

Auswirkungen einer frühen Anhäufung von Umweltrisikofaktoren auf Gewalttätigkeit und Kriminalität im Erwachsenenalter

Hannelore Ehrenreich

Klinische Neurowissenschaften

Max-Planck-Institut für Experimentelle Medizin
Göttingen

**Aufwachsen in risikobehafteten Strukturen
*Erkennen – Verstehen – gemeinsam Handeln***

LVR, Köln, 29.09.2021, 10:00-13:00 Uhr





Hannelore Ehrenreich

Clinical Neuroscience

Max Planck Institute of Experimental Medicine

Clinical Research on Neuropsychiatric Diseases



Martin Begeemann



Sabine Stolpe



Vinicius Daguano Gastaldi



Agnes Steixner



Carolin Walter



Cosima Weidinger



Wiebke Timmer

Molecular & Cellular Research

Mouse Behavior



Nadine Barnkoth



Laura Fernandez



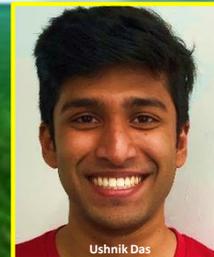
Ying Zhao



Justus Wilke



Viktoria Bonet



Ushnik Das



Martin Hindermann



Anja Ronnenberg



Yasmina Curto



Umer Javed Butt



Roman Schröder



Matthias Zillmann



Leonie Mohrmann



Liu Ye



Sahab Arinrad



Clinical Neuroscience

Max Planck Institute of Experimental Medicine



Mole



Matthias Zillmann

ses



avior



Research Focus I:

**Neuroprotective & -regenerative
strategies for patients:
*EPO & Hypoxia***

Research Focus II:

**Biological subgroups
of neuropsychiatric diseases**



Clinical Neuroscience

Max Planck Institute of Experimental Medicine

Ad: Research Focus II:

**Biological subgroups
of neuropsychiatric diseases**

Influence of environmental risk factors

*Synopsis of a deep phenotyping-based study that
started by serendipity ~8 years ago ...*



Hanns-Jörg Ehrenreich



M

M



Nadine Barnik



or



Ronnenberg



Yasmin



Matthias Zillmann



Sahab Arinrad



Clinical Neuroscience

Max Planck Institute of Experimental Medicine

Ad: Relevance of Focus II:

Let us go
from
disease to
health!

environmental factors

Synopsis of a longitudinal study that started many years ago ...

Hannelore Ehrenreich

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M

Nadine Barnick

Yasmin

Matthias Zillmann

Shahab Arinrad

Ronnenberg



GRAS (Göttingen Research Association for Schizophrenia)

Field Study 2005-2021
Travel team ...



Martin Begemann

et al...



Begemann et al *JAMA Psychiatry* 2010, Hammer et al *Molecular Psychiatry* 2013, PGC *Nature* 2014, Stepniak et al *Lancet Psychiatry* 2014
 Ehrenreich et al *Molecular Psychiatry* 2018; Mitjans et al *Molecular Psychiatry* 2018; Bansal et al *Nature Communications* 2018;
 Ursini et al *Nature Medicine* 2018; Steixner-Kumar et al *Molecular Psychiatry* 2021



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DEEP PHENOTYPING

~2000 schizophrenia patients

Additional ~5000 subjects, healthy or other neuropsychiatric diseases



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Martin Begemann

*et al...****DEEP PHENOTYPING*****~2000 schizophrenia patients****Additional ~5000 subjects, healthy or other neuropsychiatric diseases*****AXIOM® semi-custom direct genotyping: > 620 000 SNPs per subject*****Based on high quality imputations, we can make use of around **20 million SNP** information per individual**



2021



et al...

Recruitment continues – Presently focus on demyelinating diseases, mainly Multiple Sclerosis

Additional

diseases

AXIOM® sensor

per subject

Based on h... around 20 h...

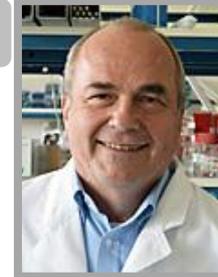
make use of per individual



GRAS serological analyses: *Infections & autoimmunity*

Viruses

- Adenovirus
- Bornavirus
- Cytomegalovirus
- Epstein-Barr virus
- Herpes simplex 1&2
- Influenza A & B
- Kaposi's sarcoma-associated herpes virus
- Measles
- Papillomaviruses
- Parotitis
- Parvo B19
- Polyomaviruses
- Rubella
- Varizella zoster



Michael Pawlita
Heidelberg



Thomas Schulz
Hannover

COLLABORATORS

Bacteria

- Borrelia
- Chlamydia
- Helicobacter
- Mycoplasma

Protozoa

- Toxoplasma gondii

Autoimmunity

- **anti-NMDAR autoantibodies as well as autoantibodies directed against 50 other brain antigens**



Winfried Stöcker
EUROIMMUN
Lübeck



GRAS: >3000 phenotypical data points per patient



Worldwide largest phenotypical data base in mental disease...

Begemann et al *JAMA Psychiatry* 2010, Hammer et al *Molecular Psychiatry* 2013, PGC *Nature* 2014, Stepniak et al *Lancet Psychiatry* 2014
Ehrenreich et al *Molecular Psychiatry* 2018; Mitjans et al *Molecular Psychiatry* 2018; Bansal et al *Nature Communications* 2018;
Ursini et al *Nature Medicine* 2018



THE GRAS DATA COLLECTION



... et al

Raw data from travel team

Screening of chart records/ medical reports identification of missing records

Collection of all psychiatric discharge letters of every single patient

Careful study & reprocessing of all collected information

Determination of age at onset, duration of prodromal symptoms, medication history, pattern of course, psychiatric and medical comorbidity

Confirmation of consensus diagnosis based on chart records (e.g. first diagnosis, first psychotic episode, current diagnosis, differential diagnosis)

Analysis and entering of questionnaire data, rating scales and neuropsychological tests
Additional verification by physicians & relatives

Result:
Data bank of > 3,000 phenotypic data points per subject

← Continuous training and calibration sessions of research assistants →

← Meticulous double-check of entered data →



THE GRAS DATA COLLECTION



Jan Seidel



Fabian Bloschke



Vinicius Daguano Gastaldi



Agnes Steixner

... et al

Screening of chart records/ medical reports/ identification of missing records

Collection of all psychiatric discharge letters of every single patient

Careful study & reprocessing of all collected information

DATA VERIFICATION
MULTIPLE QUALITY CONTROLS
CONTINUOUS RATER TRAININGS

Raw data from travel team

Result:
 Data bank of > 3,000 phenotypic data points per subject

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THE GRAS DATA COLLECTION



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Vinicius Daguano Gastaldi



Agnes Steixner

... et al

Important note:

Patients can be re-contacted for follow-up studies!

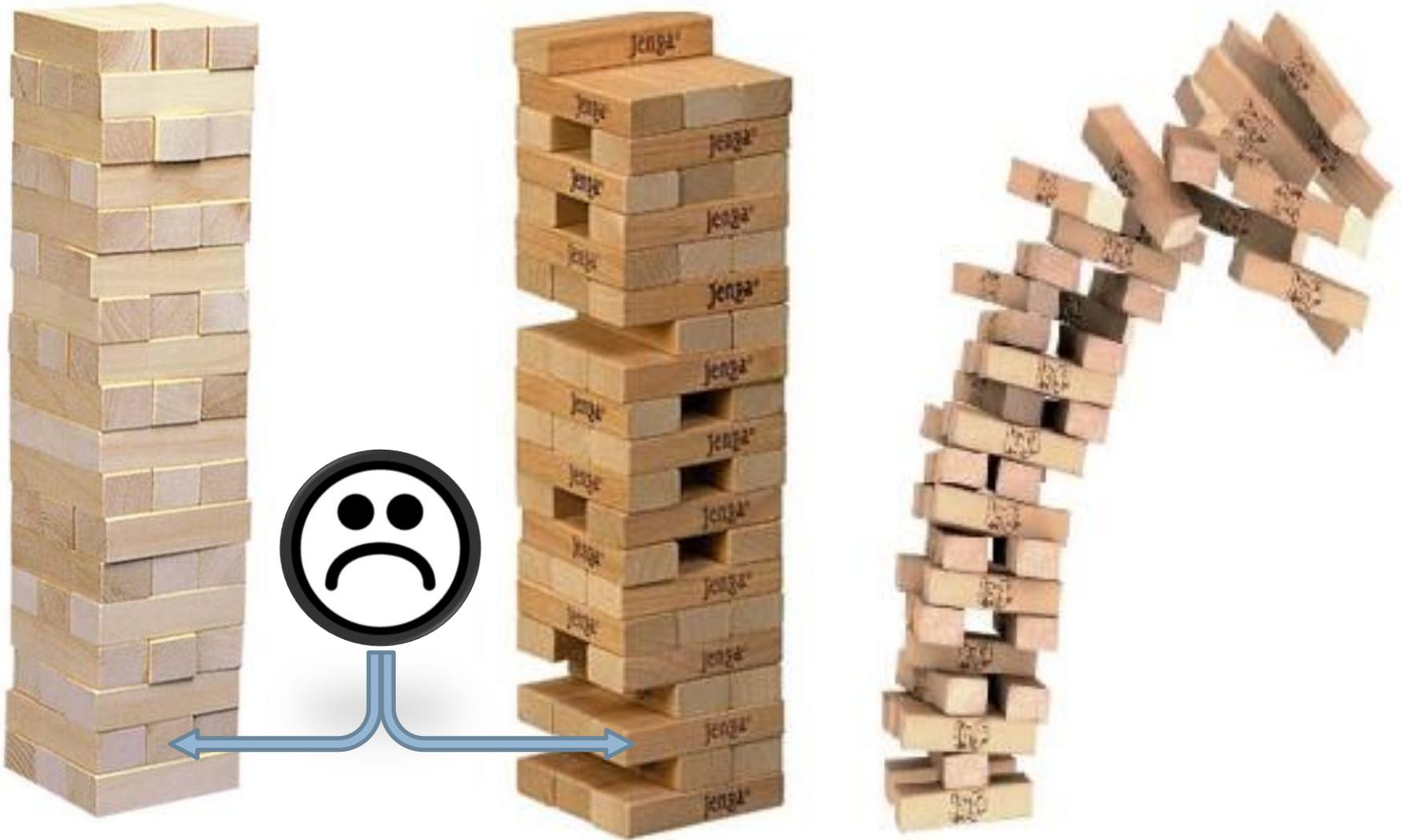
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Environment: Critical level of complexity



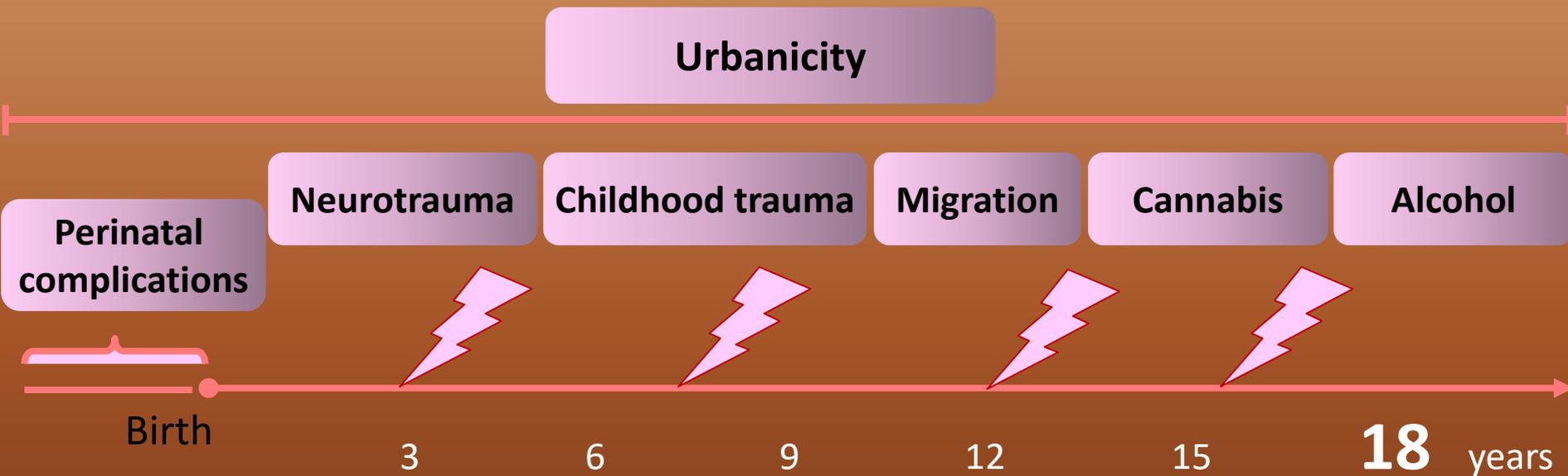
Genes load the gun

Environment pulls the trigger!





Environmental insults experienced before disease onset - until age 18

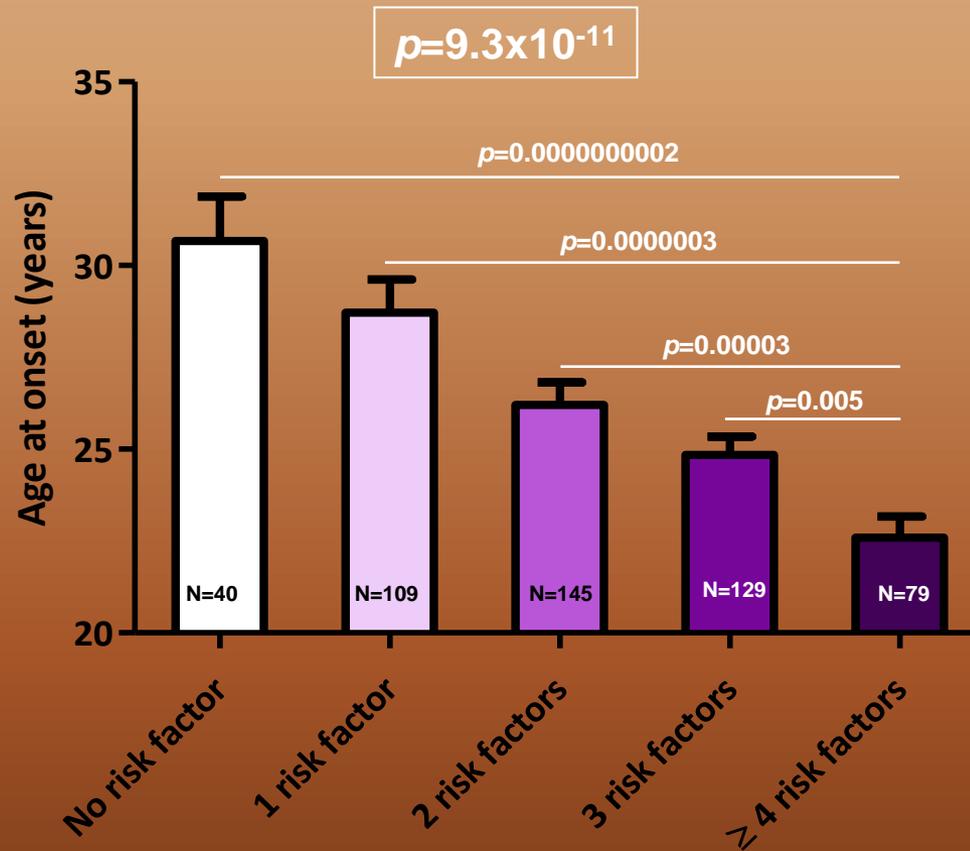


GRAS: Environmental risk study



Accumulated environmental risk and age at disease onset

Perinatal complications
Neurotrauma
Psychotrauma
Urbanicity
Migration
Cannabis



Stepniak *et al* Lancet Psychiatry 2014

Environmental influence is non-specific, affecting any predisposed subject, *BUT ENORMOUS!*

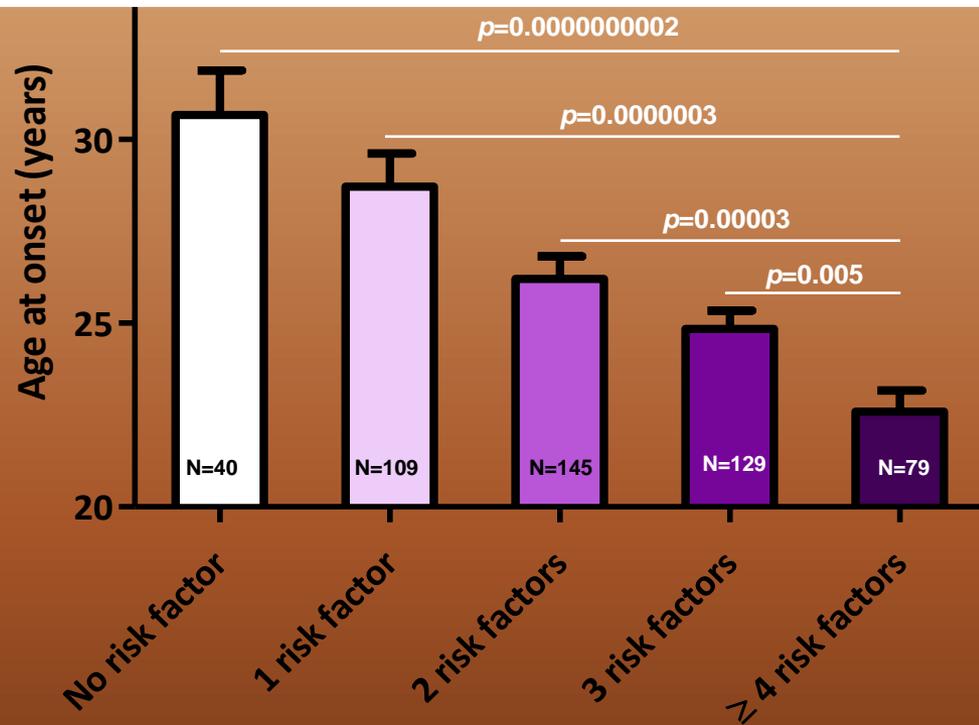




Accumulated environmental risk and age at disease onset

No genes x environment effect: *GWAS hits do not contribute....*

Perinatal complications
Neurotrauma
Psychotrauma
Urbanicity
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Stepniak et al Lancet Psychiatry 2014

Environmental influence is non-specific, affecting any predisposed subject, *BUT ENORMOUS!*





Accumulated environmental risk and age at disease onset

**No genes x environment effect:
*GWAS hits do not contribute....***

**Multiple environmental hits
before adulthood '*dose-dependently*'
predict an earlier schizophrenia onset**

Stepniak *et al* Lancet Psychiatry 2014

No risk factor

1 risk factor

2 risk factors

3 risk factors

≥ 4 risk factors

**Environmental influence is non-specific, affecting
any predisposed subject, *BUT ENORMOUS!***



GRAS: Environmental risk study

Accumulated environmental risk and age at disease onset

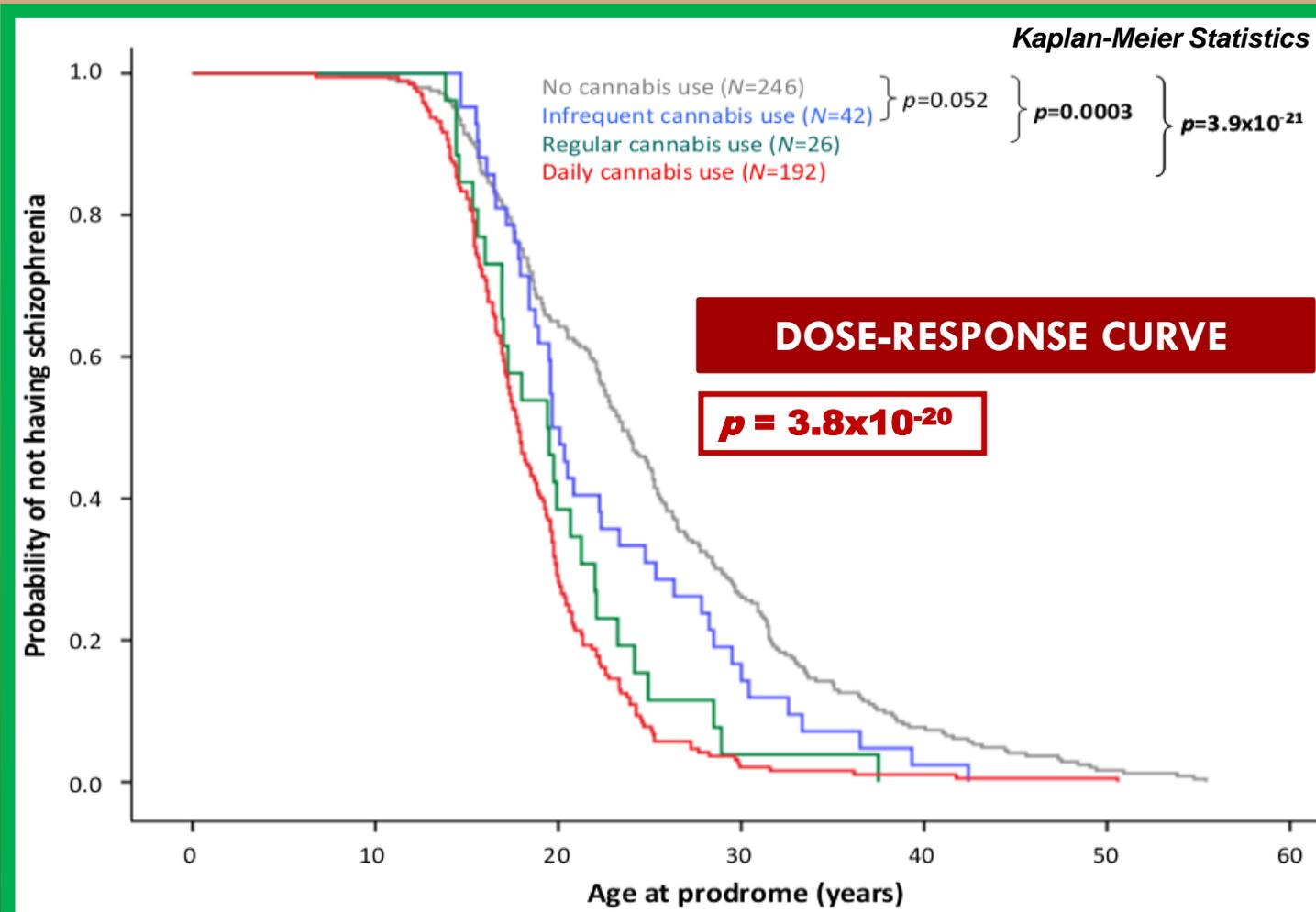


Cannabis



Only male subjects
(N>500) shown with
exact information
on cannabis dose...

Stepniak *et al*
Lancet Psychiatry 2014



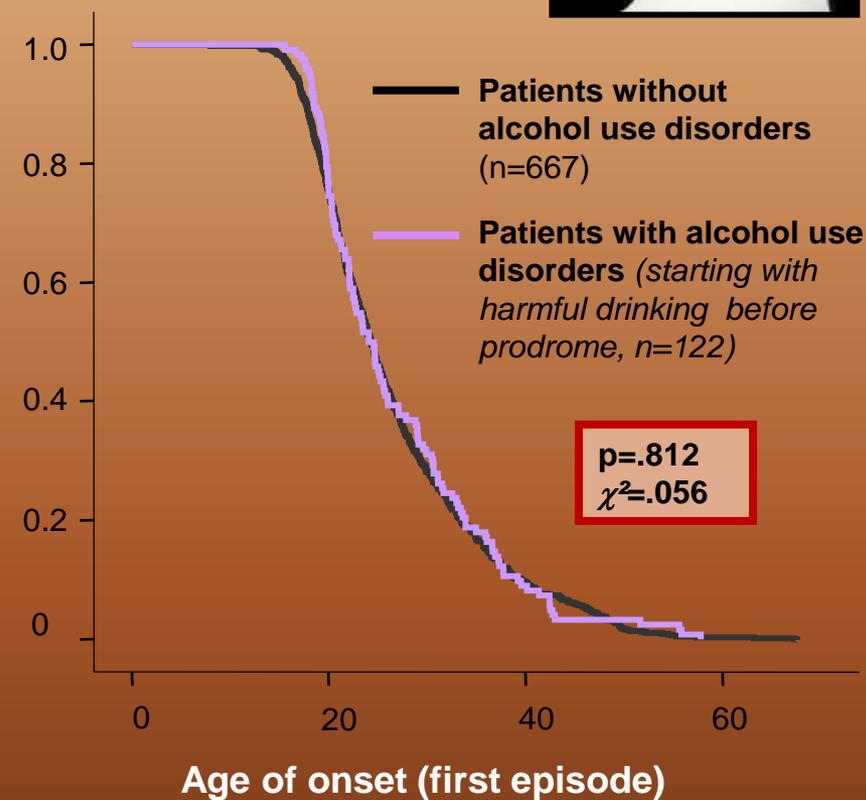
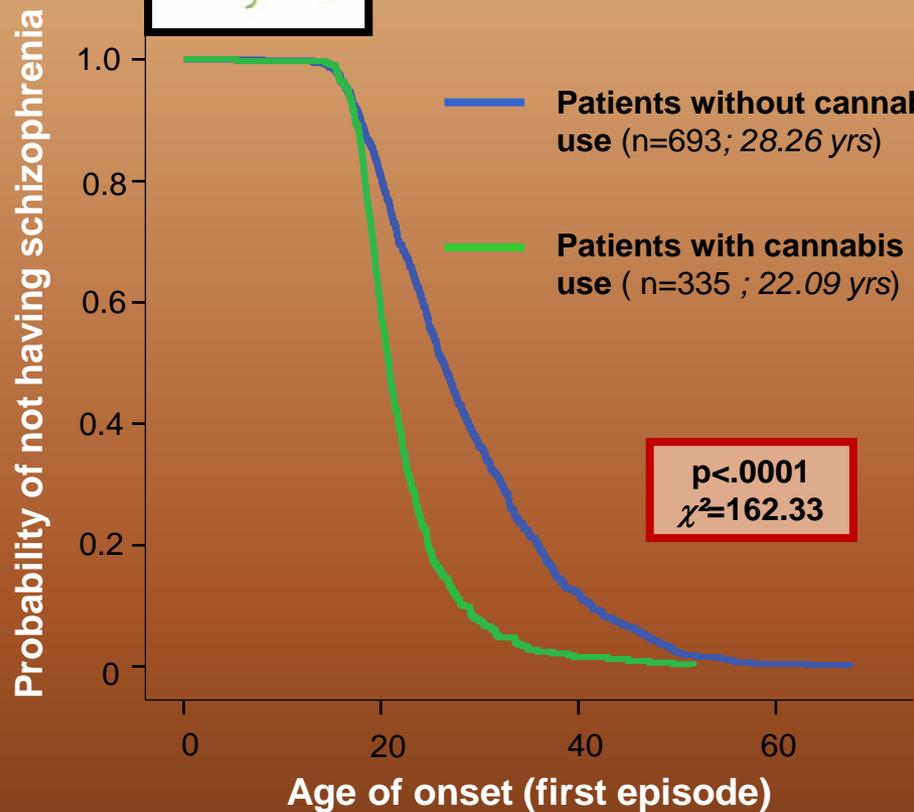
Note: Cannabis is an avoidable risk



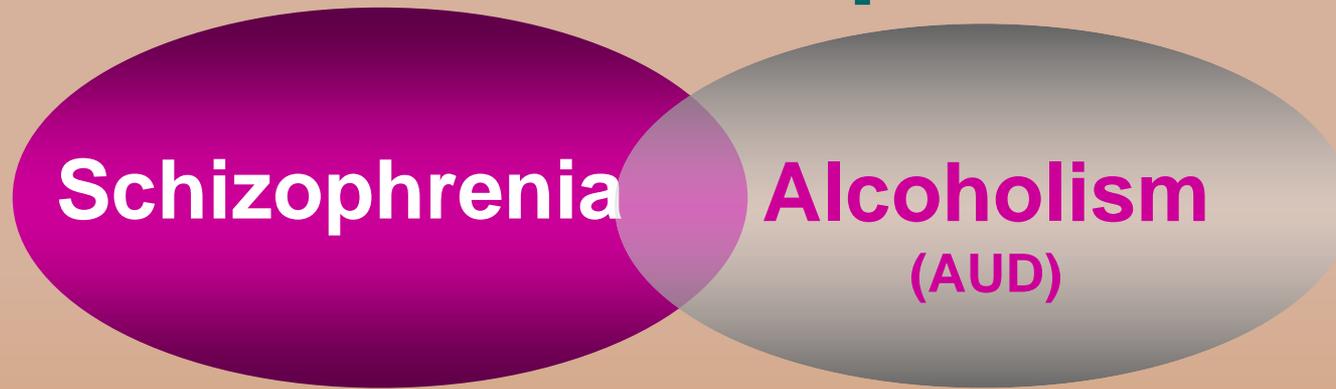
Accumulated environmental risk and age at disease onset



GRAS males and females together: N>900
- dichotomous evaluation: yes/no -



DUAL DIAGNOSIS: Schizophrenia and AUD



Life-time prevalence	General population	Patients with schizophrenia
Alcohol use disorders (AUD)	13-30%	20-40% GRAS: 35%

More severe disability
 Poorer social adjustment
 More hospitalizations
 More medical problems / mortality
 Higher non-compliance
Violence



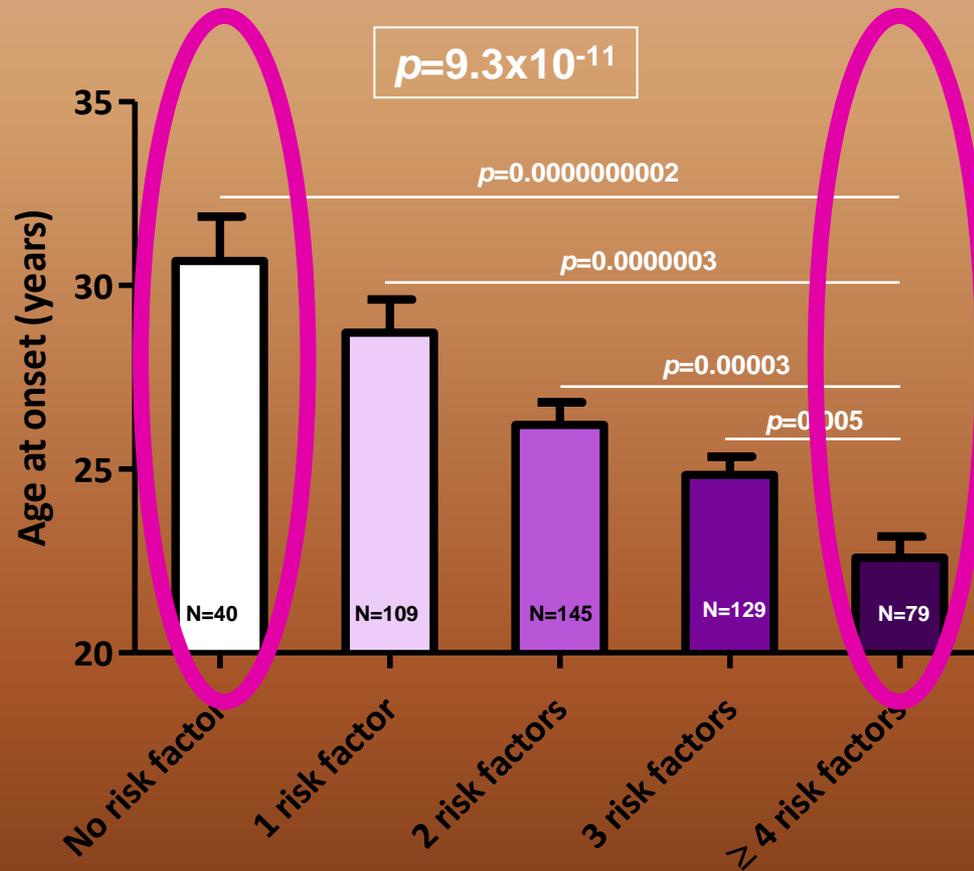
GRAS: Environmental risk study

Accumulated environmental risk and age at disease onset

extreme groups...



Perinatal complications
Neurotrauma
Psychotrauma
Urbanicity
Migration
Cannabis



Stepniak *et al* Lancet Psychiatry 2014

Environmental influence is non-specific, affecting any predisposed subject, *BUT ENORMOUS!*

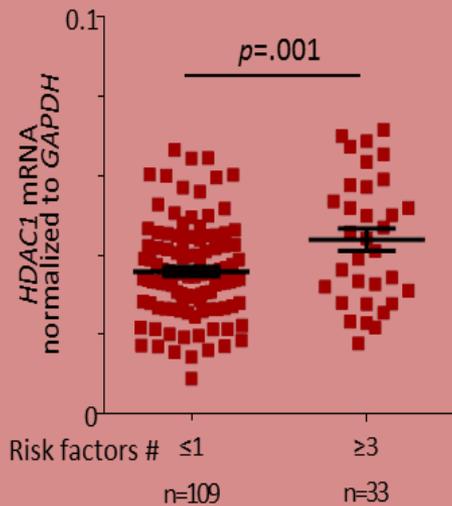


**Upon further analysis of extreme groups...
to study underlying mechanisms of environmental risk accumulation**

**Epigenetic Alterations?
DNA Methylation**

No convincing epigenetic alterations detected (via Illumina array)

♂ Extreme group subjects:
HDAC1 expression in PBMC

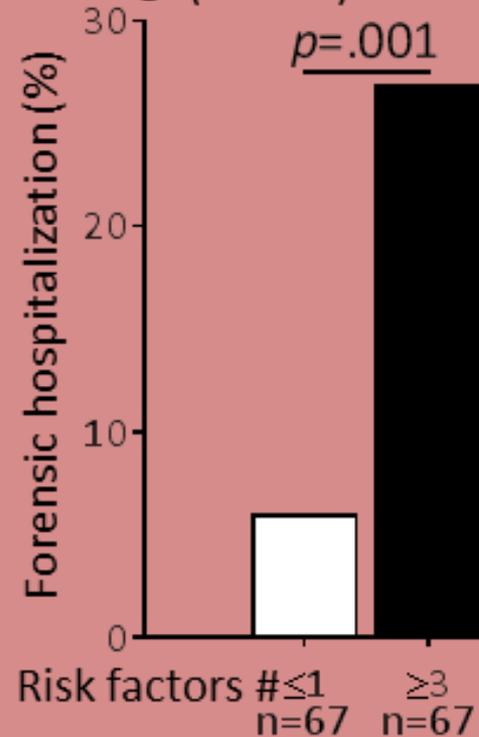


HDAC1 = Histone deacetylase 1



Discovery sample

♂ (N=134)



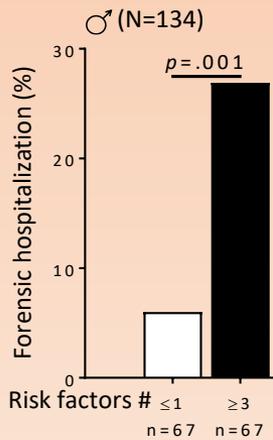
Re-contacting patients for blood sampling

(→ peripheral blood mononuclear cells, PBMCs for gene expression confirmation)

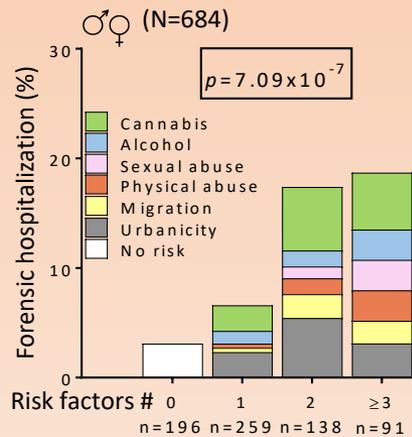


Multiple environmental hits before adulthood predict violent aggression

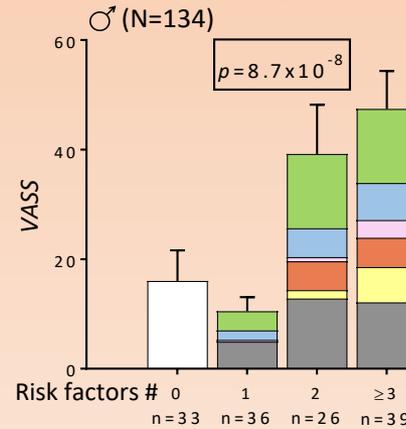
Discovery sample



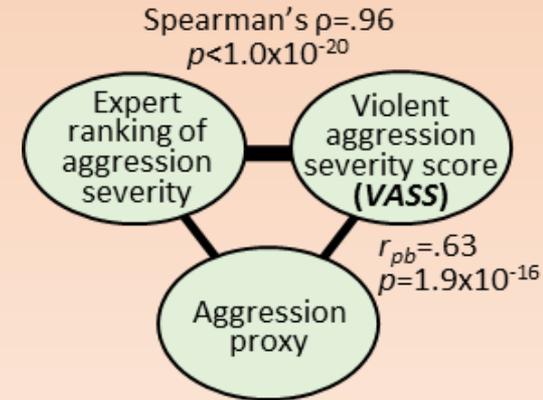
GRAS-I



Discovery sample



Intercorrelation of aggression readouts



Is forensic hospitalization a proxy of violent aggression?

Violent aggression severity score (VASS) calculation

Type of aggression	Once	Twice	>Twice
No documented aggression	0	0	0
Recurring aggressive thoughts/indirect threats	1	1	1
Deviant behavior	1.5	3	4.5
Criminality without aggression	2	4	6
Direct verbal aggression	3	6	9
Aggression against objects	4	8	12
Aggression against animals	5	10	15
Physical assaults without weapon: no injuries	7	14	21
Physical assaults without weapon: injuries	10	20	30
Rape	12	24	36
Physical assaults with weapon: no injuries	12	24	36
Physical assaults with weapon: injuries	15	30	45
Aggression with lethal consequence	100	200	300

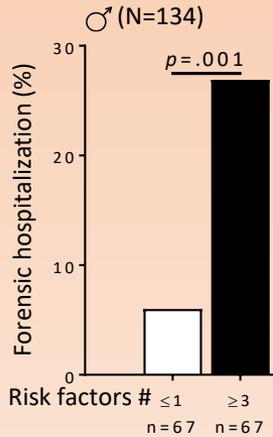
Not available for all samples – thus:

Aggression proxy
 Dichotomous variable, including history of forensic hospitalization and/or conviction for battery, sexual assault, manslaughter or murder (at least once in lifetime).

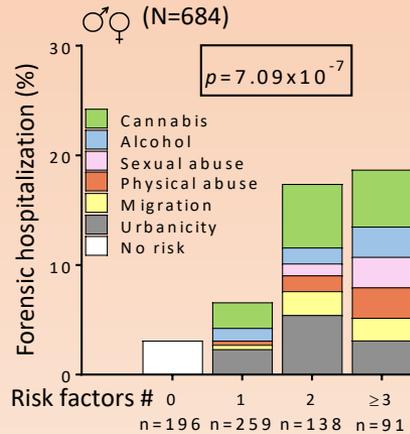


Multiple environmental hits before adulthood predict violent aggression

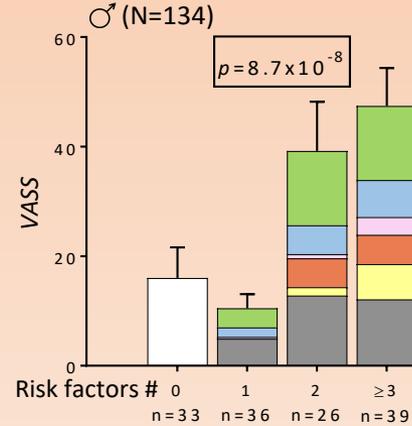
Discovery sample



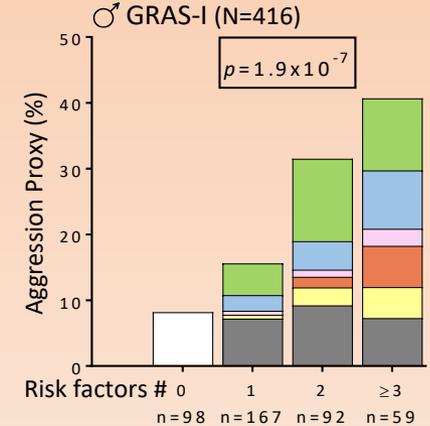
GRAS-I



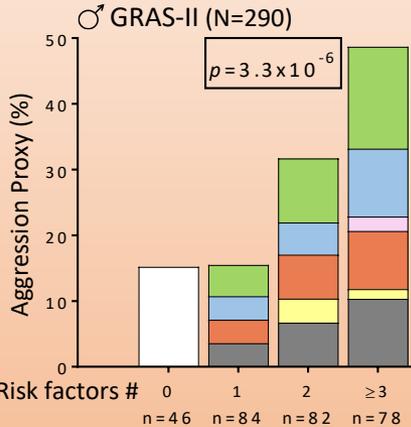
Discovery sample



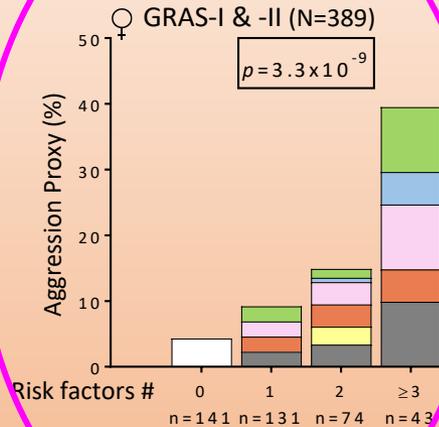
Replication sample I



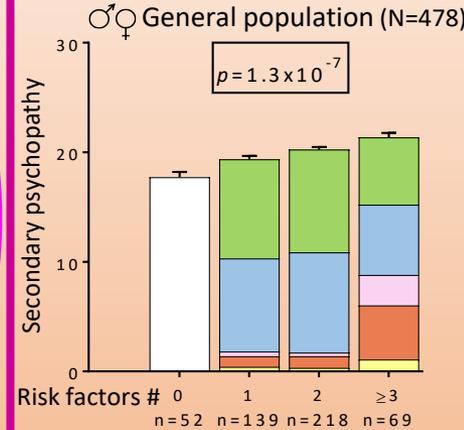
Replication sample II



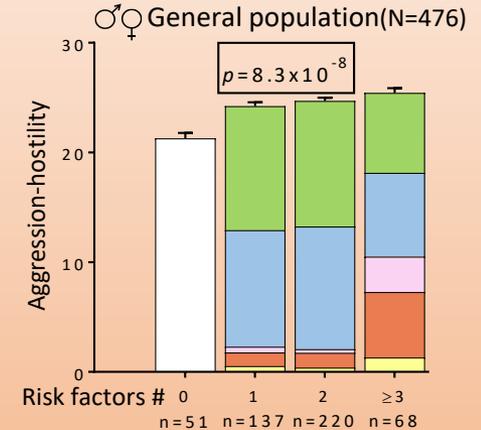
Replication sample III



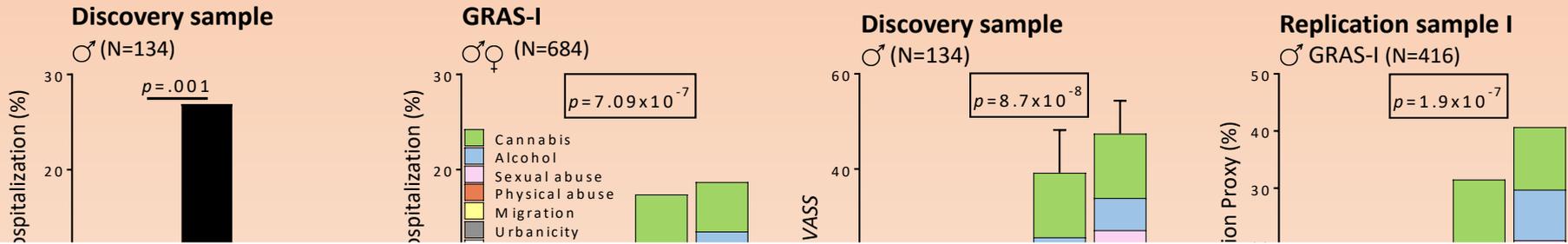
Replication IV-V



Replication IV-V



Multiple environmental hits before adulthood predict violent aggression



Multiple environmental hits before adulthood *'dose-dependently'* predict violent aggression:

- disease-independent (general population!)
- factors interchangeable ('cocktail')
- no predictive effects after age 18

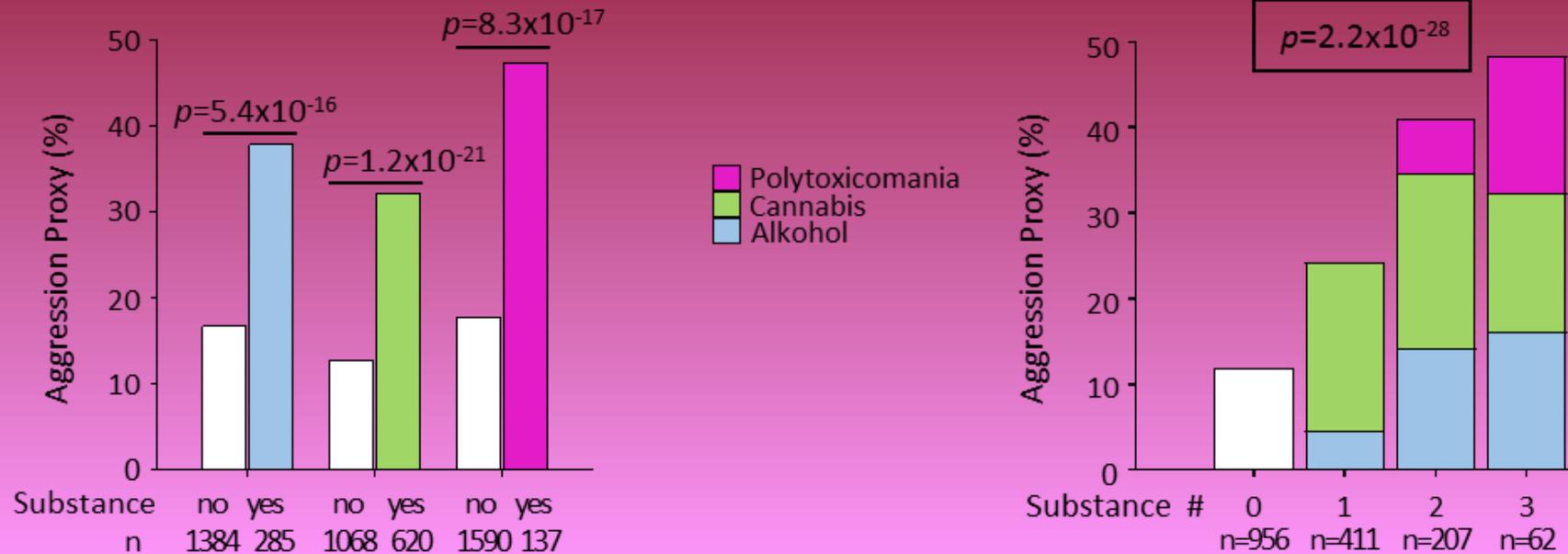


RISK FACTOR DRUGS



Focus on DRUGS only (before the age of 18 years)

Early drug use & later aggression/criminal behavior

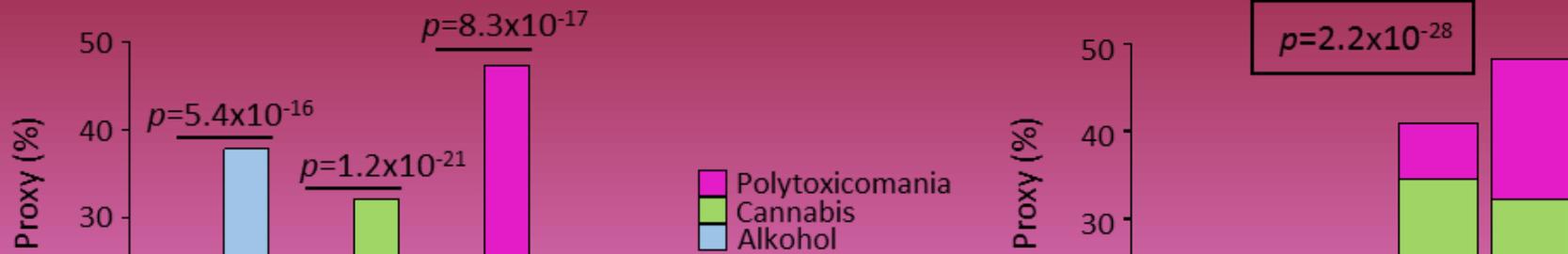


Aggression of schizophrenic subjects (GRAS) who started before age 18 and before first psychotic episode to consume alcohol, cannabis or other substances of abuse ('polytoxicomania' if at least 3 of the following: cocaine, opioids, hallucinogens, amphetamines, ecstasy, barbiturates, benzodiazepines, sniffing agents); *Pearson χ^2 , two-tailed.*



Focus on DRUGS only (before the age of 18 years)

Early drug use & later aggression/criminal behavior



Substance abuse before adulthood '*dose-dependently*' predicts violent aggression

Aggression of schizophrenic subjects (GRAS) who started before age 18 and before first psychotic episode to consume alcohol, cannabis or other substances of abuse ('polytoxicomania' if at least 3 of the following: cocaine, opioids, hallucinogens, amphetamines, ecstasy, barbiturates, benzodiazepines, sniffing agents); *Pearson χ^2 , two-tailed.*





Hypothesis:
POLYTOXICOMANIA
as a secondary
risk?
POLYTOXICOMANIA?
What comes first?





**ENVIRONMENTAL
factors
predisposing to
POLYTOXICOMANIA?**





CASE-CONTROL STUDIES

Are the differences in frequency statistically significant?

→ P - Value

How much bigger is the risk in individuals with a given constellation?

→ Odds Ratio (OR)

OR=1 No difference in risk

OR>1 Increased risk

OR<1 Lower risk (“protected”)



Adolescent risk accumulation and lifetime polytoxicomania

	no risk factors	1 risk factor	2 risk factors	≥3 risk factors
no polytoxic behavior	301 (96.8%)	353(83.8%)	169(61.7%)	117(49.0%)
polytoxic behavior	10 (3.2%)	68(16.2%)	105(38.3%)	122(51.0%)

Chi-squared test: $\chi^2 = 211.39$, $p = 1.5 \times 10^{-45}$

Cochran-Armitage test for trends:

$z = -14.43$; $p = 3.3 \times 10^{-47}$

Extreme group comparison:
no (n=311) vs. ≥3 (n=239)
risk factors

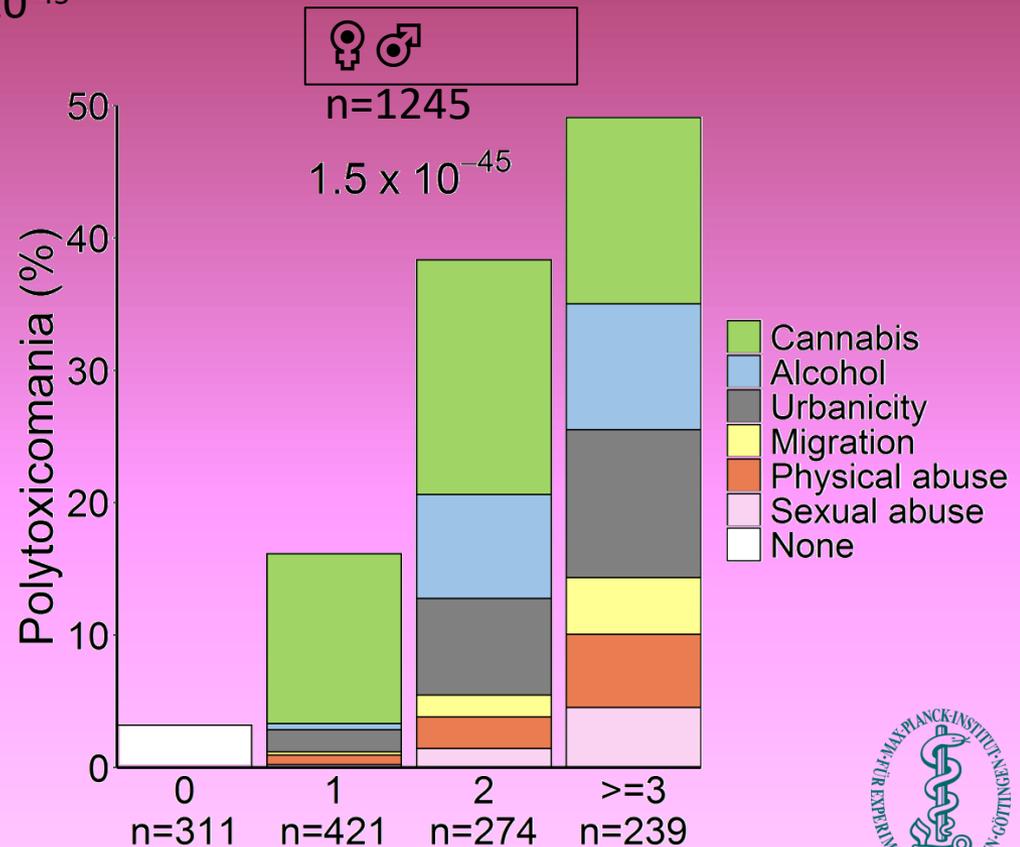
OR = 31.18

Male subjects (N=840)

OR = 29.3

Female subjects (N=405)

OR = 29.9



Adolescent risk accumulation and **lifetime** polytoxicomania

	no risk factors	1 risk factor	2 risk factors	≥3 risk factors
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Multiple environmental hits before adulthood *'dose-dependently'* predict **lifetime polytoxicomania**

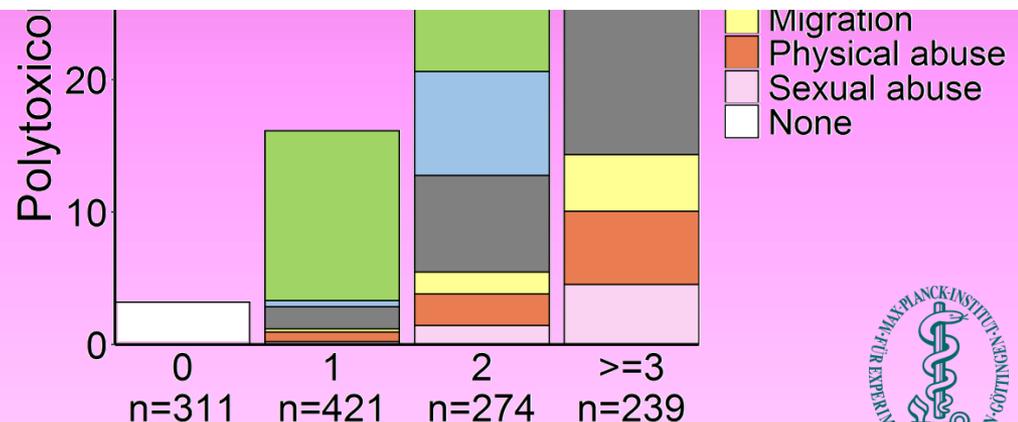
OR = 31.18

Male subjects (N=840)

OR = 29.3

Female subjects (N=405)

OR = 29.9



Adolescent risk accumulation and **preadult** polytoxicomania

	no risk factors	1 risk factor	2 risk factors	≥3 risk factors
no polytoxic behavior	299 (100%)	353 (94.4%)	167 (81.5%)	114 (65.1%)
polytoxic behavior	0 (0%)	21 (5.6%)	38 (18.5%)	61 (34.9%)

Chi-squared test: $\chi^2 = 156.58$; $p = 1.0 \times 10^{-33}$

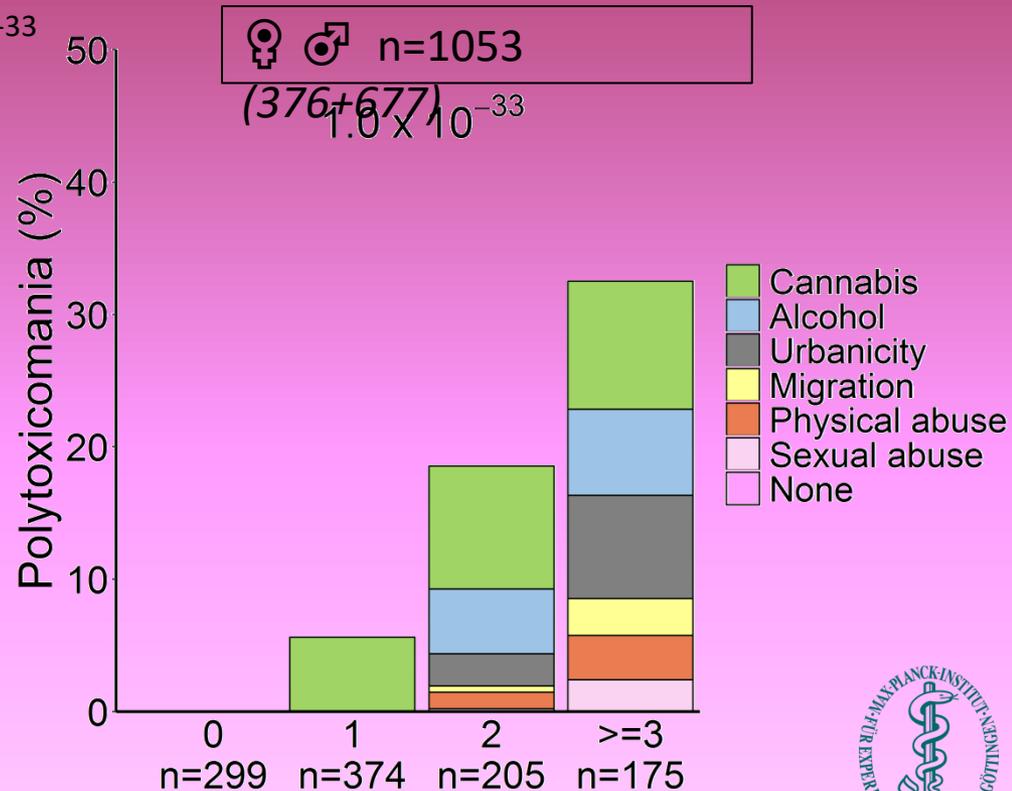
Cochran-Armitage test for trends:

$z = -12.18$; $p = 3.7 \times 10^{-34}$

Extreme group comparison:
no (n=299) vs. ≥3 (n=175) risks

OR = 227**

** OR determined via exact logistic regression based on permutation



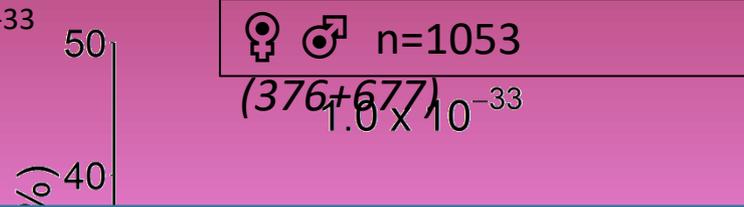
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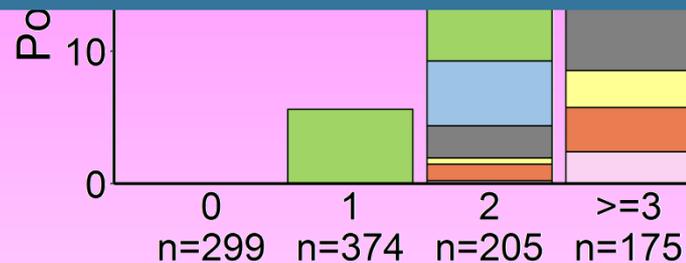
$z = -12.18; p = 3.7 \times 10^{-34}$



Extreme group comparison:
 no (n=299) vs. ≥3 (n=175) risks

OR = 227**

Which share of the risk is due to CANNABIS?
(starter drug?)



** OR determined via exact logistic regression based on permutation



Adolescent cannabis consumption and polytoxicomania

LIFETIME POLYTOX.	No preadult cannabis	Preadult cannabis
no lifetime polytoxic behavior	925 (78.0%)	261 (22.0%)
lifetime polytoxic behavior	45 (12.1%)	328 (87.9%)

Chi-squared test: $\chi^2 = 521.89$; $p = 1.6 \times 10^{-115}$

OR = 25.8



PREADULT POLYTOX.	No preadult cannabis	Preadult cannabis
no preadult polytoxic behavior	981 (69.1%)	439 (27.9%)
preadult polytoxic behavior	2 (1.3%)	151 (98.7%)

Chi-squared test: $\chi^2 = 267.81$; $p = 3.4 \times 10^{-60}$

OR = 168.1



Adolescent cannabis consumption and polytoxicomania

LIFETIME POLYTOX.	No preadult cannabis	Preadult cannabis
no lifetime polytoxic behavior	925 (78.0%)	261 (22.0%)

Multiple environmental hits before adulthood '*dose-dependently*' predict polytoxicomania

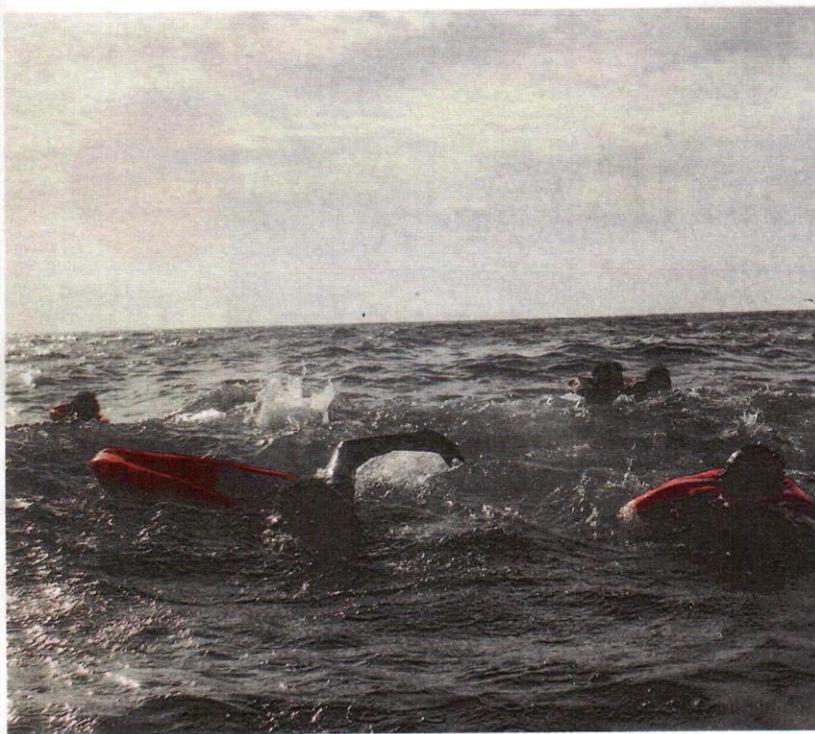
CANNABIS as 'starter drug' delivers a considerable share of risk

OR = 168.1

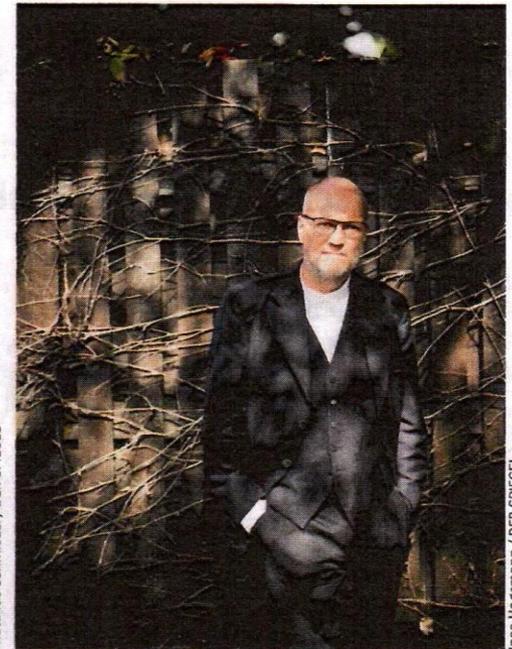


RISK FACTOR MIGRATION





Matthias Schmiedel / DER SPIEGEL



Insa Hagemann / DER SPIEGEL

Proband Hassani, Psychiater Begemann: Exkursion in die Abgründe menschlicher Erfahrung

Bootsflüchtlinge im Mittelmeer 2017

Prins McGrath / C

Wunden im Kopf

Psychiatrie Auf dem Weg nach Deutschland erleiden junge Flüchtlinge unerträgliche Schrecken. Welchen Schaden nimmt dabei ihre Seele? Eine Göttinger Studie suchte nach Antworten.

nature > news > article

30.9.2020

nature

NEWS • 12 MAY 2020

How young refugees' traumatic pasts shape their mental health

A detailed study shows that young migrants' risk of developing psychiatric disorders rises stepwise with the number of traumas experienced.

Alison Abbott

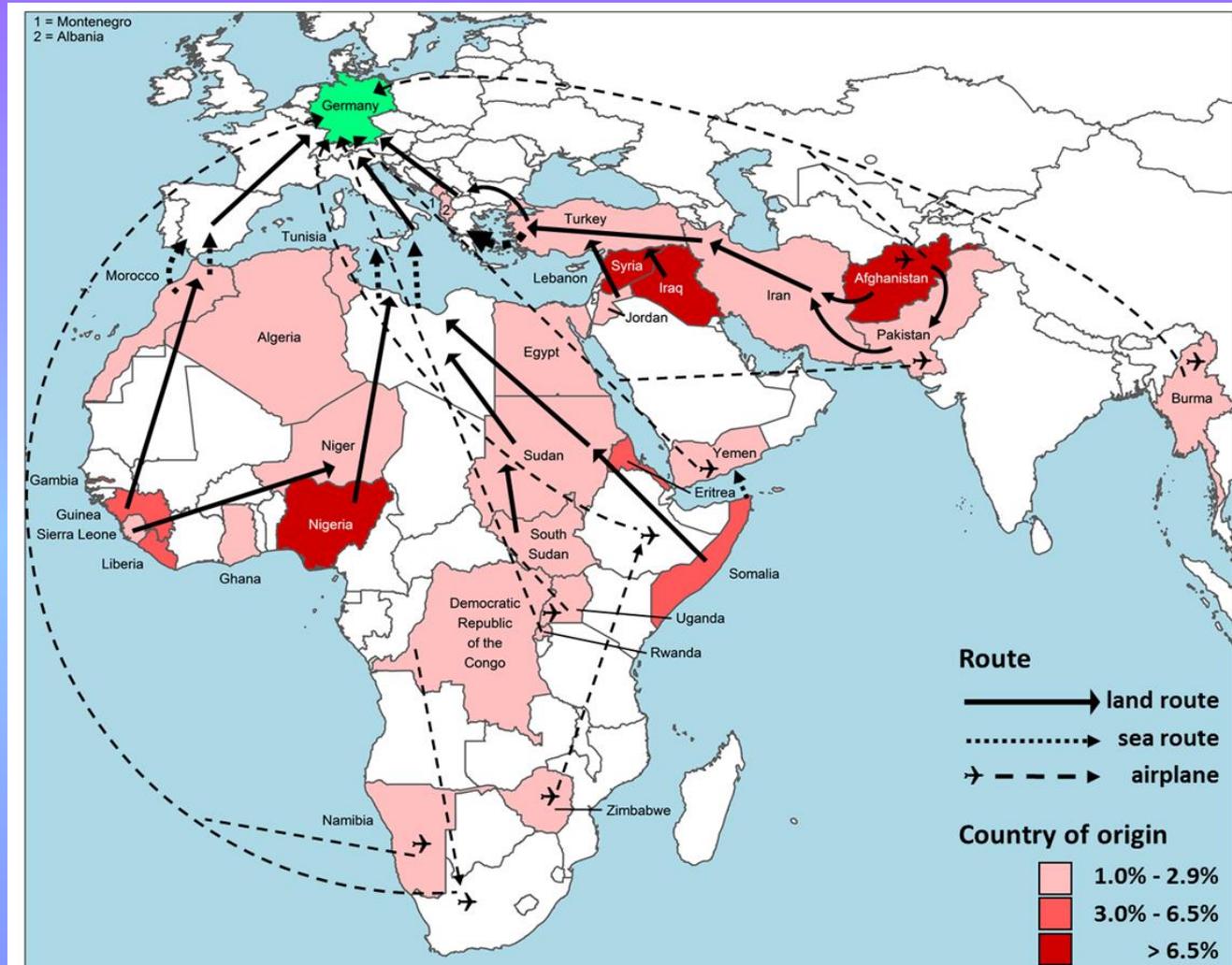


RISK FACTOR MIGRATION

**Accumulated environmental risk
in young 'healthy' refugees
*A first prospective evaluation***



Countries of origin and routes of flight to Germany (n=133)



Refugees arrived in Germany via Eastern Mediterranean/Balkan route (34.6%), from Africa via Central Mediterranean route (39.1%), by plane (17.3%) or other routes, such as Western Mediterranean or Atlantic route (9.0%).



Risk factors on top of migration/refuge (n=133)

Risk factors (+ migration)	0	1	2	3	≥4
n (%)	6 (4.5%)	34 (25.6%)	36 (27.1%)	32 (24.0%)	25 (18.8%)

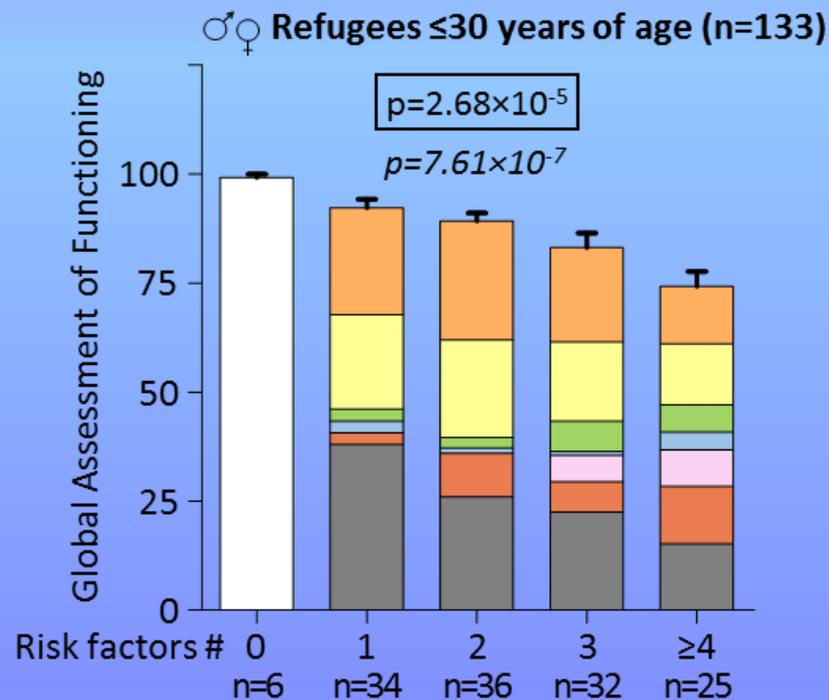
Risk factors on top of migration	yes (%)	no (%)
Trauma before flight	67 (50.4%)	66 (49.6%)
Trauma during flight	75 (56.4%)	58 (43.6%)
Urbanicity	83 (62.4%)	50 (37.6%)
Physical abuse	36 (27.1%)	97 (72.9%)
Sexual abuse	19 (14.3%)	114 (85.7%)
Alcohol	9 (6.8%)	124 (93.2%)
Cannabis	20 (15.0%)	113 (85.0%)

** Traumata before/during flight, including war, genocide, human trafficking, torture, murder, slavery, terrorist attacks

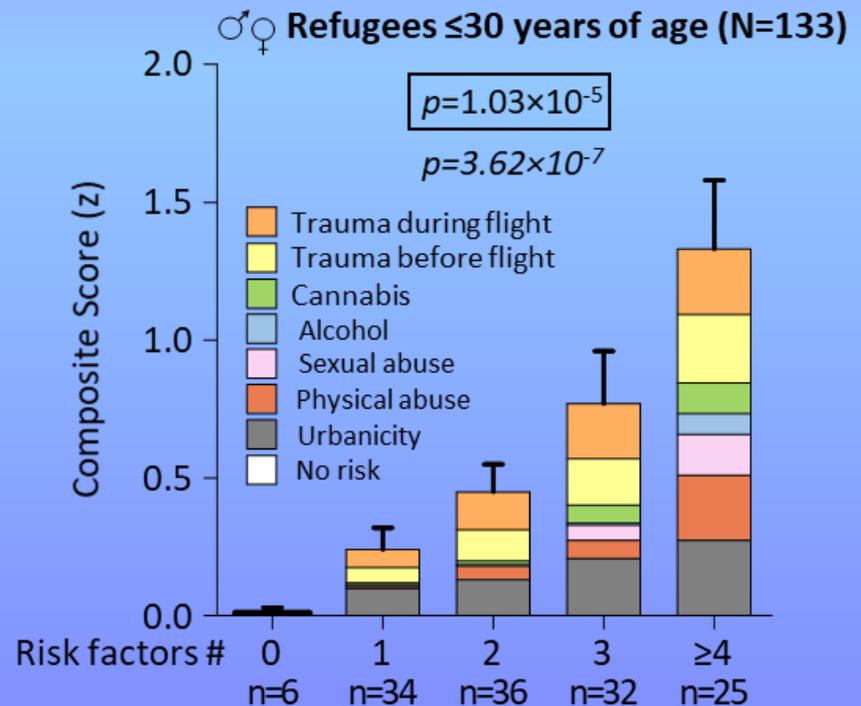


Accumulation of environmental risk factors in young 'healthy' flight migrants

Risk accumulation & functional outcome



Risk accumulation & psychopathology



Accumulation of environmental risk factors in young 'healthy' flight migrants

Risk accumulation & functional outcome

Risk accumulation & psychopathology

Young refugees, arriving in host countries already with an alarming 'risk burden', are at high risk to develop:

- global functional deficits**
- behavioral abnormalities**
- mental disorders**



Accumulation of environmental risk factors in young 'healthy' flight migrants

Risk accumulation & functional outcome

Risk accumulation & psychopathology

**Rapid proactive integration or sustainable support
of those who will return to rebuild their countries
are mandatory**

- behavioral abnormalities**
- mental disorders**



SUMMARY & CONCLUSIONS

Accumulated environmental risk before age 18 years (urbanicity, migration, physical/sexual abuse as primary, and cannabis/alcohol as secondary hits) reduces **age at schizophrenia onset**. ***Cannabis does it dose-dependently.***

Follow-up of **extreme group individuals** (≤ 1 versus ≥ 3 risks): High-risk subjects have >5 times greater probability of **later forensic hospitalization**.

In 6 independent cohorts (4 schizophrenia / **2 general population**), **pre-adult risk accumulation strongly predicts violent aggression & criminality** (overall OR 10.5).

Risk factors are interchangeable! No predictive effects after age 18!

Substance abuse before adulthood predicts **violent aggression**.

Pre-adult environmental hits predict **polytoxicomania** (pre-adult or lifetime).

Young 'healthy' refugees, arriving in host countries already with an alarming 'risk burden', are at high risk to develop **global functional deficits, behavioral abnormalities, and mental disorders** →→→ *radicalism, criminality...*



Funding

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EU-AIMS

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EU-EXTRABRAIN

N-RENNT

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Brain & Behavior Foundation

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and industry funds ...

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