

Infections and autoimmunity as risk factors for mental disorders

- Danish nationwide register and biobank studies

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The Danish Registers



CPR-number Register

Prescription Database
All redeemed
prescriptions since
1995

Hospital Registers
- Psychiatry since
1969
- Somatic since 1977

Autoimmune diseases and infections as risk factors for schizophrenia (1977-2006)

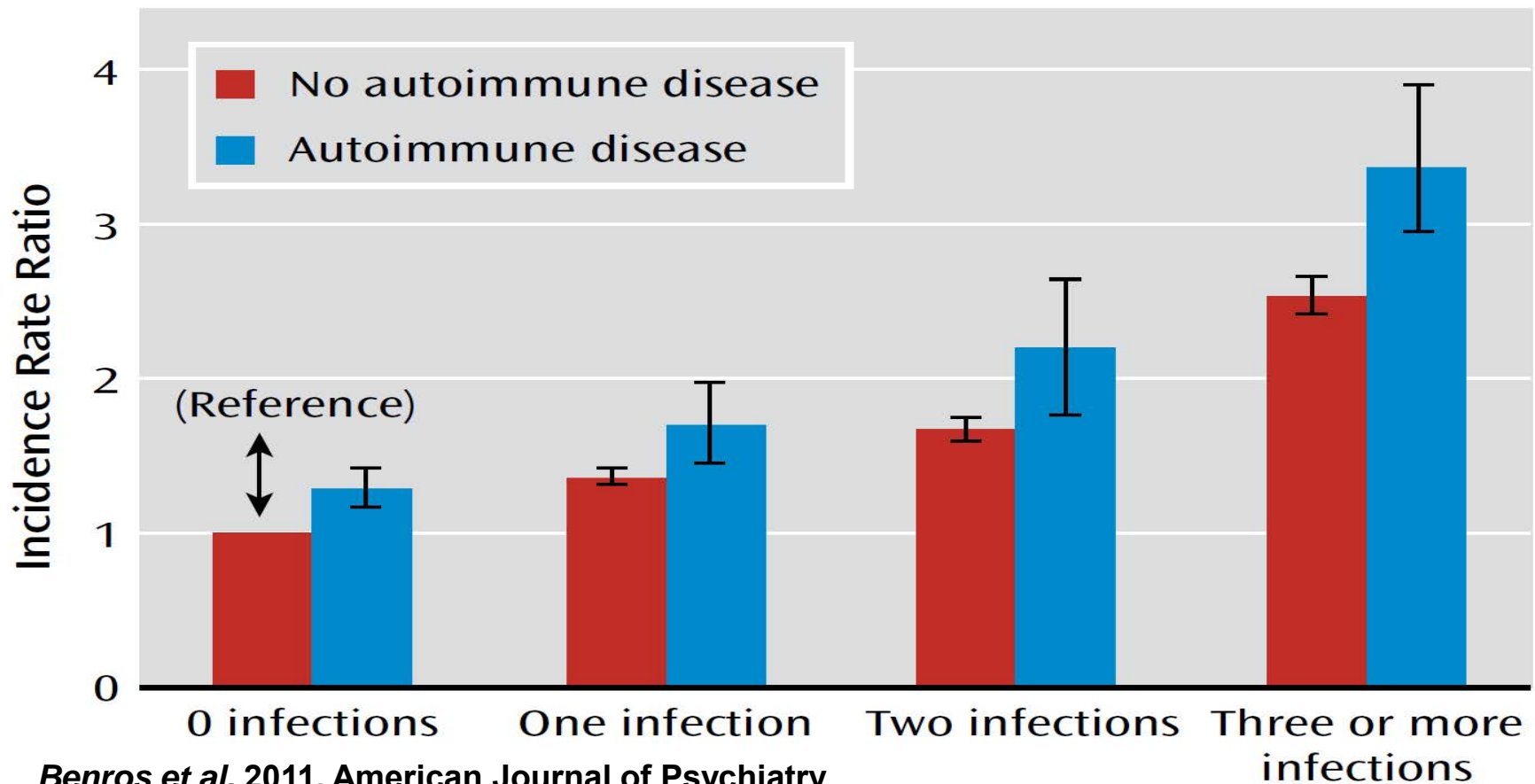
(N=3,56 million; Schizophrenia cases=39,076)

	IRR	95% CI	Cases
Infections and autoimmune diseases	2.25	2.04-2.46	444
Infection (no autoimmune disease)	1.60	1.56-1.64	8,767
Autoimmune diseases (no infections)	1.29	1.18-1.41	483
No autoimmune diseases, no infections	1.00	(reference)	29,363

Benros et al. 2011, American Journal of Psychiatry

Autoimmune diseases and infections as risk factors for schizophrenia (1977-2006)

(N=3,56 million; Schizophrenia cases=39,076)



Benros et al. 2011, American Journal of Psychiatry

Autoimmune diseases and schizophrenia risk

Autoimmune Disease	Schizophrenia Spectrum Disorders in Persons Without Infections			Schizophrenia Spectrum Disorders in Persons With Infections		
	Incidence Rate Ratio ^b	95% CI	Case Patients	Incidence Rate Ratio ^b	95% CI	Case Patients
Autoimmune disease with suspected presence of brain reactive antibodies	1.48	1.31–1.68	244	2.56	2.25–2.89	243
Autoimmune hepatitis	2.75	1.38–4.83	10	8.91	6.50–11.84	43
Autoimmune thyroiditis			3	4.57	2.09–8.51	8
Celiac disease	2.11	1.09–3.61	11	2.47	1.13–4.61	8
Guillain-Barré syndrome	1.22	0.58–2.19	9	2.84	1.52–4.76	12
Multiple sclerosis	1.44	1.03–1.94	39	2.10	1.37–3.06	24
Sjögren's syndrome	2.07	0.82–4.20	6			4
Systemic lupus erythematosus	1.84	0.92–3.23	10	2.11	1.06–3.70	10
Thyrotoxicosis (Graves' disease)	1.94	1.47–2.49	56	2.47	1.68–3.49	29
Type I diabetes	1.27	1.04–1.53	104	2.04	1.68–2.44	109
Other autoimmune diseases	1.19	1.05–1.34	256	1.95	1.70–2.23	212

Localization of the infection and schizophrenia risk

Infection	Infection Only (No Autoimmune Disease)			Autoimmune Disease		
	Incidence Rate Ratio ^b	95% CI	Case Patients	Incidence Rate Ratio ^b	95% CI	Case Patients
Sepsis	1.95	1.47–2.51	55	4.98	2.49–8.73	10
Hepatitis	4.89	4.26–5.58	212	8.89	6.03–12.53	29
Gastrointestinal	1.32	1.26–1.39	1,847	1.82	1.46–2.24	83
Skin	1.71	1.62–1.80	1,427	2.14	1.69–2.66	74
Pregnancy-related	1.14	0.98–1.31	185	1.22	0.48–2.47	6
Respiratory	1.53	1.46–1.61	1,885	2.25	1.79–2.79	77
Urogenital	1.90	1.79–2.01	1,200	2.70	2.10–3.41	66
CNS	1.28	1.09–1.50	148	2.62	1.31–4.60	10
Other	1.70	1.62–1.78	1,818	1.99	1.60–2.43	89
Persons without hospital contact for infection (reference)	1.00		29,372	1.30	1.18–1.42	483

**Risk of schizophrenia (F20)
and association with type of first infection**
(N=843,390 born 1981-2000, Schizophrenia cases=3,409)

Type of infection	IRR	95% CI	Cases
Bacterial infection only	1.73	1.55-1.92	415
Viral infection only	1.40	1.25-1.56	382
Different types	1.48	1.36-1.61	752
No infections	1.00	(reference)	1,860

Nielsen PR, Benros ME, Mortensen PB. *Schizophr Bull.* 2014

Autoimmune diseases and infections as risk factor for mood disorders

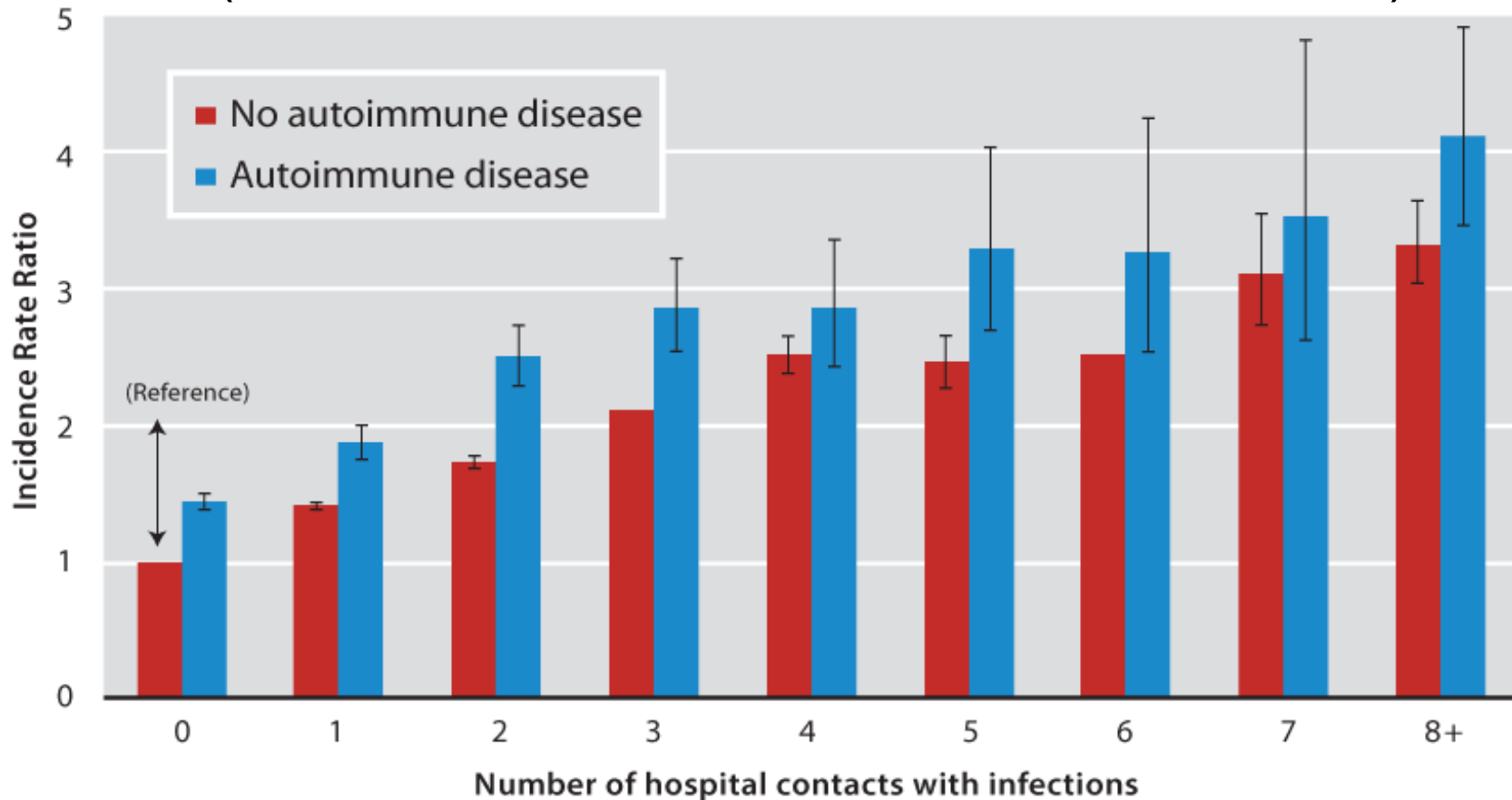
(1977-2010; N=3,56 millioner; F30-F39=91,637)

	IRR	95% CI	Cases
Infections and autoimmune diseases	2.35	2.25-2.46	2,120
Infection (no autoimmune disease)	1.62	1.60-1.64	29,313
Autoimmune diseases (no infections)	1.45	1.39-1.52	4,203
No autoimmune diseases, no infections	1.00	(reference)	60,397

Benros et al. JAMA Psychiatry. 2013

Autoimmune diseases and infections as risk factors for mood disorders (1977-2010)

(N=3,56 million; Mood disorder cases=91,637)



Benros et al. 2013, JAMA Psychiatry

Autoimmune diseases and risk of mood disorders

	IRR	95% CI	Cases
Autoimmune diseases with suspected presence of brain-reactive antibodies:	1.58	1.49-1.68	1,057
Autoimmune Hepatitis	2.28	1.53-3.40	24
Autoimmune Thyroiditis	1.05	0.72-1.52	28
Celiac Disease	1.91	1.41-2.60	41
Guillain Barre Syndrome	1.61	1.14-2.26	33
Multiple Sclerosis	1.52	1.30-1.77	162
Sjogren's Syndrome	1.79	1.23-2.61	27
Systemic Lupus Erythematosus	2.16	1.61-2.89	45
Thyrotoxicosis (Graves disease)	1.28	1.12-1.45	228
Type 1 Diabetes	1.76	1.61-1.93	469
The remaining autoimmune diseases:	1.35	1.27-1.43	1,207

Localization of the infection and risk of mood disorders

	IRR	95% CI	Cases
Sepsis infections	2.09	1.88-2.32	340
Hepatitis infections	2.87	2.63-3.13	518
Gastrointestinal infections	1.62	1.58-1.66	7,619
Skin infection	1.70	1.66-1.75	5,911
Pregnancy related infection	1.68	1.60-1.77	1,711
Respiratory infections	1.70	1.66-1.74	7,070
Urogenital infections	2.06	2.00-2.11	7,057
CNS infections	1.66	1.54-1.79	720
Other types of infections	1.83	1.78-1.88	5,792
Persons without a hospital contact with infection (ref)	1.00	(reference)	62,480

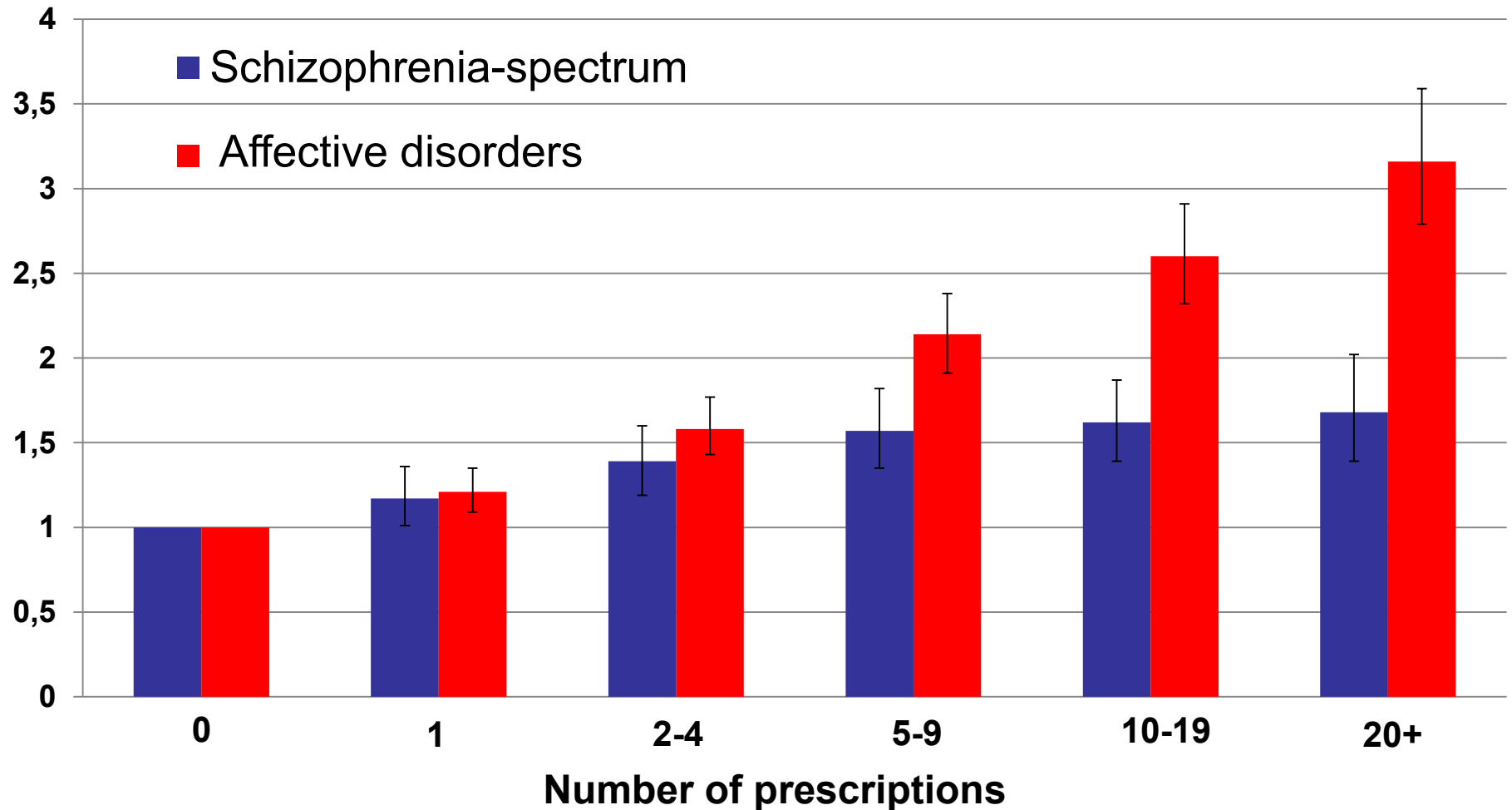
Anti-infective agent prescriptions and the risk of schizophrenia and mood disorders

Anti-infective agent:	Schizophrenia		Affective disorders	
	No. of cases (%)	HRR ¹ (95%-CI)	No. of cases (%)	HRR ¹ (95%-CI)
Total	5,759 (100)		13,044 (100)	
No anti-infective prescription	251 (4.4)	1.00 (Ref.)	414 (3.2)	1.00 (Ref.)
Any anti-infective prescription	5,508 (95.6)	1.37 (1.20-1.57)	12,630 (96.8)	1.64 (1.48-1.82)
Anti-infective prescription but no hospitalization with infection	4,496 (78.1)	1.27 (1.18-1.36)	10,196 (78.2)	1.56 (1.49-1.64)
Anti-infective prescription and a hospitalization with infection	1,012 (17.4)	2.05 (1.77-2.38)	2,434 (18.7)	2.59 (2.31-2.89)

Type of anti-infectives and risk of schizophrenia and mood disorders

Anti-infective agent:	Schizophrenia spectrum		Affective disorders	
	No. of cases (%)	HRR (95%-CI)	No. of cases (%)	HRR (95%-CI)
Total	5,759 (100)		13,044 (100)	
No anti-infective agents	251 (4.4)	1.00 (Ref.)	414 (3.2)	1.00 (Ref.)
Any anti-infective agent	5,508 (95.6)	1.37 (1.20-1.57)	12,630 (96.8)	1.64 (1.48-1.82)
Antibiotics	5,418 (94.1)	1.44 (1.25-1.66)	12,479 (95.7)	1.65 (1.49-1.84)
Broad spectrum	1,746 (30.3)	1.53 (1.32-1.71)	4,858 (37.2)	1.61 (1.47-1.76)
Moderate spectrum	1,654 (28.7)	1.50 (1.30-1.70)	4,615 (35.4)	1.50 (1.37-1.64)
Narrow spectrum	4,053 (70.4)	1.40 (1.25-1.58)	9,472 (72.6)	1.30 (1.18-1.43)
Topical	2,051 (35.6)	1.36 (1.20-1.54)	5,306 (40.7)	1.54 (1.40-1.68)
Antivirals	609 (10.6)	1.25 (0.66-2.35)	1,759 (13.5)	1.20 (0.72-2.02)
Antimycotics	2,175 (37.8)	1.27 (0.94-1.70)	5,498 (42.2)	1.07 (0.84-1.38)
Antiparasitic	1,336 (23.2)	0.94 (0.59-1.51)	3,586 (27.5)	1.24 (0.90-1.71)

Dose-response association (p<0.001)



Köhler O, Petersen L, Gasse C, Yolken R, Mortensen PB, Benros M. 2017. *Acta Psychiatr Scand*

Streptococcal infection (n=349,982) and risk of mental disorders (1996-2013)

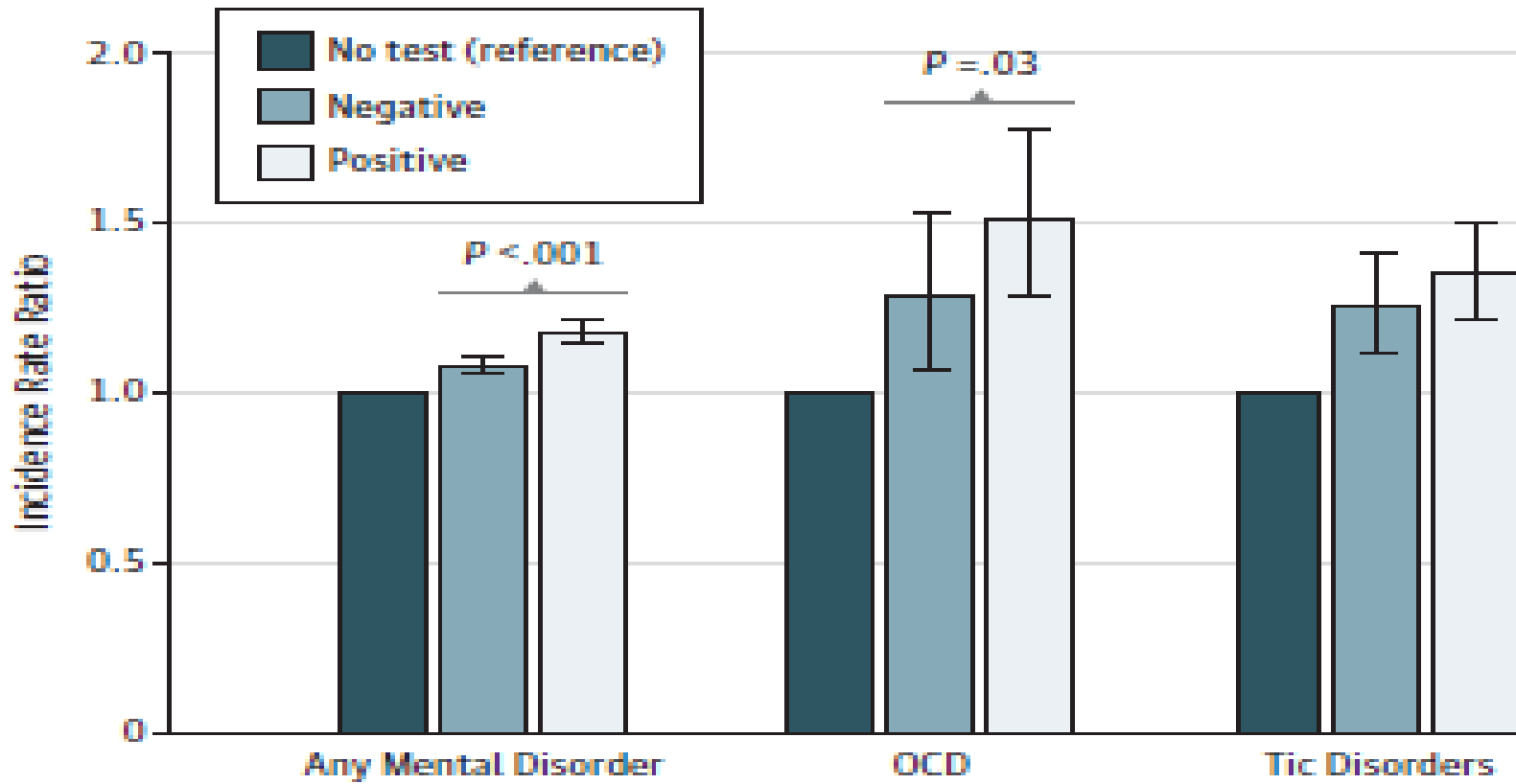
(N=1,07 million children)

	Any mental Disorder		
	No.	IRR	(95%CI)
Positive streptococcal infection	15,408	1.16	(1.14-1.20)
No test	13,712	1.00	(ref)
	OCD		
Positive streptococcal infection	556	1.49	(1.27-1.76)
No test	206	1.00	(ref)
	Tic Disorders		
Positive streptococcal infection	993	1.35	(1.21-1.50)
No test	522	1.00	(ref)

Orlovskaa, Vestergaard, Bech, Nordentoft, Vestergaard, Benros. 2017, JAMA Psychiatry

Streptococcal infection (n=349,982) and risk of mental disorders (1996-2013)

(N=1,07 million children)



Orlovská, Vestergaard, Bech, Nordentoft, Vestergaard, Benros. 2017, JAMA Psychiatry

Time since the last Streptococcal infection and risk of mental disorders

(N=1,07 million children)

Time Since the Last Positive Streptococcal Test, y	Any Mental Disorder		OCD		Tic Disorders	
	No.	IRR ^b (95% CI)	No.	IRR ^b (95% CI)	No.	IRR ^b (95% CI)
No test performed	13 712	1 [Reference]	316	1 [Reference]	522	1 [Reference]
<1	2482	1.09 (1.04-1.14) ^c	57	1.38 (1.03-1.86) ^f	128	1.17 (0.96-1.42)
1-2	4094	1.19 (1.15-1.24) ^c	96	1.30 (1.02-1.65) ^f	263	1.34 (1.15-1.55) ^c
3-5	4376	1.25 (1.20-1.30) ^c	155	1.53 (1.24-1.89) ^f	368	1.57 (1.37-1.79) ^c
6-10	3596	1.19 (1.14-1.24) ^c	202	1.67 (1.37-2.04) ^f	213	1.19 (1.01-1.41) ^c
≥11	860	1.17 (1.08-1.26) ^c	46	1.57 (1.12-2.21) ^f	21	1.17 (0.74-1.86)

Orlovská, Vestergaard, Bech, Nordentoft, Vestergaard, Benros. 2017, JAMA Psychiatry

Age at the first Streptococcal infection and risk of mental disorders

(N=1,07 million children)

Age at the First Positive Streptococcal Test, y	Any Mental Disorder		OCD		Tic Disorders	
	No.	IRR ^b (95% CI)	No.	IRR ^b (95% CI)	No.	IRR ^b (95% CI)
No test performed	13 712	1 [Reference]	206	1 [Reference]	522	1 [Reference]
0-2	4666	1.14 (1.10-1.18) ^F	113	1.47 (1.17-1.85) ^F	258	1.23 (1.06-1.42) ^F
3-11	9889	1.19 (1.15-1.22) ^F	417	1.55 (1.30-1.83) ^F	723	1.41 (1.25-1.58) ^F
≥12	853	1.73 (1.60-1.86) ^F	26	1.12 (0.73-1.71)	12	1.18 (0.65-2.14)

Orlovská, Vestergaard, Bech, Nordentoft, Vestergaard, Benros. 2017, JAMA Psychiatry

Prevalence of the potential risk factors

- A previous hospital contact for infections had occurred in 31% of individuals with mental disorders
- 96% had prior infections treated with antibiotics before the schizophrenia or mood disorder diagnosis
- Streptococcal infection had occurred prior to 38.1% of mental disorders, 51.6% of OCD, and 45.6% prior to tic disorders
- 5-6% of people with schizophrenia or mood disorders have a hospital contact with an autoimmune disease

C-reactive protein (CRP) and leucocyte levels in schizophrenia and mood disorders (n=3034)

- Highest CRP levels in **bipolar disorder (3.5 mg/L)** (particularly during manic states, 3.9 mg/L), followed by **schizophrenia (3.1 mg/L)**, and **depression (2.8 mg/L)**, - (normal CRP<1mg/L)
- CRP differed significantly between the mental disorders at baseline (P=0.01)
- **Elevated CRP levels were associated with increased all-cause mortality:** by HR=1.56 (95%CI=1.02–2.38) for CRP levels 3–10 mg/L and HR=2.07 (95%CI=1.30–3.29) for CRP levels >10 mg/L.
- Baseline leucocyte level did not differ (median $7.1 \times 10^9/L$).

Horsdal HT, Köhler O, Benros M, Gasse C. 2017. European Psychiatry

CSF studies

Systematic review and meta-analysis

- 112 CSF studies between 1942-2016, out of which 32 studies included healthy controls, but only few investigated the same parameters
- **Increased permeability of the blood-brain barrier** in both schizophrenia (54 patients; **SMD: 0.62**; 95%CI: 0.24-1.00) and mood disorders (302 patients; **SMD=0.43**; 95%CI=0.25-0.61), compared to healthy controls
- **Elevated CSF cytokine's**: IL-6, IL-8 (all $p < 0.05$)

Orlovska S, Köhler O, Brix S, Nordentoft N, Kondziella D, Krogh J, Benros M. Under review

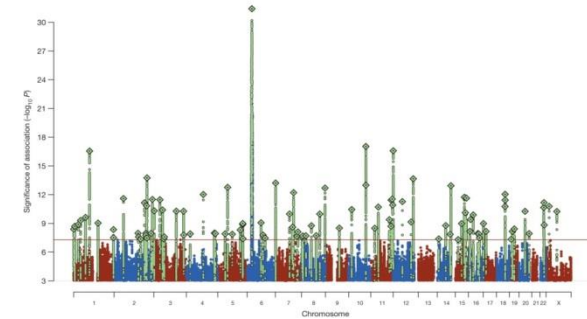
Polygenic risk score for schizophrenia

Based on the latest PGC sample (34,241 cases and 45,604 controls)

Danish Replication sample:

1,697 cases and 1,725 controls

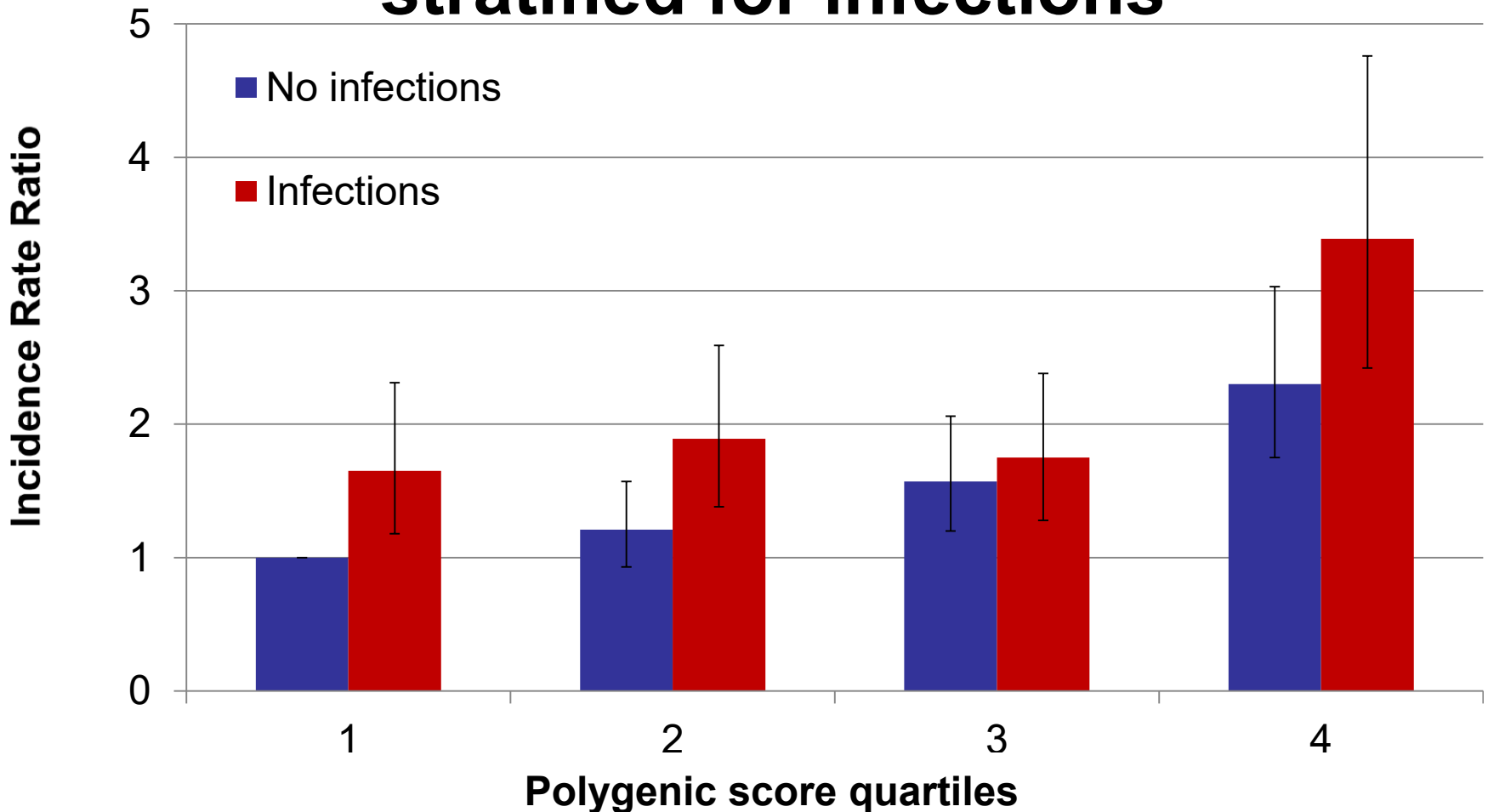
Number of SNPs: 102,366



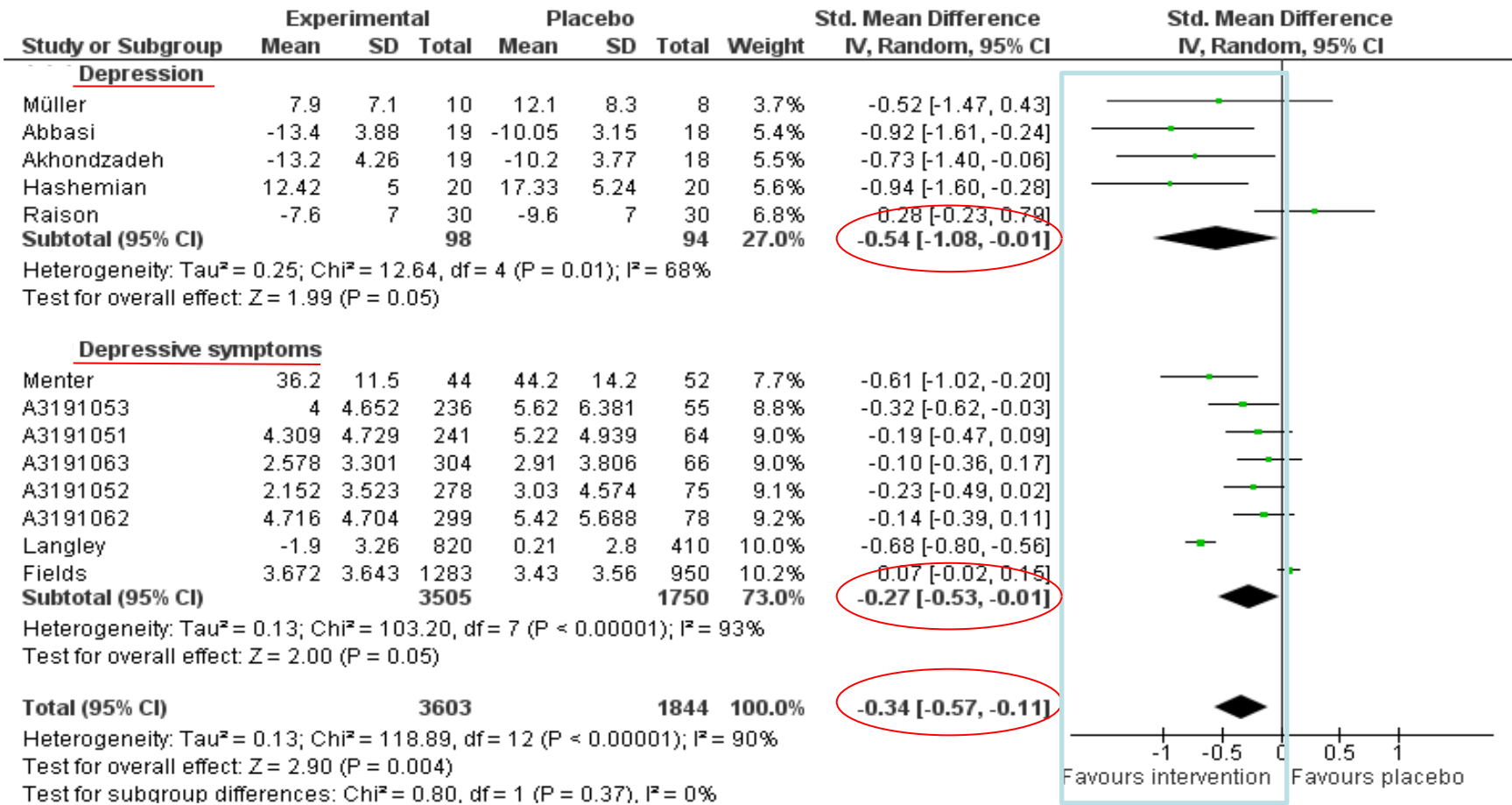
		Basic adjustment	Additional adjustment for family history with infections and psychiatric family history	Additional adjustment for the polygenic score ¹
	Cases	RR (95%CI)	RR (95%CI)	RR (95%CI)
Infection	643	1.55 (1.34-1.80)	1.42 (1.22-1.66)	1.41 (1.20-1.66)
No infection	910	1.00 (ref)	1.00 (ref)	1.00 (ref)

Benros ME, Trabjerg B, Meier S, Mortensen PB, Nordentoft M, Agerbo E. Biol Psychiatry 2016

Risk of schizophrenia dependent on Polygenic risk score in quartiles stratified for infections

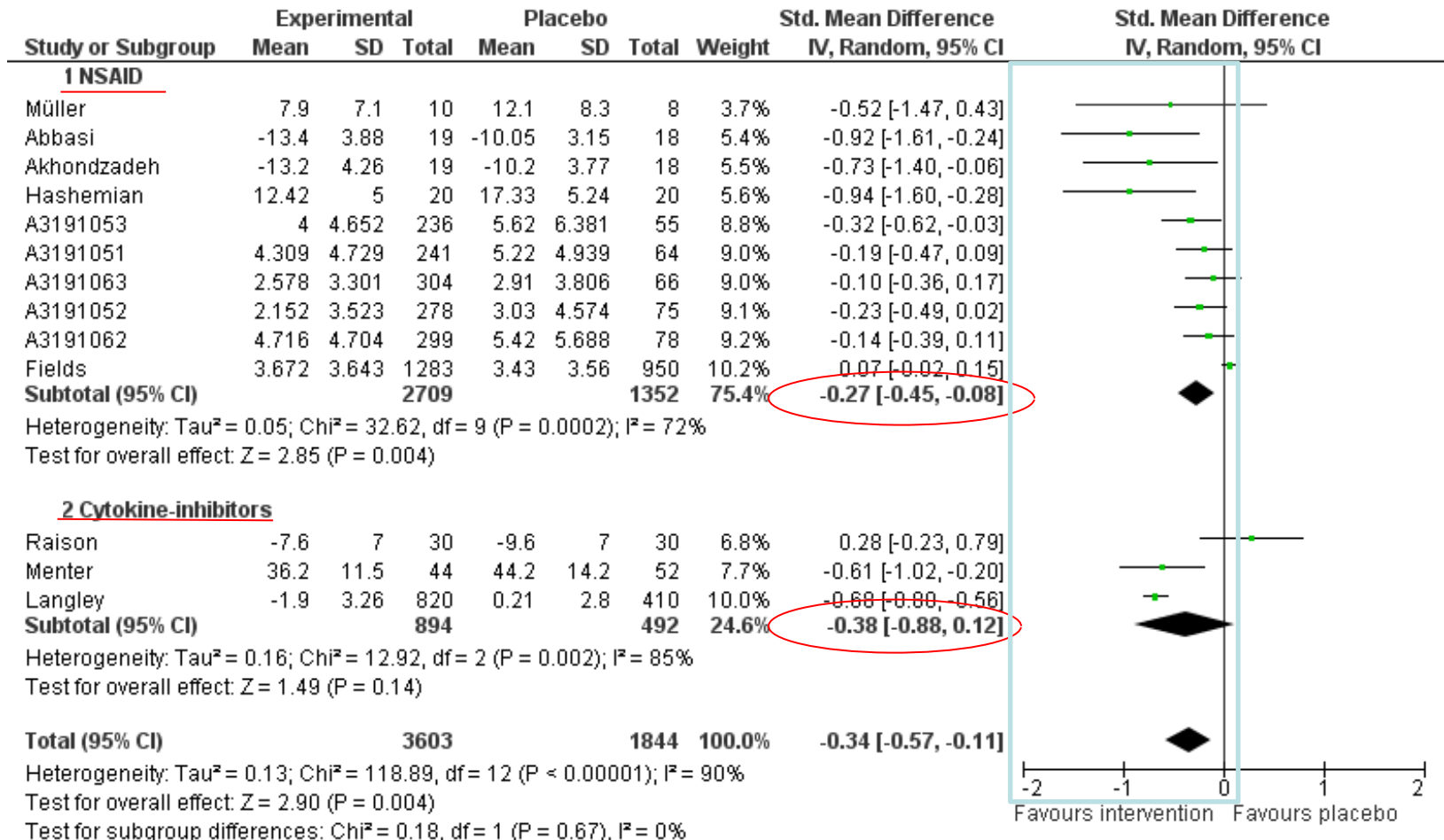


Depression vs. Depressive symptoms



Köhler O, Benros ME, Nordentoft M, Farkouh ME, Iyengar R, Mors O, Krogh J. JAMA Psych 2015

NSAIDs vs. Cytokine-inhibitors



Köhler O, Benros ME, et al. *JAMA Psychiatry*. 2014

Take home messages 1

- Out of ~1 million children a total of ~350.000 had been treated for a **streptococcal infection**
- A **streptococcal infection** was associated with an increased risk of mental disorders by 18%, a 51% increased risk of OCD, and a 35% increased risk of tic disorders
- The risk of any mental disorder and OCD was also more elevated than after a non-streptococcal infection
- However, **individuals with a non-streptococcal infection also had increased risks and the increased risk did not seem to be confined only to childhood**

Take home messages 2

- Autoimmune diseases and particularly infections increases the risk of schizophrenia and mood disorders in a dose-response relationship
- At diagnosis there are increased levels of peripheral inflammation, increased BBB permeability and increased CSF cytokine levels
- Some of the psychiatric symptoms could be caused by infections, inflammation or brain-reactive antibodies
- RCT's with anti-inflammatory treatment has a moderate effect on depression and depressive symptoms – **but RCT's based on immune-related biomarkers is needed!**

Thank you for your attention!

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