoft et al. (2006)	ICD-10 criteria for Schizotypal disorder	ICD-10 diagnosis of a psychotic disorder within the F2 spectrum Raters were not blind	Intensive treatment with family intervention Duration = 24 months N = 42 Dropout = 5	Standard care Duration = 24 months N = 37 Dropout = 7	FT = 3/37 (8.1%) C = 10/30 (33.3%)	Within 2 years FT = 9/36 (25.0%) C = 14/29 (48.2%) Dropout = 14 (6/8)
Amminger et al. (2010)	UHR criteria equivalent to PACE criteria based on PANSS	Transition to psychosis using cut-off points on PANSS	Omega-3 PUFAs 1.2 g Duration = 3 months N = 41 Dropout = 3	Placebo Duration = 3 months N = 40 Dropout = 2	FT = 2/41 (4.8%) C = 11/40 (27.5%)	

Abbreviations and explanations:
PACE = Personal Assessment and Crisis Evaluation (PACE) Clinic in Melbourne.
CAARMS = Comprehensive Assessment of At-Risk Mental States.
PANSS = Positive and Negative Syndrome Scale.
SIPS = Structured Interview for Prodromal Syndromes, which operationally defines the PACE UHR criteria.
ICD-10 = International Classification of Diseases, tenth edition, World Health Organization.
CBT = Cognitive Behavioral Therapy.
CT = Cognitive Therapy.
PUFAs = Polyunsaturated Fatty Acids.
Suprathreshold levels of psychosis: a score of 3 or more on the hallucinations subscale, a score of 4 or more on the unusual thought content subscale (plus a score 3 for delusional conviction on the Comprehensive Assessment of Symptoms and History), or a score of 4 or more on the conceptual disorganization subscale of the Brief Psychiatric Rating Scale; all for a duration greater than 1 week.
Transition to psychosis using cut-off points on PANSS: 4 or more on hallucinations, 4 or more on delusions and 5 or more on conceptual disorganization; all for a duration greater than 1 week.
Conversion to psychosis according to the Presence of Psychosis Scale: any psychotic disorder in the DSM-IV schizophrenia spectrum on the basis of scores on the Presence of Psychosis Scale (unspecified threshold).
*Data on transition to psychosis are on a intention-to-treat basis.

Ultra High Risk

Staging schizophrenia

Psychological Medicine (2014), **44**, 17–24.
doi:10.1017/S0033291713000184

REVIEW ARTICLE

Lessons learned from the psychosis high-risk state: towards a general staging model of prodromal intervention

P. Fusar-Poli[1]*, A. R. Yung[2,3], P. McGorry[3] and J. van Os[1,4,5]

Conclusions. In the general population, mixed and non-specific expression of psychosis, depression, anxiety and subthreshold mania is common and mostly transitory. When combined with distress, it may be considered as the first, diagnostically neutral stage of potentially more severe psychopathology, which only later may acquire a degree of diagnostic specificity and possible relative resistance to treatment. Therefore, rather than creating silos of per-disorder ultra-HR syndromes, an early intervention focus on the broad syndrome of early mental distress, requiring phase-specific interventions, may be more profitable.

From: **Association Between Duration of Untreated Psychosis and Outcome in Cohorts of First-Episode Patients: A Systematic Review**

Arch Gen Psychiatry. 2005;62(9):975-983. doi:10.1001/archpsyc.62.9.975

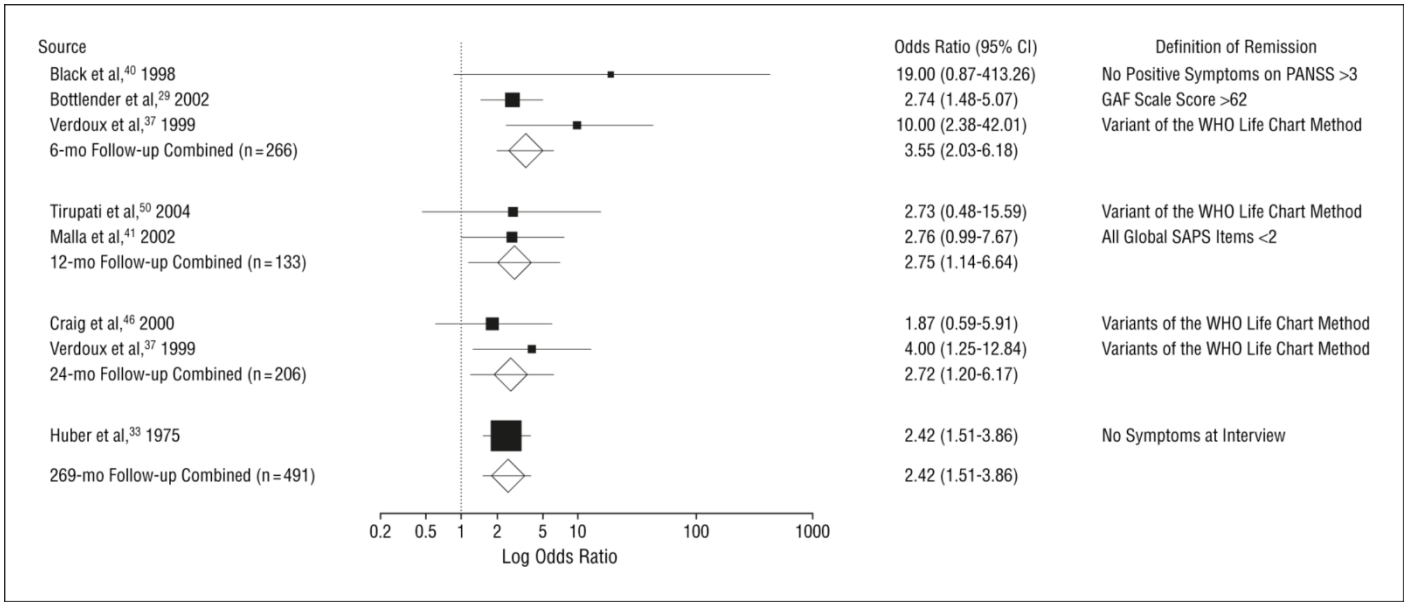
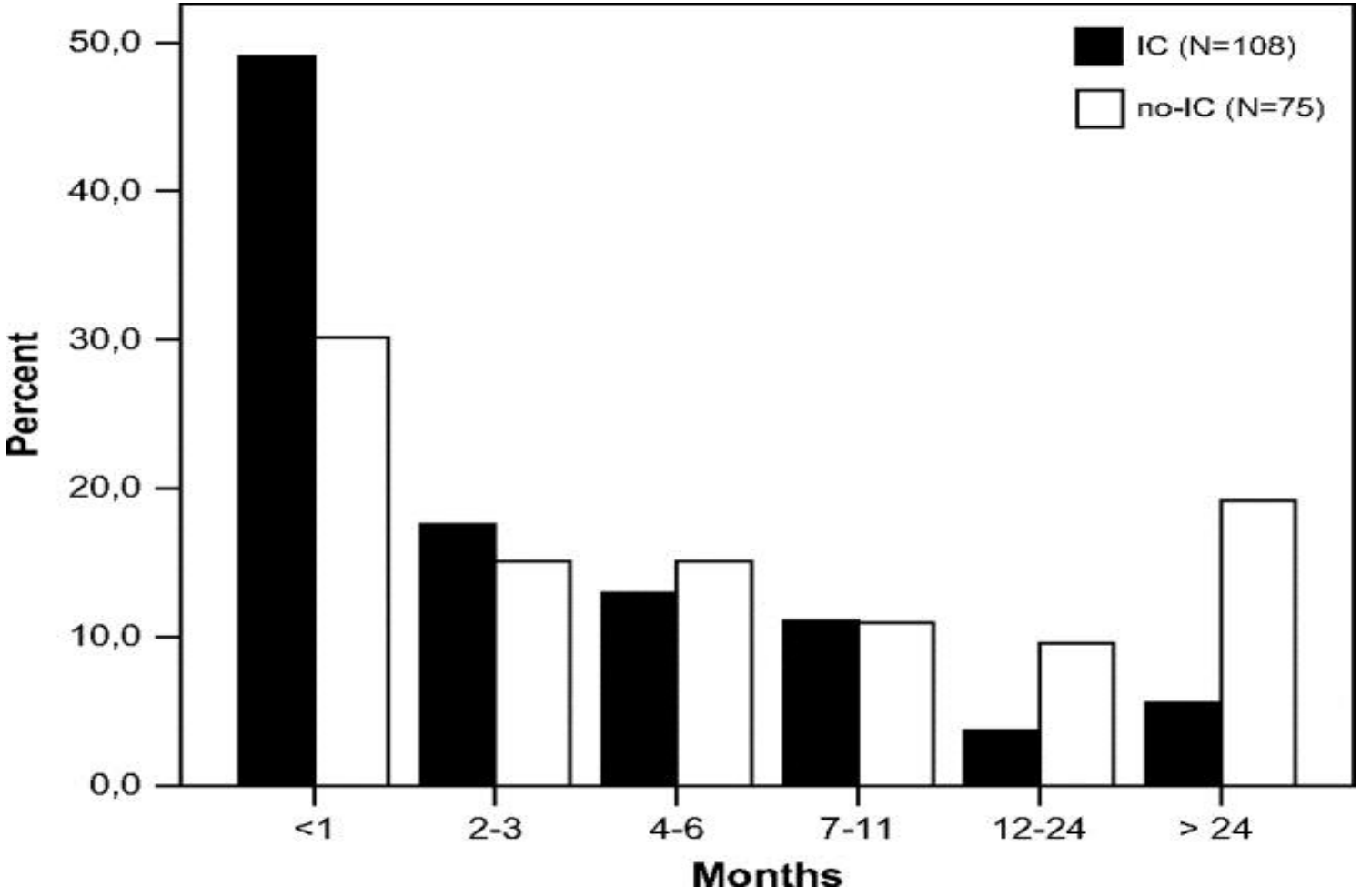


Figure Legend:

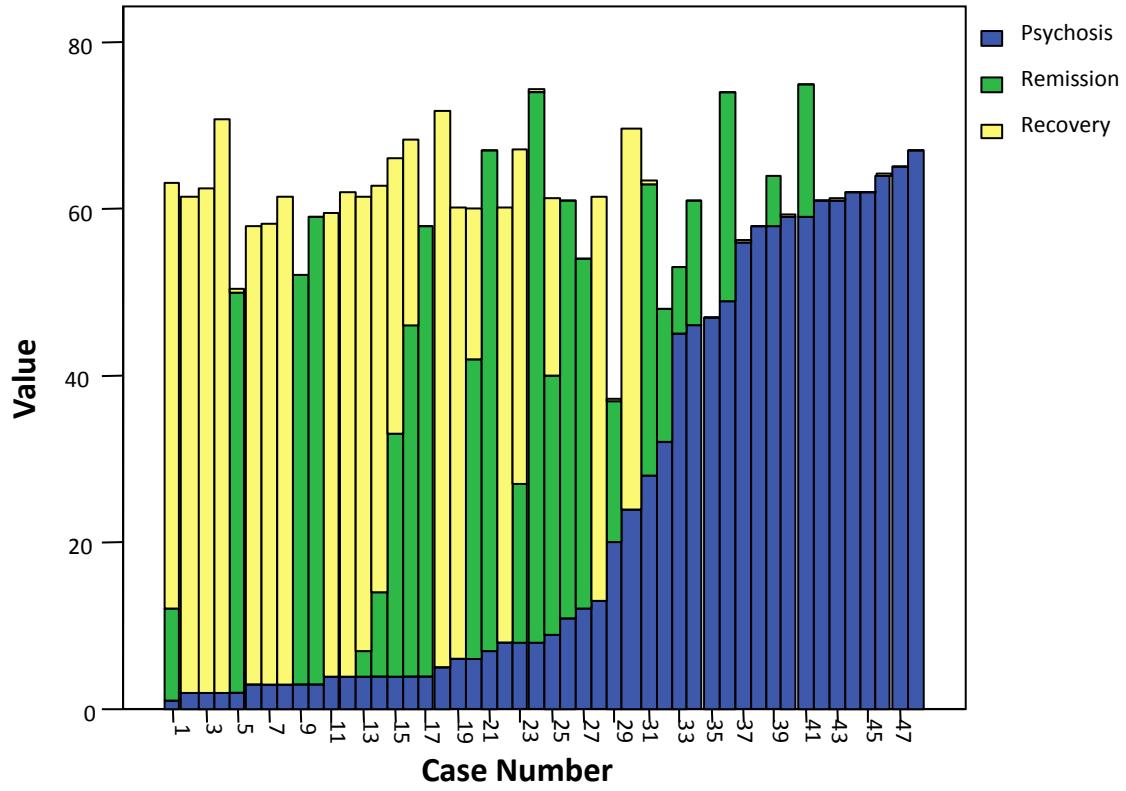
Odds of no remission in the long vs short duration of untreated psychosis (DUP) groups. An odds ratio greater than 1 indicates that individuals in the long DUP group were more likely not to be in remission at the follow-up point. CI indicates confidence interval; PANSS, Positive and Negative Syndrome Scale; GAF, Global Assessment of Functioning; WHO, World Health Organization; and SAPS, Scale for the Assessment of Positive Symptoms. Squares indicate the size of the contribution to the study of the summary odds ratio (diamonds).

Shortening the DUP with national campaign about psychosis - Norway

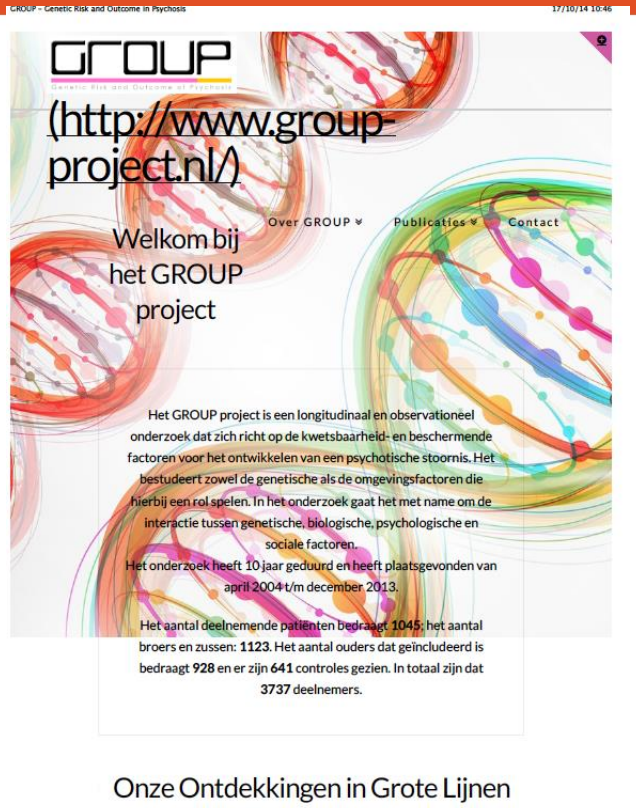


Inge Joa, et al. Schizophr Bull. 2008

Psychosis over time - 5 year follow up



Cahn et al.
Eur.Neuro. Psychoph 2009



Onze Ontdekkingen in Grote Lijnen

Long term outcome of schizophrenia spectrum disorder

A six year follow up in 1000 patients

Table 2 Demographic and clinical characteristics of participants in the GROUP study, means (standard deviations in parentheses) and absolute numbers

Variable	Patients ($N = 1120$)	Siblings ($N = 1057$)	Parents ($N = 919$)	Controls ($N = 590$)
Age (years) at T0	27.7 (8.0)	27.8 (8.3)	54.7 (6.9)	30.4 (10.6)
Gender, male (%)	76.2	45.6	42.7	45.8
Education, Verhage[a]	4.0 (2.1)	5.1 (2.1)	5.1 (2.3)	5.4 (1.8)
WAIS-III Estimated IQ	94.9 (16.1)	102.6 (15.6)	103.1 (17.0)	109.6 (15.2)
Ethnicity, Caucasian (%)	79.1	83.2	88.9	92.0
Marital status (%)				
Not married	87.9	57.4	4.7	55.0
Married/living together	9.2	40.3	70.7	41.0
Other	2.9	2.3	24.7	4.0
Residential status (%)				
Single	33.7	20.5	8.3	22.1
With parents(s)	39.5	27.7	5.5	26.8
With partner/family	10.3	46.3	84.8	46.9
Sheltered living	9.7	0.1	0.0	0.0
Other	6.8	5.3	1.4	4.3
Lifetime psychopathology				
Depressive disorder				
Male (%)	0	5.8	12.5	3.0
Female (%)	0.4	13.6	20.9	12.5
Bipolar disorder				
Male (%)	1.3	0.8	0.5	0
Female (%)	1.5	1.2	1.0	0.3
Substance abuse				
Male (%)	45.6	17.6	3.8	13.7
Female (%)	17.2	8.7	2.1	3.8

Korver et al. Int J Methods Psychiatr Res. 2012

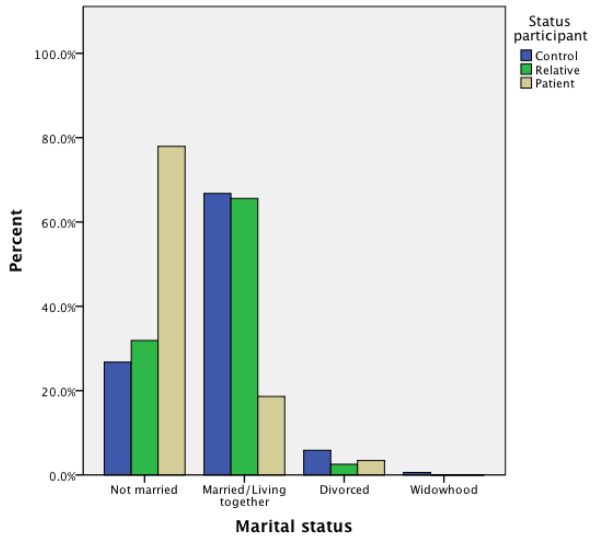
Drop-out 6 years – patients only

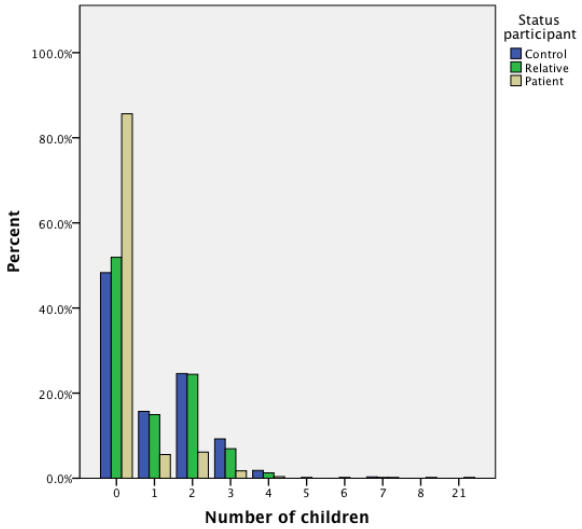
	Drop-out	In study (6 years)	Statistics
AGE at T0	27.7 (8.4)	27.4 (7.4)	n.s.
GENDER (m/f)	455/134	397/133	n.s.
IQ	93.2 (16)	97.4 (16)	p<0.001
Ethnicity (Caucasian/other)	414/146	443/80	p<0.001
CAN-unmet needs	3.54 (2.9)	2.91 (3.2)	p<0.01
PANSS TOTAL	5.7 (1.9)	1.6 (0.7)	p<0.001
Pos.	1.9	1.7	P<0.01
Neg.	2.1	1.9	P<0.001
Gen.	1.8	1.7	P<0.001
Remission Yes/no	217/314	250/255	P<0.01

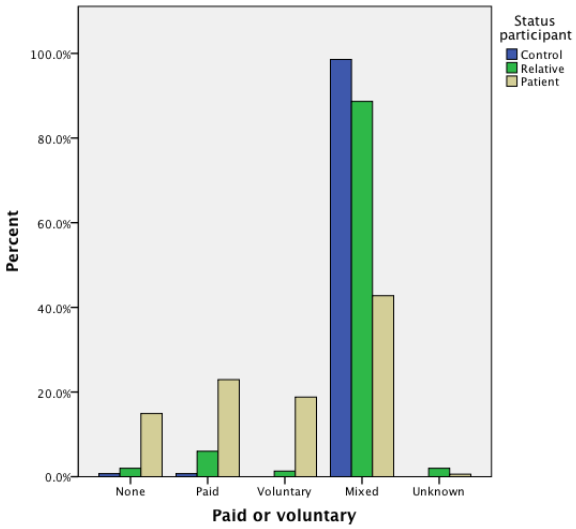
DROP OUT IS 35% AND 58% IN SYMPTOMATIC REMISSION

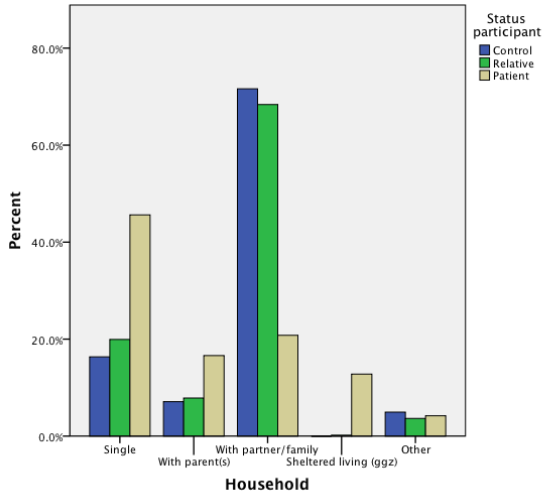
GROUP in preparation

Functional outcome after 6 years









Neurocognition and remission status after three year follow up

Table 3. Results of Multinomial Logistic Regression Analysis with cognitive predictors for Remission

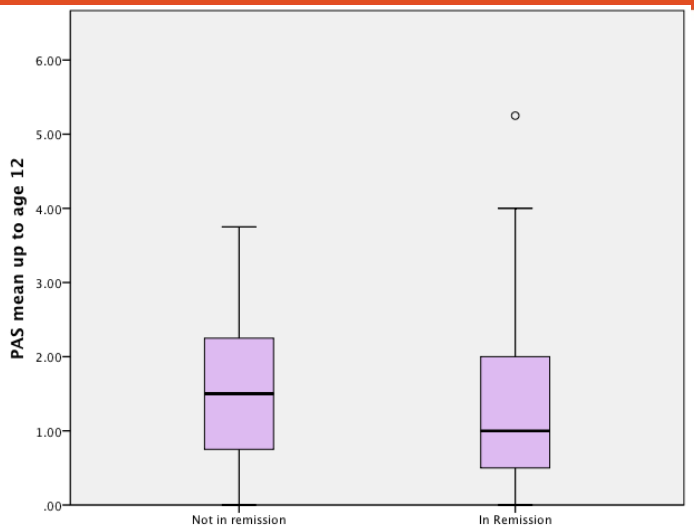
		95% CI for Odds Ratio		
	b (SE)	Lower	Odds ratio	Upper
Intercept	1,38 (2,56)			
Age	- 0,04 (0,03)	0,90	0,96	1,03
Education	0,14 (0,10)	0,94	1,16	1,41
Duration of illness	0,08 (0,06)	0,97	1,09	1,22
Number of psychotic episodes	**- 0,64 (0,22)** *	0,34	0,53	0,82
Benton score	0,03 (0,08)	0,88	1,03	1,21
Hinting score	- 0,04 (0,07)	0,84	0,96	1,10
Correct immediate RAVLT	0,40 (0,04)	0,97	1,04	1,12
WAIS-III Block design score	- 0,04 (0,07)	0,84	0,96	1,09
WAIS-III Arithmetic score	**0,17 (0,07)** *	1,03	1,19	1,37
WAIS-III Digit symbol score	0,01 (0,07)	0,88	1,01	1,17
WAIS-III Information score	**0,22 (0,09)** *	0,67	0,81	0,97
Drug during tests	0,53 (1,67)	0,06	1,71	45,26
Gender	- 0,04 (1,70)	0,04	0,97	26,91
Drugs x Gender	- 0,09 (1,75)	0,03	0,92	28,07

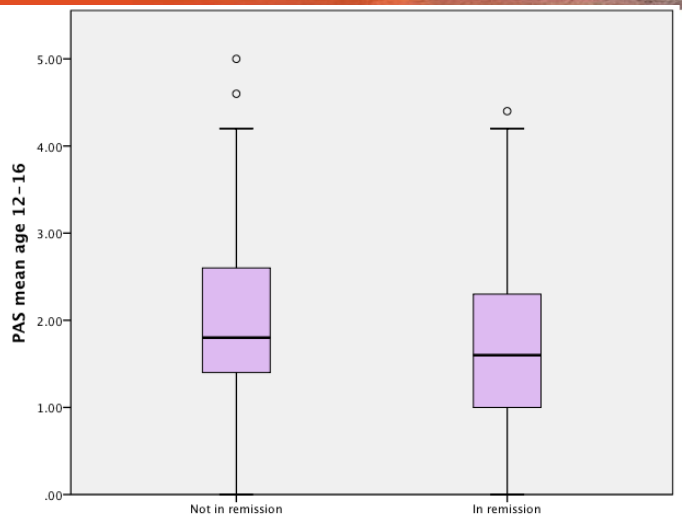
*Note, R2 = ,14 (Cox &Snell); ,20 (Nagelkerke); Model X2 (14) = 215,16, *p < ,05*

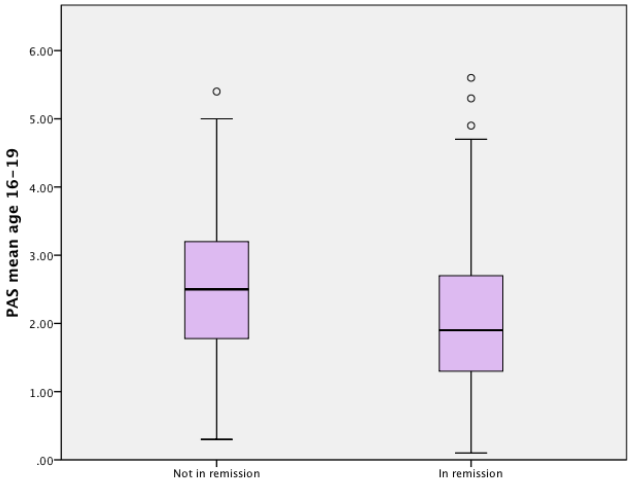
Higher verbal IQ predicts remission status at 3 year follow-up

Nijs et al, 2015

Premorbid Adjusment and remission status at follow up







PAS scores

		N	Mean	Std. Deviation
PAS mean up to age 12	NRem	194	1.5387	.94598
	Rem	286	1.2547	.91299
	Total	480	1.3694	.93594
PAS mean age 12-16	NRem	195	2.0123	.94615
	Rem	283	1.7004	.91936
	Total	478	1.8276	.94199
PAS mean age 16-19	NRem	188	2.5481	1.04090
	Rem	273	2.0555	1.04092
	Total	461	2.2564	1.06765
PAS overall score	NRem	191	2.1889	.84970
	Rem	286	1.7802	.84693
	Total	477	1.9439	.87055

P<0.001

Schizophrenia Is a Cognitive Illness
Time for a Change in Focus

René S. Kahn, MD, PhD; Richard S. E. Keefe, PhD

Schizophrenia is currently classified as a psychotic disorder. This article posits that this emphasis on psychosis is a conceptual fallacy that has greatly contributed to the lack of progress in our understanding of this illness and hence has hampered the development of adequate treatments. Not only have cognitive and intellectual underperformance consistently been shown to be risk factors for schizophrenia, several studies have found that a decline in cognitive functioning precedes the onset of psychosis by almost a decade. Although the question of whether cognitive function continues to decline after psychosis onset is still debated, it is clear that cognitive function in schizophrenia is related to outcome and little influenced by antipsychotic treatment. Thus, our focus on defining (and preventing) the disorder on the basis of psychotic symptoms may be too narrow. Not only should cognition be recognized as the core component of the disorder, our diagnostic efforts should emphasize the changes in cognitive function that occur earlier in development. Putting the focus back on cognition may facilitate finding treatments for the illness before psychosis ever emerges.

JAMA Psychiatry. 2013;70(10):1107-1112. doi:10.1001/jamapsychiatry.2013.155
Published online August 7, 2013.

Editorial page 1009

Author Affiliations: Department of Psychiatry, Rudolf Magnus Institute of Neuroscience, UMC Utrecht, Utrecht, the Netherlands (Kahn); Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, North Carolina (Keefe).

Corresponding Author: René S. Kahn, MD, PhD, Department of Psychiatry, Rudolf Magnus Institute of Neuroscience, UMC Utrecht, Utrecht, Heidelberglaan 100, 3508 GA Utrecht, PO Box 85500, the

Machine learning

https://www.youtube.com/watch?v=ty-kTUzMnjk

Treatment- Psychoeducation

[Intervention Review]

Psychoeducation for schizophrenia

Jun Xia[1], Lars Bertil Merinder[2], Madhvi R Belgamwar[3]

[1]Cochrane Schizophrenia Group, University of Nottingham, Nottingham, UK. [2]Dept of Psychiatric Demography, Institute of Basic Psychiatric Research, University Hospital of Aarhus, Risskov, Denmark. [3]Radbourne Unit, Royal Derby Hospital, Derby, UK

Contact address: Jun Xia, Cochrane Schizophrenia Group, University of Nottingham, Institute of Mental Health, Sir Colin Campbell Building,, University of Nottingham Innovation Park, Triumph Road,, Nottingham, NG7 2TU, UK. Jun.Xia@nottingham.ac.uk.

Editorial group: Cochrane Schizophrenia Group.
Publication status and date: Edited (no change to conclusions), published in Issue 11, 2011.
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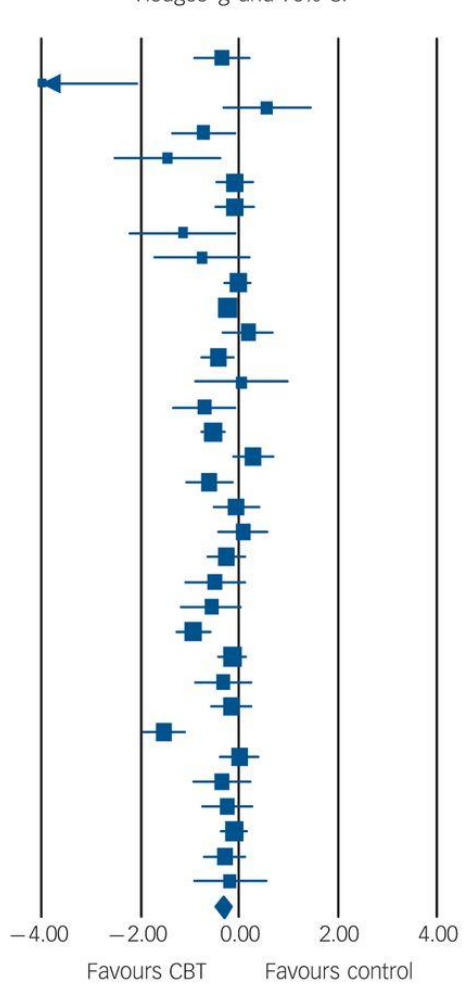
Citation: Xia J, Merinder LB, Belgamwar MR. Psychoeducation for schizophrenia. *Cochrane Database of Systematic Reviews* 2011, Issue 6. Art. No.: CD002831. DOI: 10.1002/14651858.CD002831.pub2.

Main results

This review includes a total of 5142 participants (mostly inpatients) from 44 trials conducted between 1988 and 2009 (median study duration = 12 weeks, risk of bias - moderate). We found that incidences of non-compliance were lower in the psychoeducation group in the short term (n = 1400, RR 0.52 CI 0.40 to 0.67, NNT 11 CI 9 to 16). This finding holds for the medium and long term. Relapse appeared to be lower in psychoeducation group (n = 1214, RR 0.70 CI 0.61 to 0.81, NNT 9 CI 7 to 14) and this also applied to readmission (n = 206, RR 0.71 CI 0.56 to 0.89, NNT 5 CI 4 to 13). Scale-derived data also suggested that psychoeducation promotes better social and global functioning. In the medium term, treating four people with schizophrenia with psychoeducation

Treatment - Forest plot of studies in the meta-analysis of overall symptoms.CBT, cognitive-behavioural therapy.

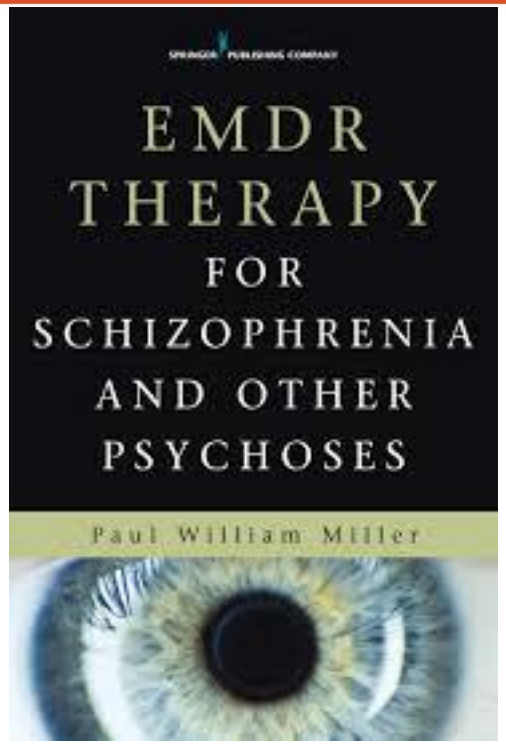
Study name	Statistics for each study: Hedges' *g*	Lower limit	Upper limit	Sample size: CBT	Control
Kuipers *et al* (1997)[1]	−0.342	−0.908	0.225	23	24
Levine *et al* (1998)[78]	−3.970	−5.871	−2.069	6	6
Haddock *et al* (1999)[79]	0.567	−0.338	1.472	8	10
Pinto *et al* (1999)[80]	−0.718	−1.370	−0.067	19	18
Bradshaw (2000)[53]	−1.453	−2.540	−0.366	8	7
Leclerc *et al* (2000)[63]	−0.087	−0.481	0.306	55	44
Sensky *et al* (2000)[8]	−0.082	−0.492	0.328	46	44
Turkington *et al* (2000)[81]	−1.136	−2.225	−0.047	10	5
Granholm *et al* (2002)[82]	−0.744	−1.735	0.247	8	7
Lewis *et al* (2002)[9]	−0.014	−0.293	0.265	78	131
Turkington *et al* (2002)[13]	−0.225	−0.420	−0.029	257	165
Durham *et al* (2003)[73]	0.190	−0.330	0.709	22	38
Gumley *et al* (2003)[83]	−0.417	−0.746	−0.089	72	72
Jolley *et al* (2003)[70]	−0.058	−0.896	1.013	7	8
Rector *et al* (2003)[84]	−0.698	−1.316	−0.081	24	18
Wang *et al* (2003)[85]	−0.524	−0.774	−0.273	126	125
Bechdolf *et al* (2004)[10]	0.290	−0.128	0.709	40	48
Startup *et al* (2004)[86]	−0.598	−1.086	−0.110	34	32
Granholm *et al* (2005)[54]	−0.047	−0.527	0.434	32	33
Valmaggia *et al* (2005)[89]	0.083	−0.436	0.604	35	23
Barrowclough *et al* (2006)[91]	−0.252	−0.646	0.142	54	45
Gaudiano & Herbert (2006)[62]	−0.482	−1.099	0.136	21	19
Penadés *et al* (2006)[92]	−0.554	−1.173	0.066	20	20
Deng *et al* (2008)[94]	−0.919	−1.281	−0.556	64	64
Garety *et al* (2008)[11] (no carer)	−0.124	−0.415	0.167	90	90
Garety *et al* (2008)[11] (carer)	−0.314	−0.899	0.271	21	23
Lecomte *et al* (2008)[69]	−0.150	−0.573	0.274	36	51
Wu *et al* (2008)[96]	−1.517	−1.960	−1.075	48	52
Farhall *et al* (2009)[34]	0.014	−0.391	0.420	45	47
Fowler *et al* (2009)[35]	−0.345	−0.938	0.248	20	23
Haddock *et al* (2009)[36]	−0.235	−0.749	0.279	28	29
van der Gaag *et al* (2011)[14]	−0.095	−0.368	0.178	109	97
Lincoln *et al* (2012)[38]	−0.288	−0.724	0.149	40	40
Rathod *et al* (2013)[97]	−0.176	−0.910	0.557	13	14
	−0.327	−0.467	−0.187		

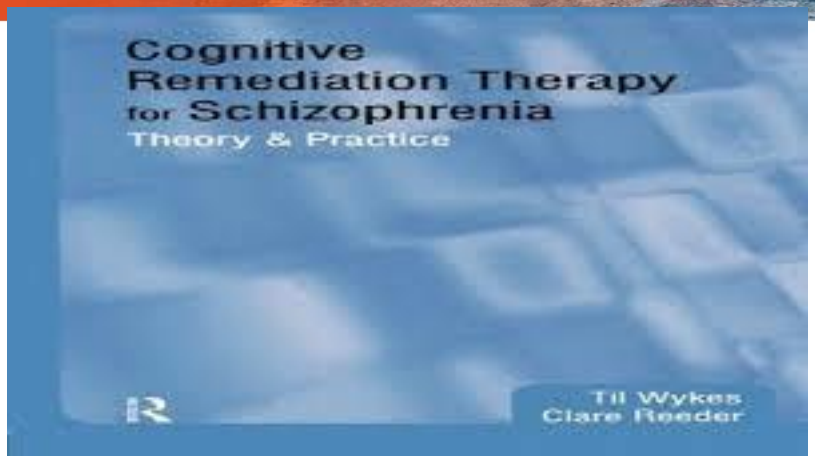


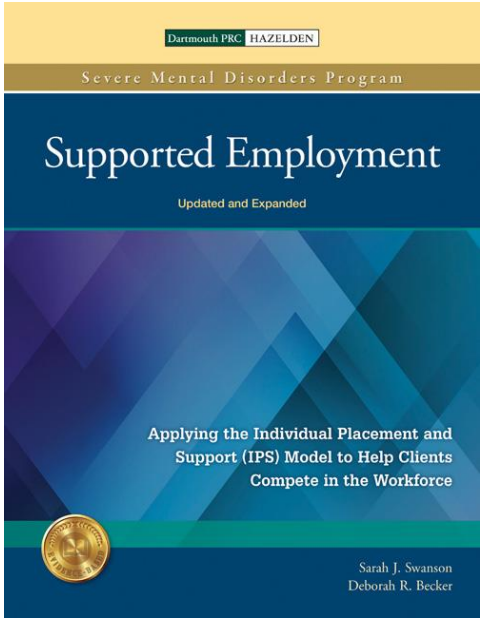
S. Jauhar et al. BJP 2014;204:20-29

THE BRITISH JOURNAL OF PSYCHIATRY

Other treatments







Questions

- To reduce the prevalence of psychotic disorders we should:

1. Set up pecialized clinics for subjects who have prodromal symptoms
2. Follow-up subjects seen in the child and adolescent psychiatry department
3. Screen the pre-adolescent population
4. Other

- Are we able to detect all subjects who will develop a psychotic disorder if we do all of the above?

1. Yes
2. No

Questions

- What is the percentage of patients with a first episode psychosis receiving a diagnosis of schizophrenia spectrum disorder?

a. **60 %**

b. 70%

c. 80%

- Which treatment is not proven effective yet for patients with schizophrenia?

a. Cognitive behavioral treatment

b. EMDR

c. Psychoeducation (family/patients)

Prevention of early death and improving quality of life in schizophrenia

Life-style

- What percentage of patients with schizophrenia smoke?

a. 30%-50%

b. 50%-80%

c. 80%-100%

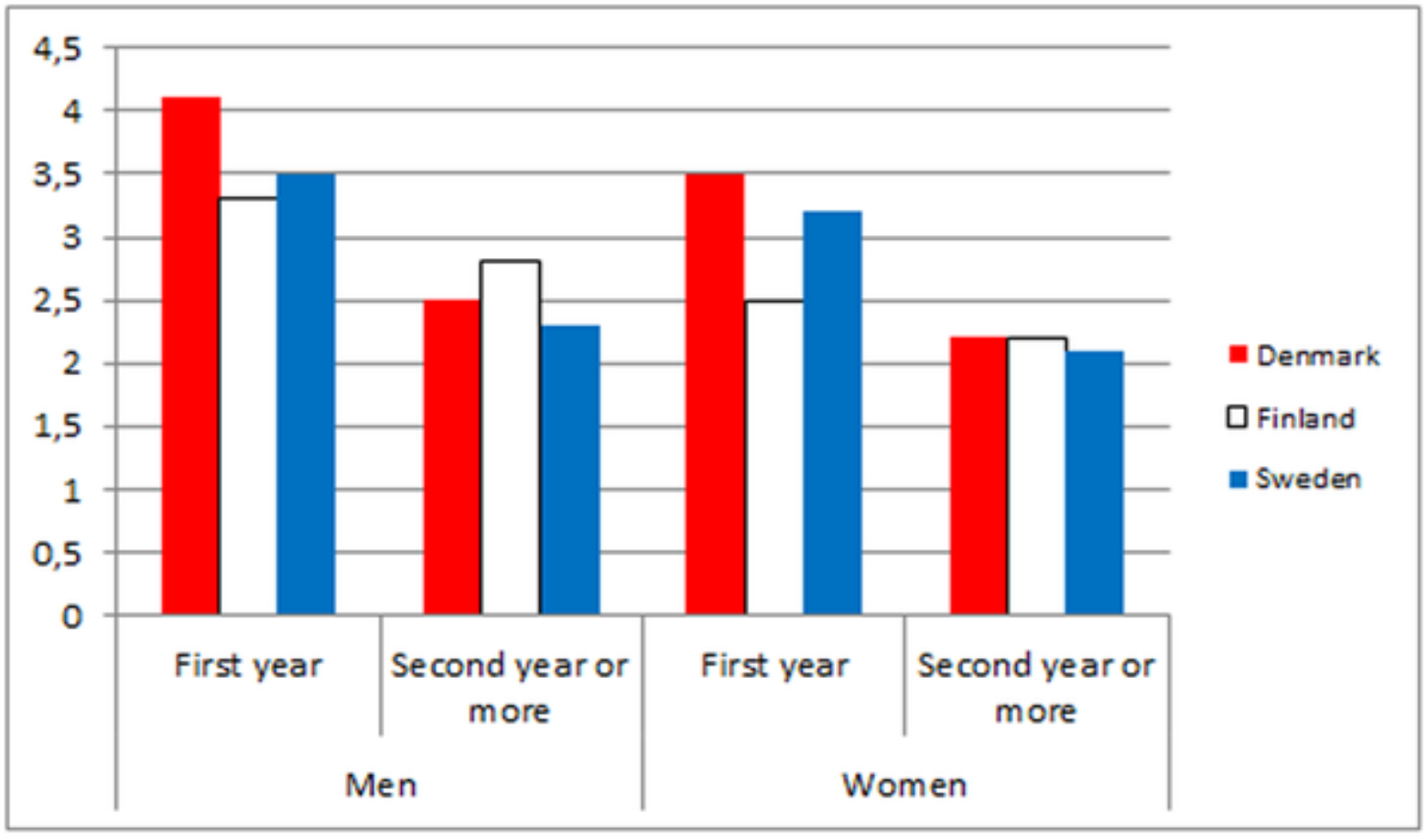
- Percentage of metabolic syndrome in schizphrenia?

a. 20%

b. 40%

c. 60%

Life expectancy and specific causes of death for substance-related disorders, schizophrenia-like psychoses, affective disorders and personality disorders in patients 2000–2006 in Denmark, Finland and Sweden.



15 years reduced in women

20 years reduced in men

2-3 x other medical problems

3-77 x suicide and other

Nordentoft M, Wahlbeck K, Hällgren J, Westman J, et al. (2013) Excess Mortality, Causes of Death and Life Expectancy in 270,770 Patients with Recent Onset of Mental Disorders in Denmark, Finland and Sweden. PLoS ONE 8(1): e55176. doi:10.1371/journal.pone.0055176
http://www.plosone.org/article/info:doi/10.1371/journal.pone.0055176

PLOS | ONE

Cardiovascular disease and diabetes in people with severe mental illness position statement from the European Psychiatric Association (EPA), supported by the European Association for the Study of Diabetes (EASD) and the European Society of Cardiology (ESC)

M. De Hert [a,*], J.M. Dekker [b], D. Wood [c], K.G. Kahl [d], R.I.G. Holt [e], H.-J. Möller [f]

[a] University Psychiatric, Centre Catholic University, Leuven campus Kortenberg, Leuvensesteenweg 517, 3070 Kortenberg, Belgium
[b] Department of Epidemiology and Biostatistics and the EMGO, Institute for Health and Care Research, VU University Medical Centre, van der Boechorststraat 7, 1081 BT Amsterdam, The Netherlands
[c] National Heart and Lung Institute Cardiovascular Science, Imperial College, Charing Cross Campus, W6 8RP London, United Kingdom
[d] Department of Psychiatry, Social Psychiatry and Psychotherapy, Hannover Medical School, Carl-Neubergstrasse. 1, 30625 Hannover, Germany
[e] Endocrinology & Metabolism, Developmental Origins of Health and Disease, School of Medicine, University of Southampton, Southampton SO16 6YD, United Kingdom
[f] Department of Psychiatry, Ludwig-Maximilians-University, Nussbaumstrasse 7, 80336 Munich, Germany

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Available online 13 August 2009

Table 1
Estimated prevalence and relative risk of modifiable cardiovascular disease risk factors in schizophrenia and bipolar disorder compared to the general population [39,47].

Estimated prevalence and relative risk		
Modifiable risk factors	Schizophrenia	Bipolar disorder
Obesity	45–55% RR: 1.5–2	21–49% RR: 1–2
Smoking	50–80% RR: 2–3	54–68% RR: 2–3
Diabetes	10–15% RR: 2	8–17% RR: 1.5–2
Hypertension	19–58% RR: 2–3	35–61% RR: 2–3
Dyslipidemia	25–69% RR: ≤ 5	23–38% RR: ≤ 3
Metabolic Syndrome	37–63% RR: 2–3	30–49% RR: 1.5–2

RR: relative risk.

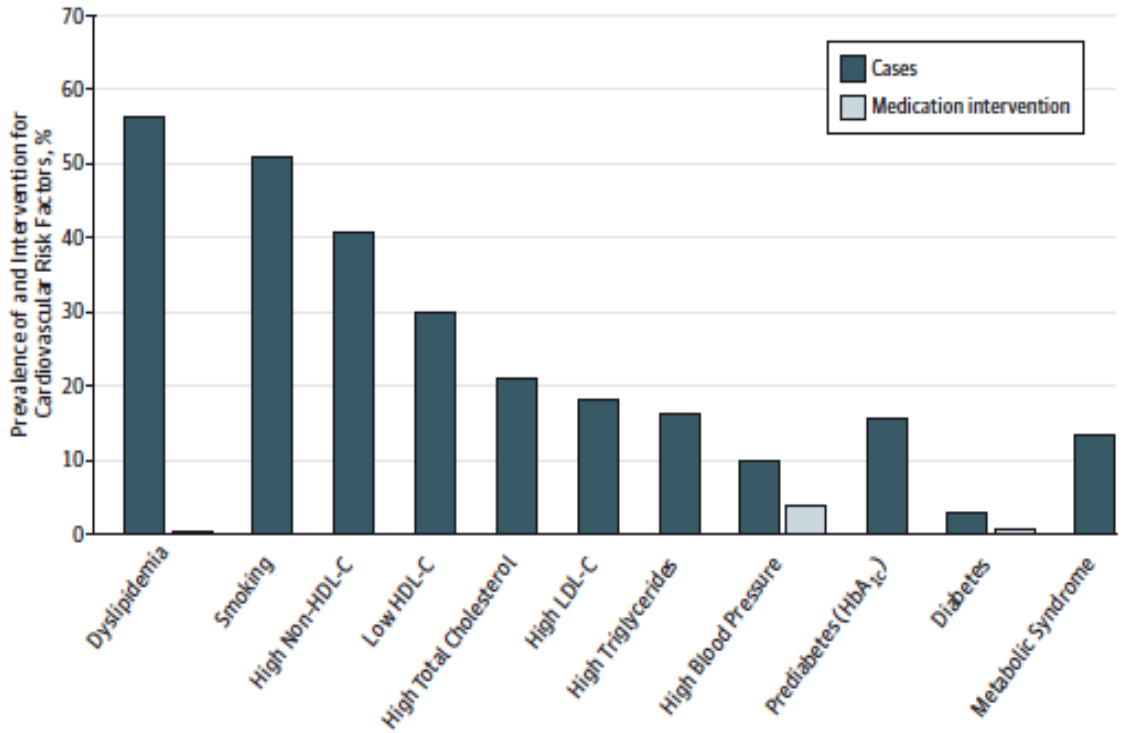
Original Investigation

Cardiometabolic Risk in Patients With First-Episode Schizophrenia Spectrum Disorders

Baseline Results From the RAISE-ETP Study

Christoph U. Correll, MD; Delbert G. Robinson, MD; Nina R. Schooler, PhD; Mary F. Brunette, MD; Kim T. Mueser, PhD; Robert A. Rosenheck, MD; Patricia Marcy, BSN; Jean Addington, PhD; Sue E. Estroff, PhD; James Robinson, MEd; David L. Penn, PhD; Susan Azrin, PhD; Amy Goldstein, PhD; Joanne Severe, MS; Robert Heinssen, PhD; John M. Kane, MD

Figure 2. Prevalence of Smoking, Lipid Abnormalities, Hypertension, Diabetes, and Metabolic Syndrome and Respective Medication Treatment for the Conditions



Dyslipidemia indicates an elevated low-density lipoprotein cholesterol (LDL-C) level (≥130 mg/dL; to convert to millimoles per liter, multiply by 0.0259), an elevated non–high-density lipoprotein cholesterol (HDL-C) level (≥130 mg/dL; to convert to millimoles per liter, multiply by 0.0259), an elevated triglycerides level (≥150 mg/dL; to convert to millimoles per liter, multiply by 0.0113), or a low HDL-C level (<40 mg/dL in males and <50 mg/dL in females; to convert to millimoles per liter, multiply by 0.0259). HbA_{1c} indicates hemoglobin A_{1c}.

JAMA Psychiatry December 2014
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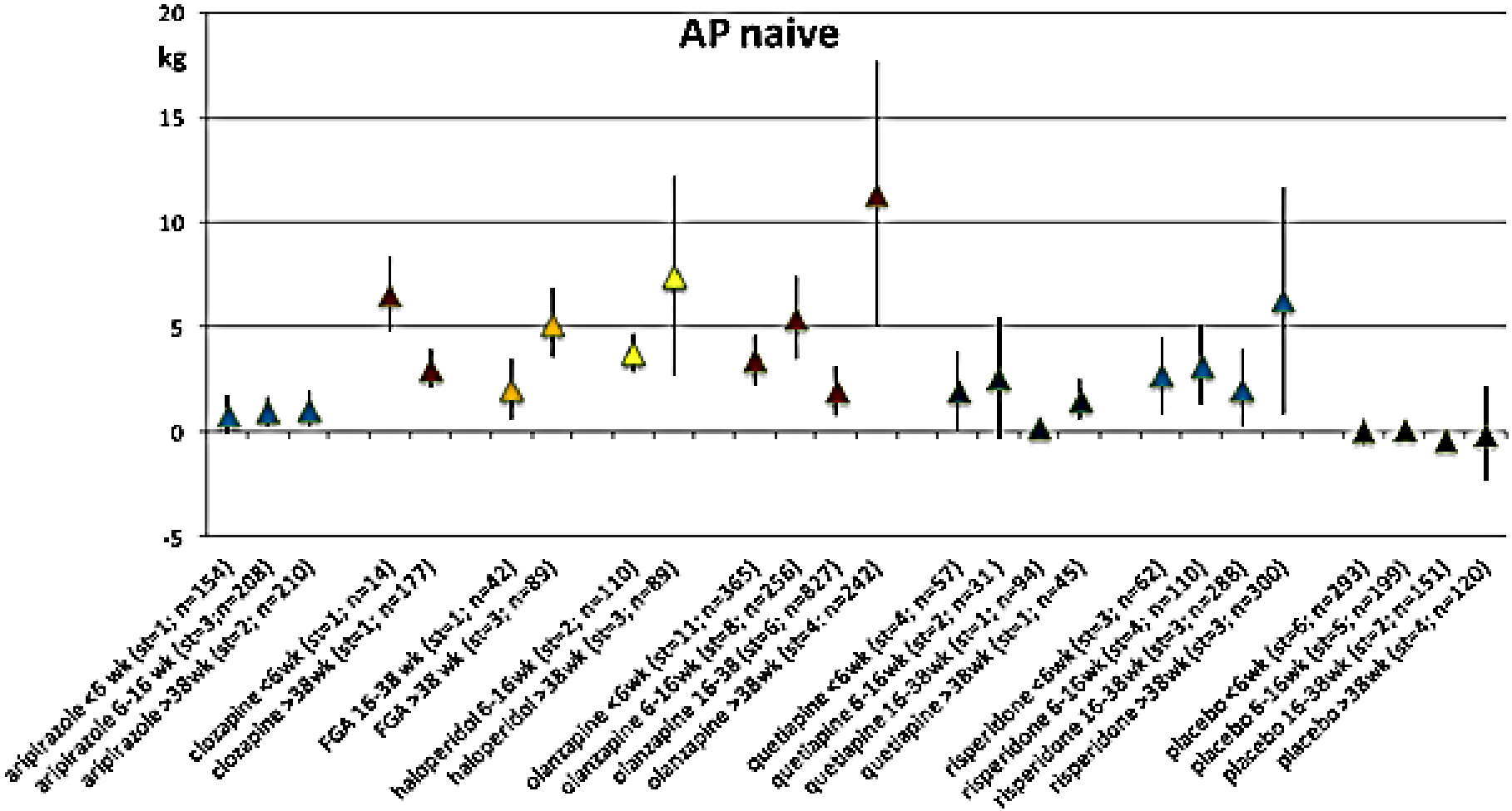
Life expectancy is decreased because of:

1. Disease itself (suicide/self neglect)
2. Antipsychotics other medication and their side-effects
3. Unhealthy lifestyles (i.e. smoking and unhealthy diet)
4. Gene x enviromental overlap with somatic disease (i.e. Diabetes, CVD, CVA)

Weight Change in Antipsychotic naïve patients



Bak M, Fransen A, Janssen J, van Os J, et al. (2014) Almost All Antipsychotics Result in Weight Gain: A Meta-Analysis. PLoS ONE 9(4): e94112. doi:10.1371/journal.pone.0094112
http://www.plosone.org/article/info:doi/10.1371/journal.pone.0094112

PLOS | ONE

Side-effects of other medication used in the treatment of psychotic disorders

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Side effects of antidepressants during long-term use in a naturalistic setting

Pierre M. Bet[a,b,*], Jacqueline G. Hugtenburg[a,c], Brenda W.J.H. Penninx[b,c,d,e,f], Witte J.G. Hoogendijk[b,d,g]

[a]Department of Clinical Pharmacology and Pharmacy, VU University Medical Center, De Boelelaan 1117, 1081 HV Amsterdam, the Netherlands
[b]Neuroscience Campus Amsterdam, VU University, Amsterdam, the Netherlands
[c]EMGO Institute, VU University Medical Center, Amsterdam, the Netherlands
[d]Department of Psychiatry, VU University Medical Center, Amsterdam, the Netherlands
[e]Department of Psychiatry, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands
[f]Department of Psychiatry, University Medical Center, Leiden, the Netherlands
[g]Department of Psychiatry, Erasmus Medical Center, Rotterdam, the Netherlands

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Table 2 Prevalence of side effects (SEs in %) to different types of antidepressant (n=927).

Type of antidepressant	SSRI n=584	TCA n=97	VEN n=145	MIR n=58	Overall p-value	SJW n=24	Other ADs n=19
Number of SEs per case							
Zero SEs (%)	36[a]	28	27[a]	36	0.09	100	47
One or two SEs (%)	33	33	37	40	0.55	0	26
Three or more SEs (%)	31	39	36	24	0.16	0	26
Type of SE							
Sleeplessness (%)	7	5	10	5	0.50	0	16
Sleepiness during the day (%)	21	14[a]	20	30[a]	0.16	0	16
Restlessness (%)	9	6	10	12	0.64	0	11
Muscle spasms, twitching (%)	9[a]	12	15[a]	7	0.09	0	5
Dry mouth (%)	22[a]	49[a,b,c]	23[b]	22[c]	<0.001[e]	0	16
Profuse sweating (%)	20[a]	20[b]	32[a,b,c]	14[c]	0.01[e]	0	11
Sexual dysfunction (%)	23[a,b]	20[c]	31[a,c,d]	10[b,d]	0.01[e]	0	11
Nausea (%)	10	4	9	5	0.16	0	11
Constipation (%)	8[a]	20[a,b,c]	10[b,d]	2[c,d]	0.001[e]	0	0
Diarrhea (%)	7	4	5	5	0.58	0	0
Weight gain (%)	19	22	17	29	0.24	0	16
Dizziness (%)	12[a]	11	19[a]	12	0.15	0	5

AD=antidepressant, SE=side effect, SSRI=selective serotonine reuptake inhibitor, TCA=Tricyclic Antidepressant, VEN=Venlafaxine, MIR=Mirtazapine, SJW=St John's wort.

[a,b,c,d]Difference in SE prevalence between two types of AD in univariate analysis, $p<0.05$.

Treatment of weight gain

Conclusion: **When nonpharmacological strategies alone are insufficient, and switching antipsychotics to relatively weight-neutral agents is not feasible, the literature supports the use of concomitant metformin as first choice among**

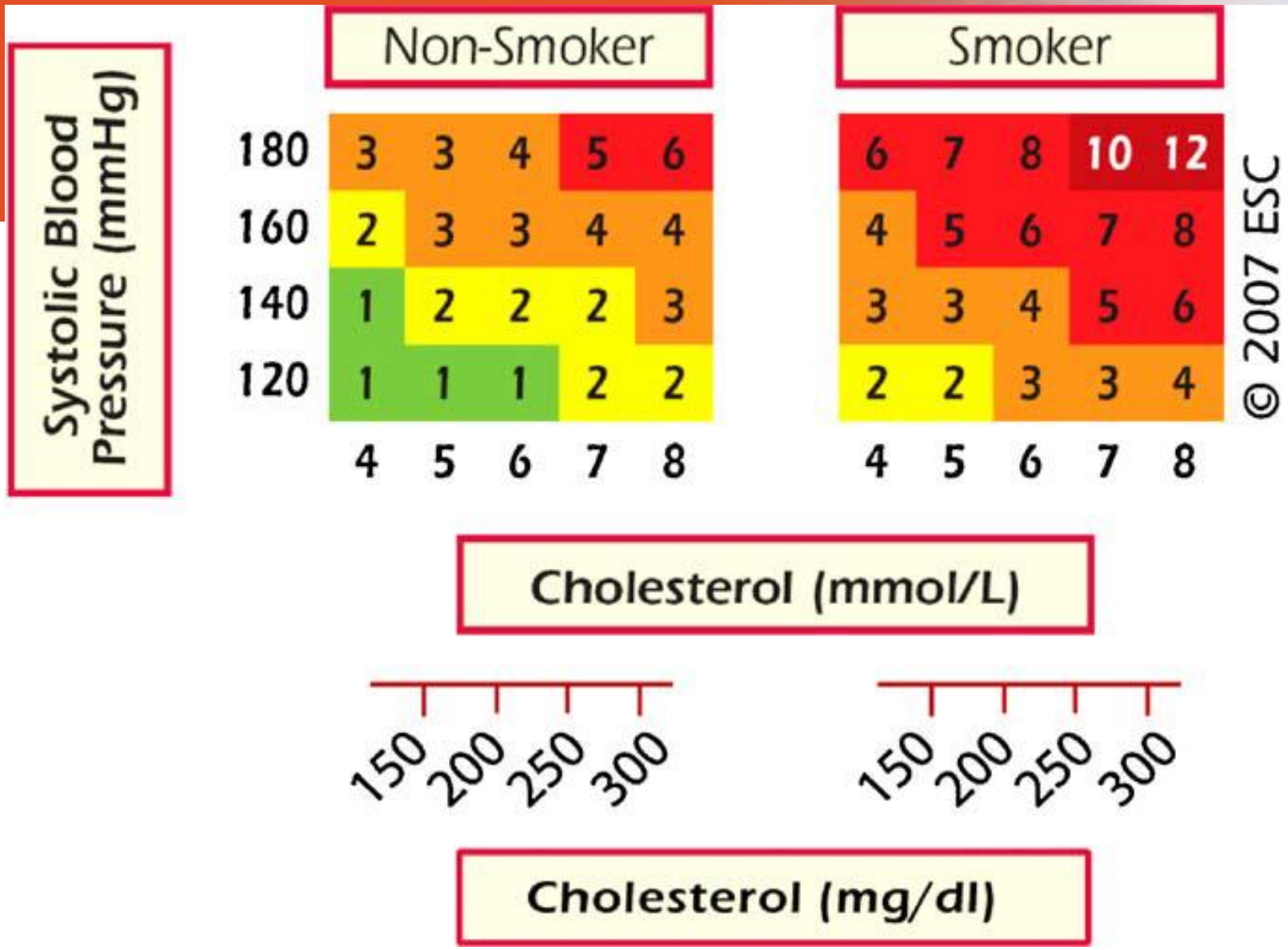
Mizuno et al. 2014
schiz. bull

CI: −4.44 to −1.90 kg) compared to placebo. Pooled effects for topiramate, sibutramine, aripiprazole, and reboxetine were also different from placebo. Furthermore, metformin and rosiglitazone improved insulin resistance, while aripip-razole, metformin, and sibutramine decreased blood lipids.

Metformin for Weight Gain and Metabolic Abnormalities Associated With Antipsychotic Treatment

Meta-Analysis of Randomized Placebo-Controlled Trials

Wei Zheng, MD, Xian-Bin Li, MD,†‡ Yi-Lang Tang, MD, PhD,†§ Ying-Qiang Xiang, MD, PhD,†*
Chuan-Yue Wang, MD, PhD,†‡ and Jose de Leon, MD‖¶#



Relative risk of fatal cardiovascular disease

Smoking

BMJ Open

Meta-analysis: the effects of smoking on the disposition of two commonly used antipsychotic agents, olanzapine and clozapine

Yoshiyuki Tsuda,[1] Junji Saruwatari,[1] Norio Yasui-Furukori[2]

Conclusions: We suggest that the doses of olanzapine and clozapine should be reduced by 30% and 50%, respectively, in non-smokers compared with smokers in order to obtain an equivalent olanzapine or clozapine concentration.

NICE GUIDELINE UPDATE

Consider one of the following to help people stop smoking:

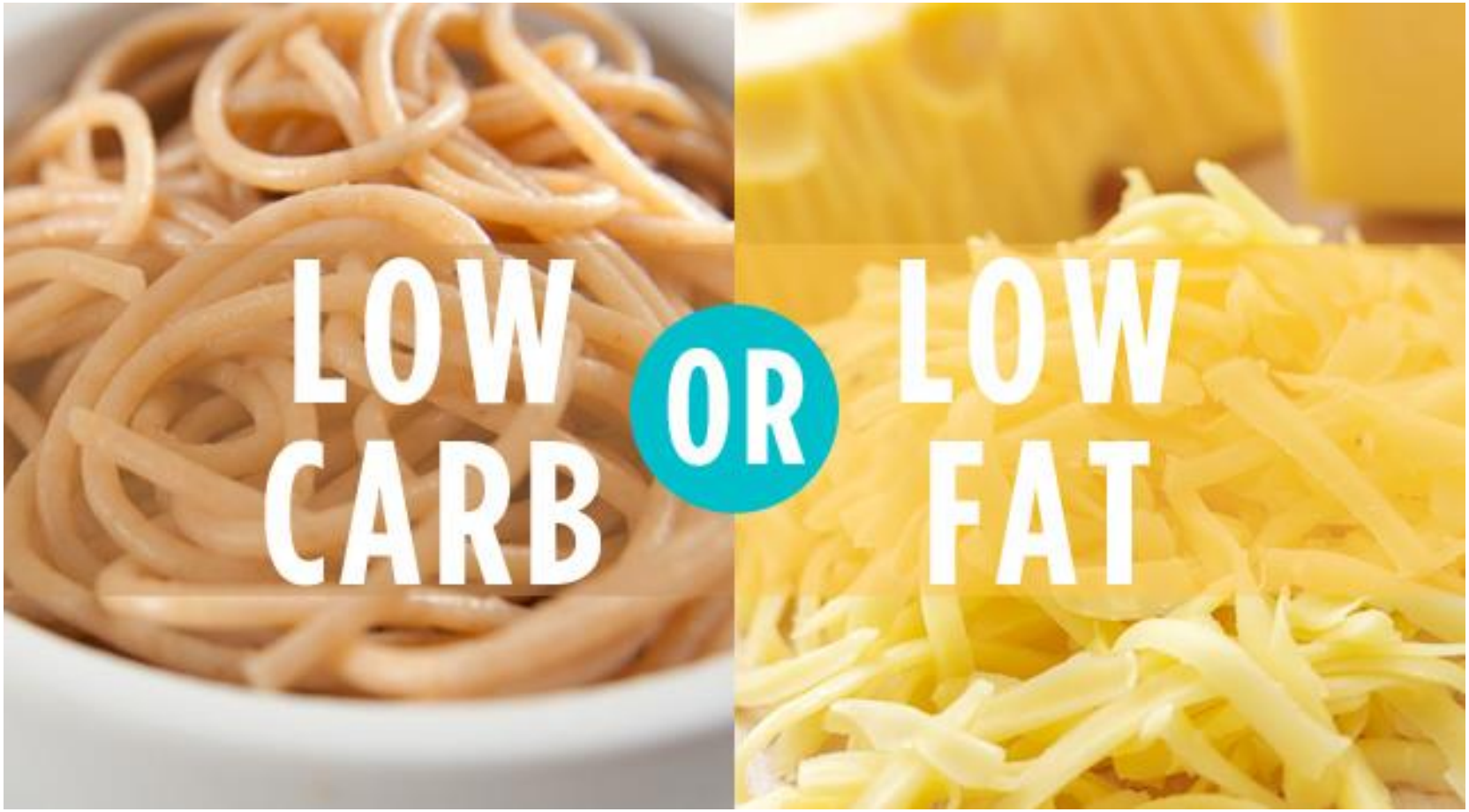
- Nicotine replacement therapy (usually a combination of transdermal patches with a short acting product such as an inhalator, gum, lozenges, or spray) for people with psychosis or schizophrenia

1. Bupropion for people with a diagnosis of schizophrenia
2. 2. Varenicline for people with psychosis or schizophrenia.

[*Based on very low to moderate quality evidence from randomised controlled trials*]

- Warn people taking bupropion or varenicline that there is an increased risk of adverse neuropsychiatric symptoms and monitor them regularly, particularly in the first two to three weeks of treatment. (New recommendation.) [*Based on the experience and opinion of the GDG*]

Diet????



Physical activity (PA)

Stubbs et al. 2016. How much physical activity do people with schizophrenia engage in? A systematic review, comparative meta-analysis and meta-regression

They found:

1. less moderate and vigorous PA in schizophrenia

2. Only 56% met the recommended 150 min of moderate physical activity per week

3. Depressive symptoms and older age were associated with less vigorous PA

Physical Fitness

frontiers in PSYCHIATRY

ORIGINAL RESEARCH ARTICLE
published: 30 October 2014
doi: 10.3389/fpsyt.2014.00148

High aerobic intensity training and psychological states in patients with depression or schizophrenia

Jørn Heggelund[1,2]*, Kim Daniel Kleppe[3], Gunnar Morken[2,4] and Einar Vedul-Kjelsås[2,4]

[1] Division of Psychiatry, Department of Østmarka, St. Olavs University Hospital, Trondheim, Norway
[2] Department of Neuroscience, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway
[3] Hamar District Psychiatric Centre, Innlandet Hospital Trust, Ottestad, Norway
[4] Division of Psychiatry, Department of Research and Development (AFFU), St. Olavs University Hospital, Trondheim, Norway

Edited by:
Jan Hoff, Norwegian University of Science and Technology, Norway

Reviewed by:
Eivind Wang, Norwegian University of Science and Technology, Norway
Øyvind Steen, Telemark University College, Norway

***Correspondence:**
Jørn Heggelund, Department of Østmarka, Division of Psychiatry, St. Olavs University Hospital, Box 3008 Lade, Trondheim N-7441, Norway
e-mail: Jorn.Heggelund@ntnu.no

Aim: To explore changes in psychological states in response to a bout of high aerobic intensity training (HIT) in patients with depression or schizophrenia compared to healthy individuals.

Methods: After familiarization training of HIT, 20 patients with schizophrenia, 13 patients with depression, and 20 healthy individuals performed a no-training day followed by a training day. HIT was 4 × 4 min intervals at 85–95% of peak heart rate, intermitted by 3 min active rest periods at 70% of peak heart rate. Self-evaluation questionnaires of positive affect, negative affect, state anxiety, well-being, distress, and fatigue were completed before training, 15 min after, and 3 h after training. The two latter measures were also completed the no-training day.

Results: All three groups improved in positive affect and well-being 15 min after HIT ($p < 0.01$), but only patients with depression had maintained the effect after 3 h ($p = 0.007$, $p = 0.012$). The duration of the improved positive affect was longer in depression ($p = 0.002$) and schizophrenia ($p = 0.025$) than in healthy individuals ($F_{2,50} = 5.83$, $p < 0.01$). Patients with depression or schizophrenia had reduced distress and state anxiety 15 min after HIT and 3 h after HIT ($p < 0.05$). The improvement in distress 15 min after HIT was larger in patients with depression ($p = 0.028$) compared to healthy individuals ($F_{2,50} = 5.05$, $p < 0.01$). No changes were found during the no-training day ($p > 0.05$).

Conclusion: High aerobic intensity training used as an acute intervention improved positive affect and well-being and reduced distress and state anxiety in patients with depression and schizophrenia.

ClinicalTrials.gov identifier: NCT01310998.

Keywords: exercise, intensity, affect, anxiety, transitory emotions

Life-style

- What percentage of patients with schizophrenia smoke?

a. 30%-50%

b. 50%-80%

c. 80%-100%

- Percentage of metabolic syndrome in schizphrenia?

a. 20%

b. **40%**

c. 60%

Conclusions

- Polygenic risk score explains 20% in the development of schizophrenia. In particular genes involved in the immune system appear to play a role in schizophrenia.
- Prevention psychiatry should target a broad range of psychiatric complaints
- Studies with the aim to improve cognition in all stages of schizophrenia are needed
- Focus on life-styles and reduction of side-effects – room for improvement

Neuroimaging findings an endophenotype - Enigma

Fig. 2 ENIGMA founding sites. The first ENIGMA project (Stein et al. 2012) was initiated in 2009, by a consortium of research groups worldwide involved in neuroimaging and genetics. Several existing consortia and research networks are taking part, including IMAGEN, EPIGEN, SYS, FBIRN, and ADNI. Many of these efforts pre-dated ENIGMA and continue today; each conducts its own projects in addition to their collaborative work within ENIGMA. ADNI collects data at 58 sites around the U.S.; for clarity, not all data collection sites are shown here. Each *symbol* represents a site contributing to ENIGMA, as of June 2013

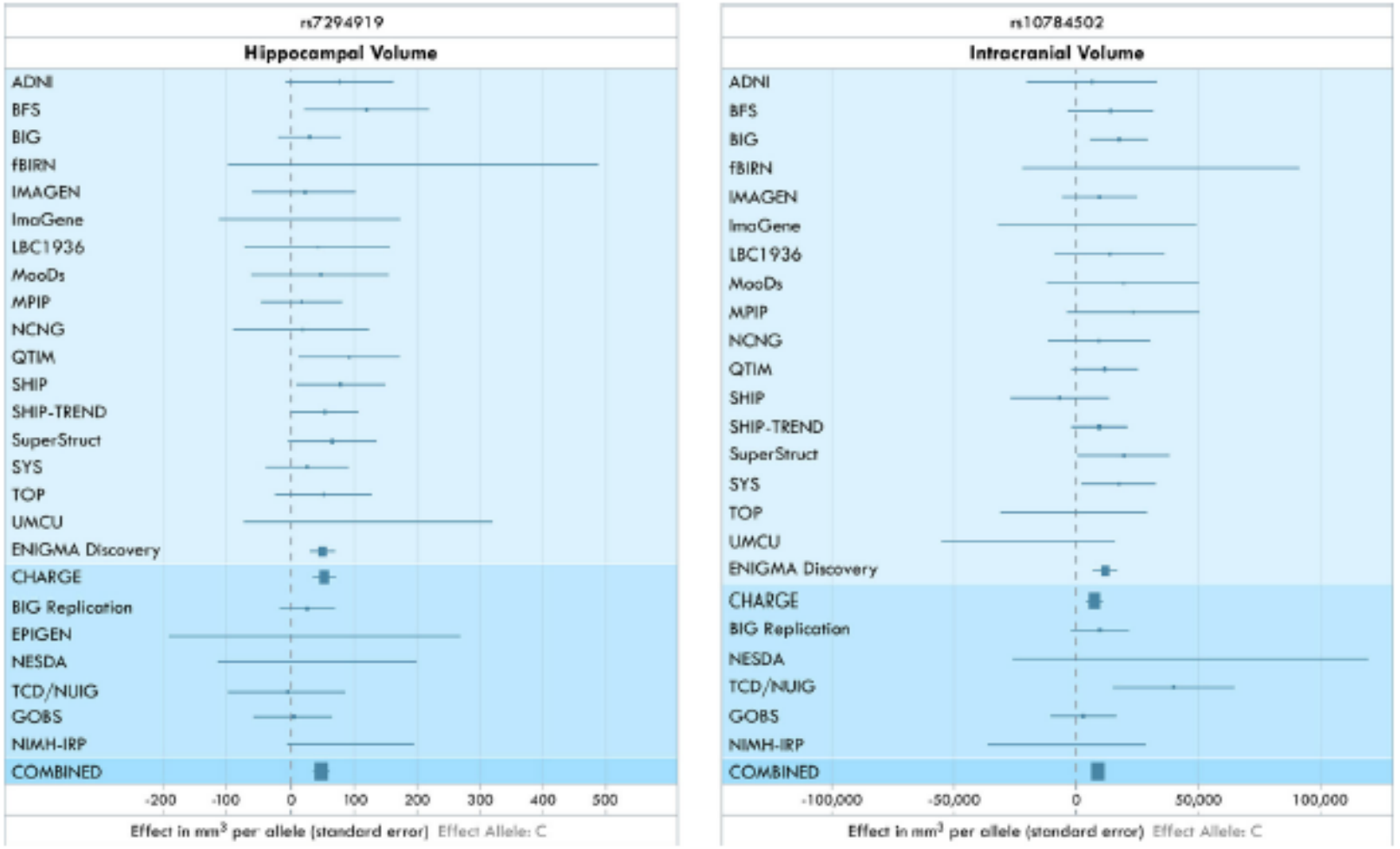


Fig. 3 Forest plots from the ENIGMA1 study (adapted from Stein et al. 2012). Forest plots are a graphical display designed to illustrate the relative strength of an effect in different cohorts. In the *left panel*, we show the effect of the genetic variant at rs7294919 on the hippocampal volume, in a range of cohorts in ENIGMA. In ADNI, for example, the confidence interval on the effect overlaps zero, which means that there is no evidence to reject the hypothesis of no effect, if only that cohort were considered. The "ENIGMA Discovery" line combines the effects of all cohorts above it. At the bottom of the figure, the meta-analysis of all effects above the line includes data from another large consortium, CHARGE, and several replication samples. The area of each square is proportional to the study's weight in the meta-analysis. The *right panel* shows a similar plot for the effect on intracranial volume of the common genetic variant at rs10784502. It is not necessary for the effect to be detected in all cohorts for the meta-analysis to support the effect. The abbreviations denote the names of the different cohorts in ENIGMA (please see Stein et al. 2012, for details). [Adapted, with permission, from Stein et al., *Nature Genetics,* April 15 2012]

Neuroimaging findings and enviromental factors

Reduced Cortical Thickness as an Outcome of Differential Sensitivity to Environmental Risks in Schizophrenia

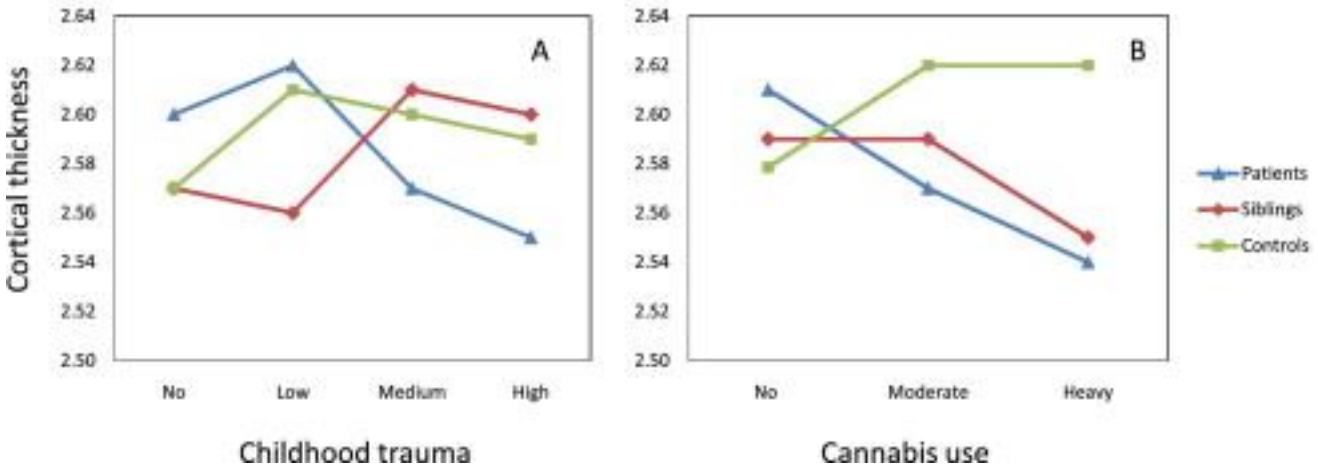


Figure 2. Interaction between environmental risk factors and group on cortical thickness. (A) Interaction between childhood trauma and group (linear trauma × group interaction, p = .01). (B) Interaction between cannabis use and group (cannabis x group interact...

Habets et al Biological Psychiatry, Volume 69, Issue 5, 2011, 487–494

Brain volume changes in schizophrenia

S. V. Haijma et al

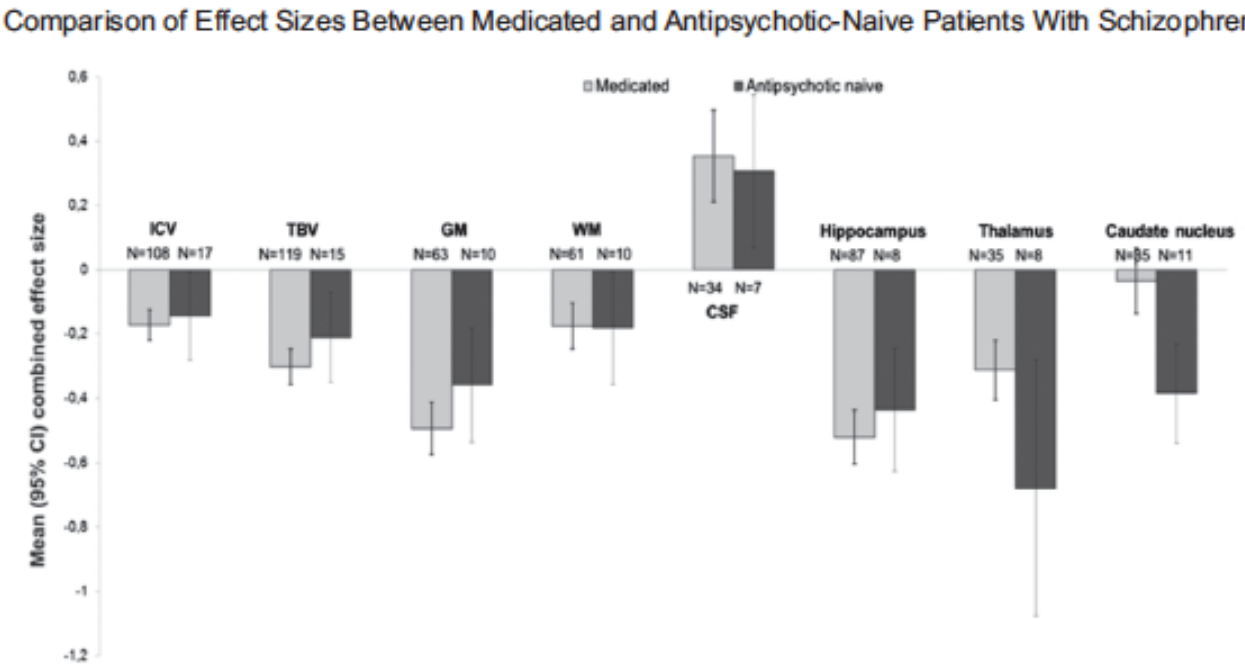
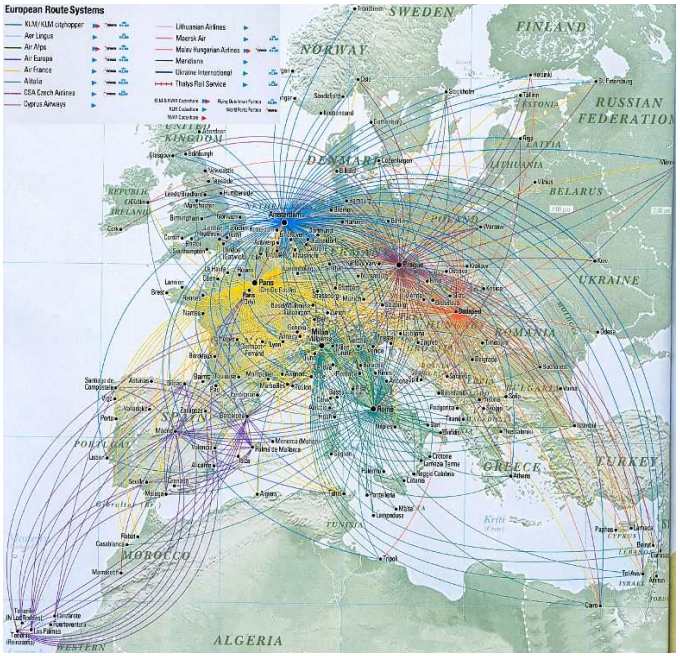
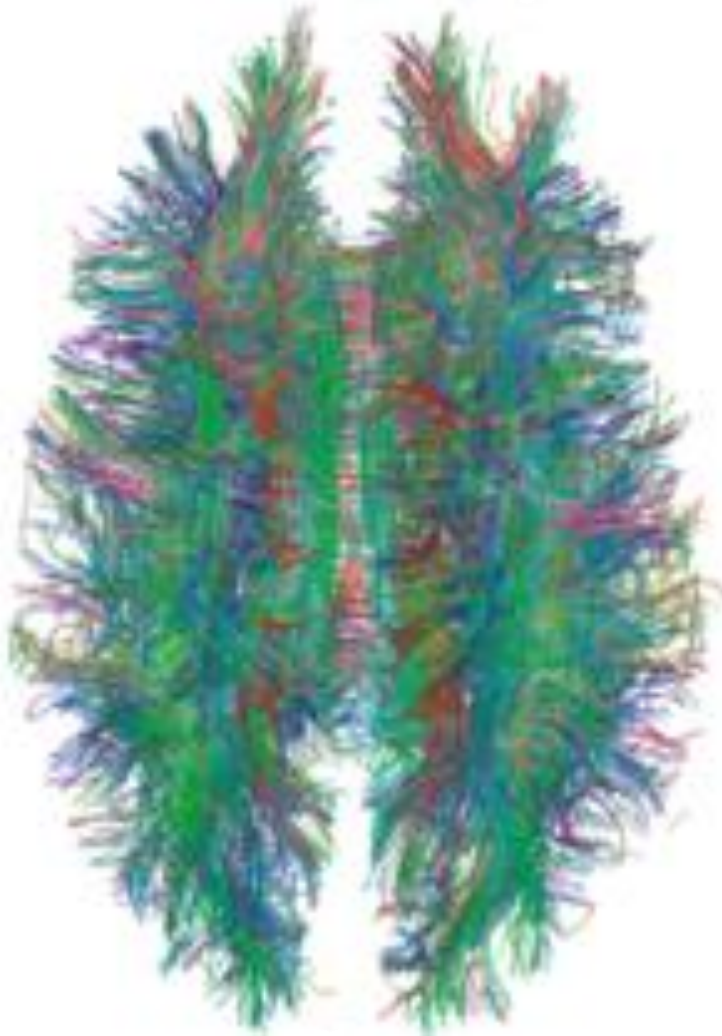


Fig. 1. The numbers of included studies are indicated for each brain region (N). *Abbreviations*: ICV, intracranial volume; TBV, total brain volume; GM, total gray matter volume; WM, total white matter volume; CSF, total cerebrospinal fluid volume.

Human connectome

http://www.myconnectome.nl





Impaired Connectivity

Schizophrenia Bulletin vol. 40 no. 2 pp. 438–448, 2014
doi:10.1093/schbul/sbt162
Advance Access publication December 2, 2013

Impaired Rich Club Connectivity in Unaffected Siblings of Schizophrenia Patients

Guusje Collin*[,1,2], René S. Kahn[1,2], Marcel A. de Reus[1,2], Wiepke Cahn[1,2], and Martijn P. van den Heuvel[1,2]

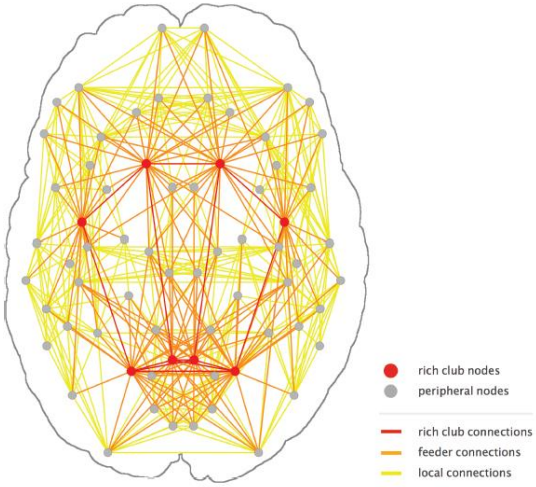


Fig. 1. Rich club. Schematic representation of a group-averaged reconstructed structural brain network. Nodes are categorized into rich club and nonrich club peripheral nodes and connections are color coded to indicate rich club, feeder, or local connections.

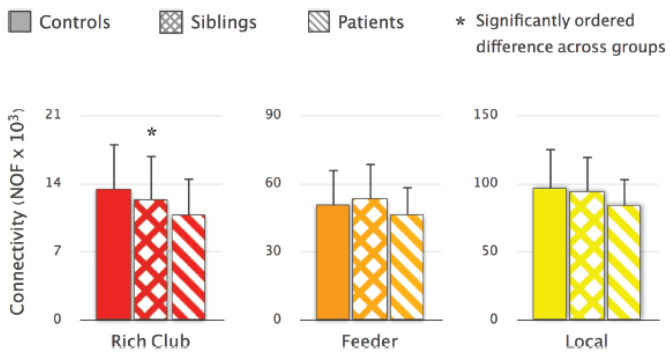


Fig. 2. Rich club, feeder, and local connectivity. Bar graphs indicate connectivity strength (ie, sum of reconstructed fibers), for rich club, feeder, and local connections. A significant ordered difference, such that controls > siblings > patients, was found for rich club connectivity ($P = .014$).

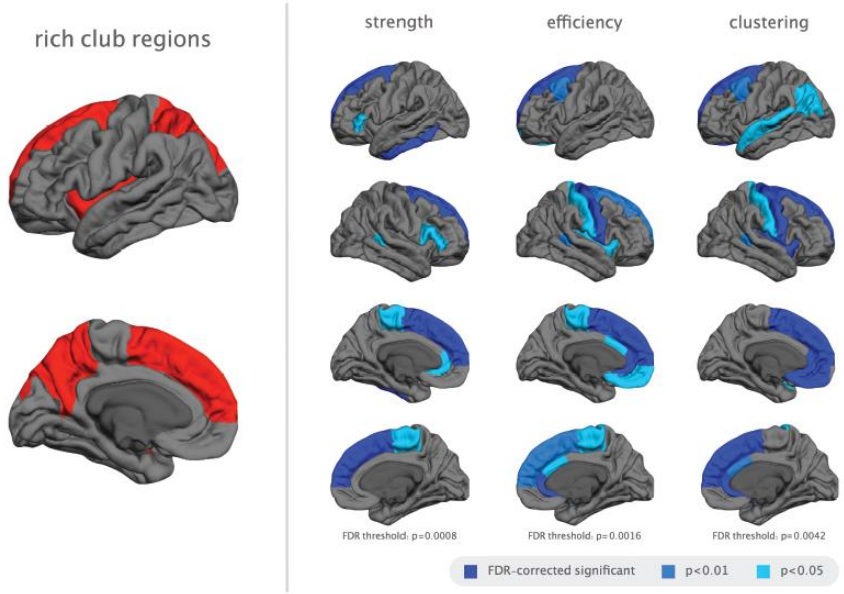


Fig. 3. Node-specific abnormalities. Cortical regions for which differential reductions (ie, controls > siblings > patients) in S_i, E_i, and C_i were found. Regions are color-coded according to P-value, with dark blue regions surviving FDR-correction, marking the bilateral superior frontal and rostral anterior cingulate gyri, left medial orbitofrontal and inferior temporal gyri, and right precentral and insular gyri, (all $q < .05$).

Connectome organization is related to longitudinal changes in general functioning, symptoms and IQ in chronic schizophrenia

G. Collin *, J. de Nijs, H.E. Hulshoff Pol, W. Cahn [1], M.P. van den Heuvel [1]

Department of Psychiatry, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht, The Netherlands

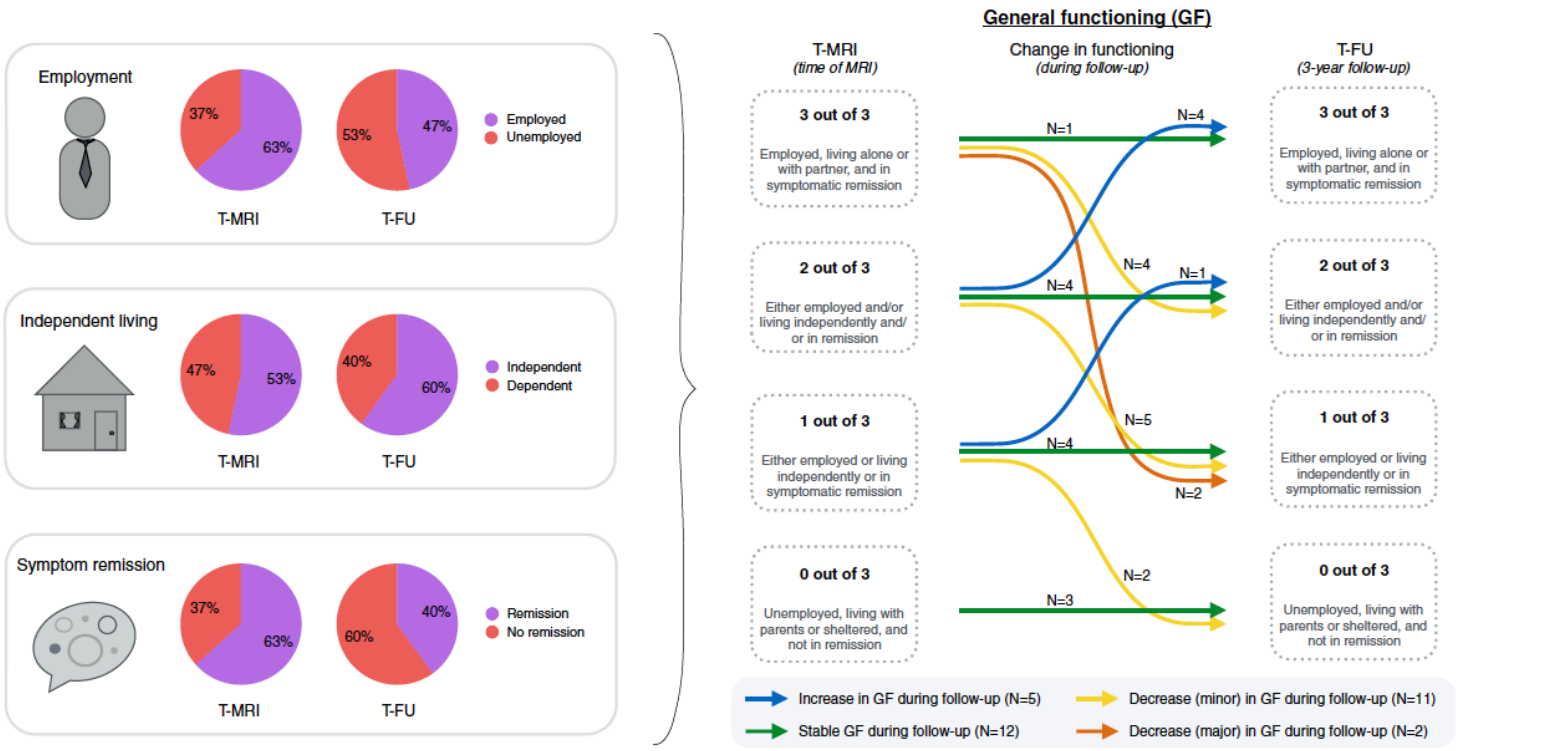


Fig. 1. Three intuitive measures of real-world functioning in schizophrenia (employment, independent living and symptom remission) were combined in one composite measure of general functioning (GF). GF was assessed at the time of MRI acquisition (T-MRI) and 3-year follow-up (T-FU). Four major trajectories of change in GF during follow-up were discerned (increase in GF, stable GF, minor decrease in GF, major decrease in GF) and patients were grouped accordingly.

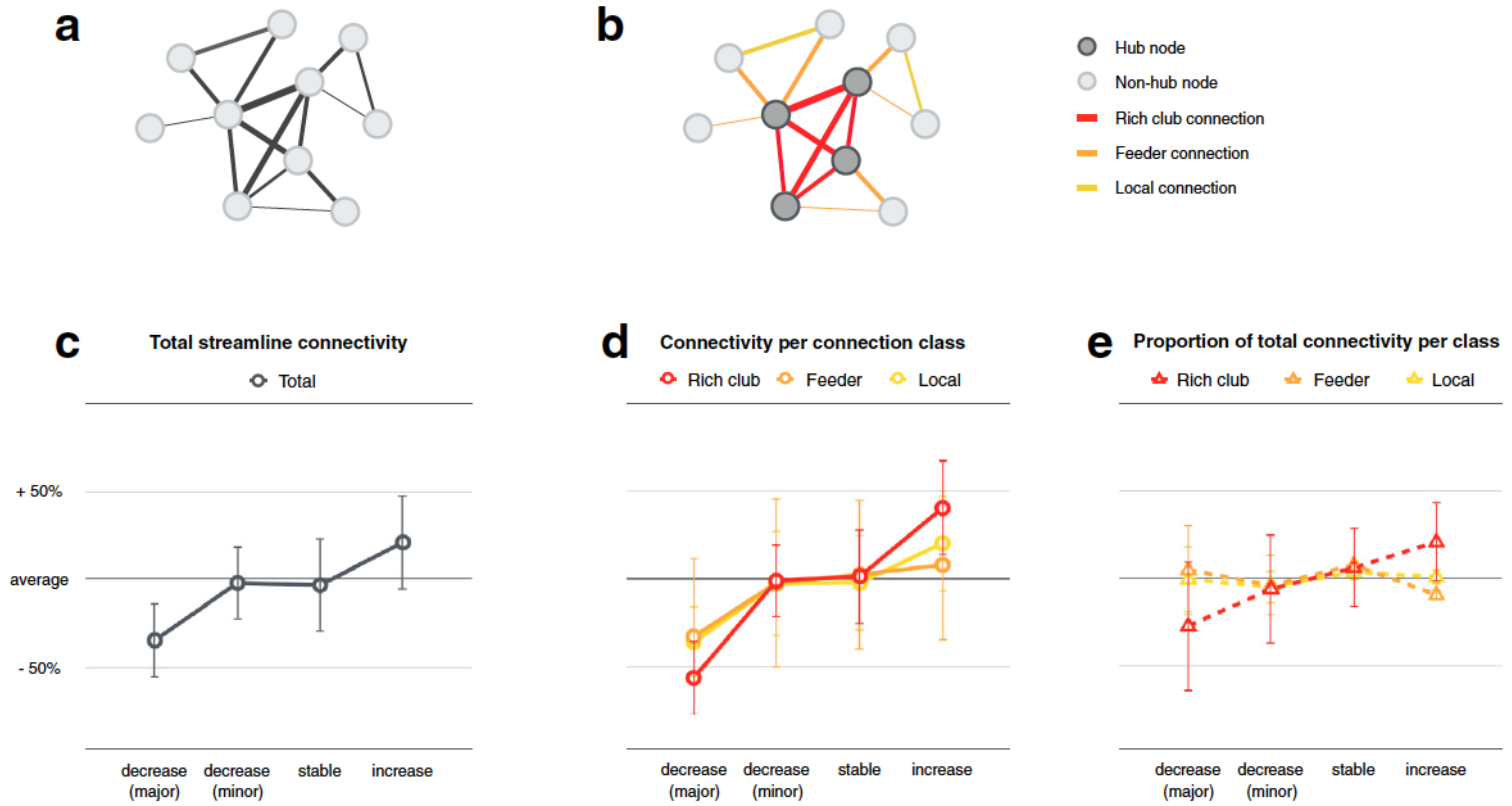
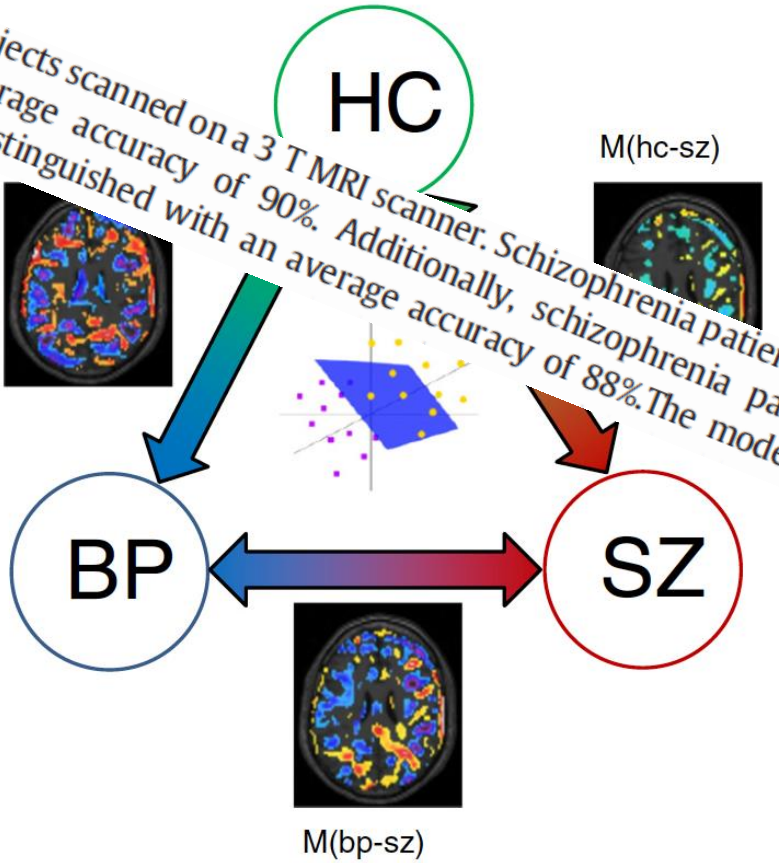


Fig. 3. Overall connectivity *S* (a) and connection classes (rich club, feeder and local connections) (b) were examined for a link with change in general functioning (GF) during follow-up. Total connectivity showed a trend-level effect with subsequent change in GF (c); rich club and local connectivity both showed significant associations (d), but only rich club connections remained significantly associated with GF change when examined as a proportion of *S* (e).

Machine learning and neuroimaging for diagnostics



jects scanned on a 3 T MRI scanner. Schizophrenia patients could be separated from healthy subjects with an average accuracy of 90%. Additionally, schizophrenia patients and patients with bipolar disorder could be distinguished with an average accuracy of 88%. The model delineating bipolar patients from healthy subjects

Fig. 1. Classification scheme. The three groups (healthy subjects (HC), patients with bipolar disorder (BP) and schizophrenia patients (SZ)) are depicted by circles. The three models that are trained to perform pair-wise separations of the groups are indicated by arrows, labeled with the model's name (M) and a symbolic picture of its discriminative brain pattern (w-map). In the center a schematic picture of the support vector machine (SVM): an optimal separation plane (OSH; blue) separates the two classes of subjects based on their positions in a high-dimensional feature space (yellow and purple dots).