Somatische und psychiatrische Komorbiditäten von Affektstörungen

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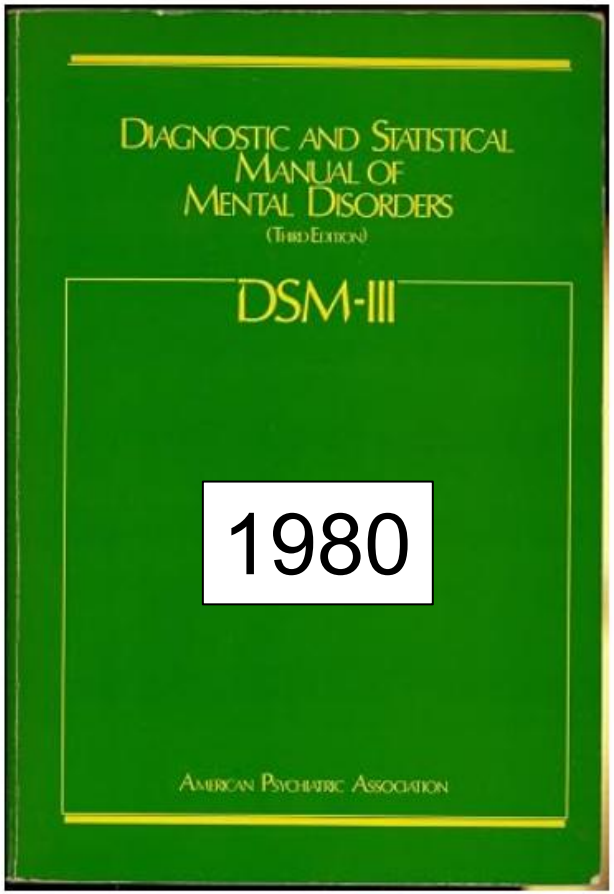
Content

- Introduction
- Comorbidity of bipolar disorders
- Comorbidity of major depressive disorders

Comorbidity and classification



A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

Note: Do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations.

1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (eg, feels sad or empty) or observation made by others (eg, appears tearful). Note: In children and adolescents, can be irritable mood.
2. Markedly diminished interest in pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others).
3. Significant weight loss when not dieting or weight gain (eg, a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. Note: In children, consider failure to make expected weight gains.
4. Insomnia or hypersomnia nearly every day.
5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
6. Fatigue or loss of energy nearly every day.
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B. The symptoms do not meet criteria for Mixed Episode.

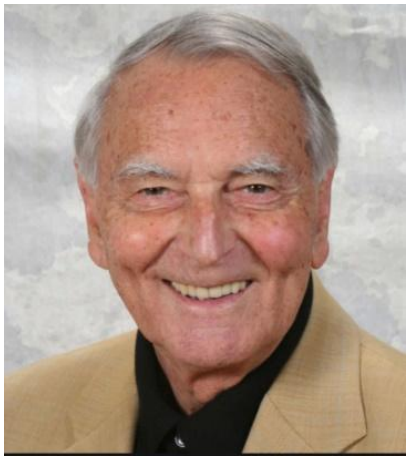
C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. The symptoms are not due to the direct psychological effects of a substance (eg, a drug of abuse, a medication) or a general medical condition (eg, hypothyroidism).

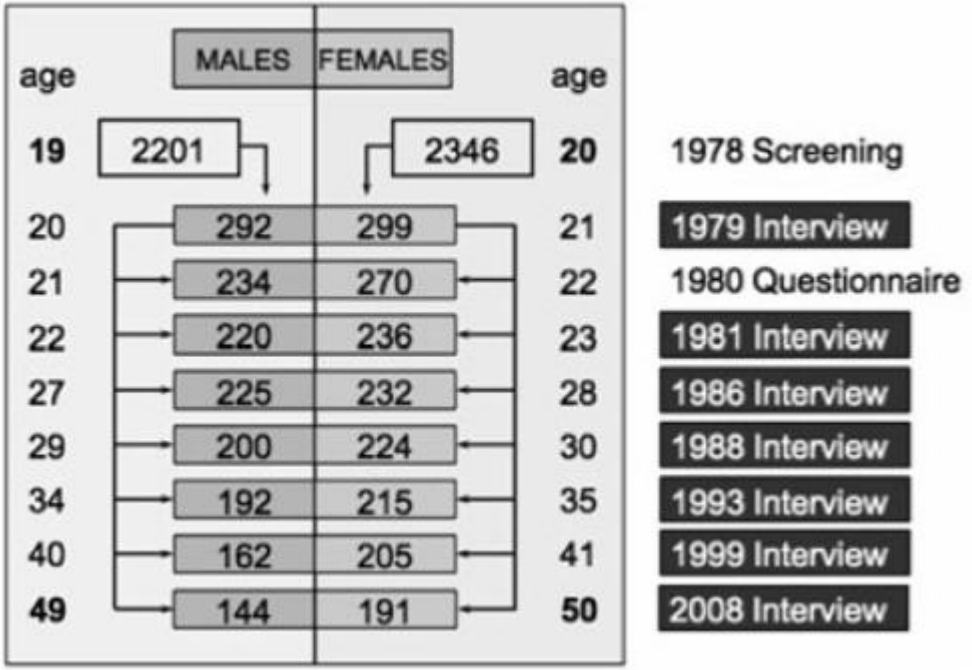
E. The symptoms are not better accounted for by bereavement (ie, after the loss of a loved one), the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

- Introduction of operationalized diagnostic criteria
- Few hierarchical rules among diagnoses

Zurich Cohort Study



Jules Angst



Comorbidity of depression and anxiety disorders in the Zurich Cohort Study

International Clinical Psychopharmacology (1993), **8 Suppl. 1,** 21 - 25

Comorbidity of anxiety, phobia, compulsion and depression

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INTRODUCTION

Since the introduction of DSM-III in 1980 the dominant classification of psychiatric disorders can no longer claim to define actual diseases. Rather, it is a system purely for the description of syndromes, but is thereby more operational and reproducible. The term "comorbidity" in this context therefore does not denote the association of diseases in the traditional sense, but rather the association of simultaneously or successively present psychopathologic syndromes. Dual or multiple syndrome diagnoses are frequently made especially on a longitudinal basis. The course and sequence of such longitudinally associating syndromes will thus naturally become an especially important subject for future research. The clinical significance of comorbid disorders arises from their degree of severity and therapeutic consequences. In methodologic terms, prospective follow-up studies and especially family studies will be necessary to verify causal models of associations. Like the early botanists, we are currently still at the stage of describing and collecting syndromal phenomena and their interrelationships. This has the advantage that rigid classifications are abandoned in favour of more functional models of psychiatric disorder.

EPIDEMIOLOGY

This paper presents comorbidity findings from the perspective of an epidemiological cohort study in progress for more than 15 years, with reference to the following three disorders: (1) social phobia; (2) generalized anxiety disorders and (3) obsessive-compulsive syndromes. The methodology of the study itself, the "Zürich study", has been described previously (Angst *et al.*, 1984). This article is therefore confined to presenting several results.

Table I presents the lifetime prevalence rates up to the age of 30 years, based on four interviews conducted since the age of 20 years. The diagnoses of affective syndromes are based on DSM-III-R criteria (1987), the others on DSM-III criteria (1980). Some syndromal diagnoses were developed in Zürich, for example those of recurrent brief depression (Angst, 1988, 1990), minor depression (Angst, 1992), hypomania (Wicki and Angst, 1992), obsessive-compulsive syndromes (Degonda *et al.*, 1993) and binge eating (Vollrath *et al.*, 1992).

Because of the repeated examinations, the Zürich study occasionally shows relatively high prevalences compared with simple cross-sectional studies, but considering these methodological differences they are within the expected range. Social phobias were present in 5.3%, generalized anxiety disorders in 2.9% and obsessive-compulsive syndromes in 5.7%, whereas actual obsessive-compulsive disorders as defined according to DSM-III criteria were present in only 1.0%.

This last finding illustrates the major importance of

TABLE I. Lifetime prevalence rates (age 30)

	%		%
Major depression	12.3	Panic disorder	2.7
Dysthymia	1.5	Sporadic panic	8.8
Recurrent brief depression	14.1	Generalized anxiety disorder	2.9
Minor depression	9.3	Recurrent brief anxiety syndromes	2.9
Bipolar syndromes	7.5	Social phobia	5.3
Obsessive-compulsive disorders	1.0	Agoraphobia	4.5
Obsessive-compulsive syndromes	5.7	Simple phobia	11.8

[1]Project No. 32-33580.92 of the Swiss National Fund

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Angst J. Int Clin Psychopharmacol. 1993 Sep;8 Suppl 1:21-5.

Comorbidity of depression with gastrointestinal complaints



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ORIGINAL PAPER

B. Hochstrasser · J. Angst

The Zurich Study: XXII

Epidemiology of gastrointestinal complaints and comorbidity with anxiety and depression

Received: 21 January 1994 / Accepted: 18 April 1996

Abstract A representative cohort of Swiss adults recruited at age 20 years and interviewed at ages 23, 28 and 30 years was studied regarding the symptomatology, prevalence and longitudinal course of functional gastrointestinal symptoms and their association with psychiatric syndromes. A functional gastrointestinal complaint was identified if a proband reported symptoms at least eight times in the past year or for a duration of at least 2 weeks without medical explanation and with a moderate degree of distress. Of the population, 9.4–17.7% was found to suffer from functional stomach complaints and 4.9–16% from functional intestinal complaints. Women reported functional gastrointestinal complaints two to three times more often than men, and increasingly so with age. The overlap of stomach and intestinal complaints was modest with 2.0–6.7%. Cross sectionally, functional stomach complaints were significantly associated with major depression (DSM-III-R), recurrent brief depression (RBD), subthreshold RBD and dysthymia, and with subthreshold panic disorder, agoraphobia, social phobia and recurrent brief anxiety. Functional intestinal complaints showed a consistently significant association with RBD, dysthymia, major depression, subthreshold RBD, panic disorder, subthreshold panic disorder, agoraphobia, simple and social phobia and generalized anxiety disorder. Individuals who at younger ages suffered from functional gastrointestinal complaints did not show an increased risk for a subsequent development of an anxiety or depressive disorder. Functional gastrointestinal complaints reflect an unspecific concomitant vegetative disturbance common to depression and anxiety; they do not reflect a risk factor for the development of a specific anxiety or depressive disorder.

Key words Epidemiology · Prevalence · Functional gastrointestinal complaints · Depressive disorders · Anxiety disorders

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Introduction

Gastrointestinal (GI) symptoms considered to be of functional origin, such as stomach burning, nausea, bloating, constipation, diarrhoea or abdominal cramps, are experienced quite frequently, albeit intermittently, by a normal population. The hallmark of a functional symptom is the absence of structural or biochemical abnormalities, which could explain it adequately (Talley 1994). The pathogenesis of functional gastrointestinal symptoms still remains to be clarified. Visceral hypersensitivity, disturbances in gut motility and psychological factors have been implied (Zighelboim and Talley 1993). Although most functional symptoms are short lived and minimally distressing, more distressing and longer lasting gastrointestinal symptom complexes have been reported in clinical and population based samples. Yet, even these longer lasting gastrointestinal symptoms appear to come and go (Talley et al. 1992). The first description of a functional abdominal syndrome dates back to Da Costa (1871), when he reported on seven patients with a syndrome reminiscent of the irritable bowel syndrome. Recently, the concept of irritable bowel syndrome has been defined more clearly by establishing criteria (Manning and Rome criteria) for its diagnosis (Manning et al. 1978; Tohmpson 1983; Talley et al. 1990; Thompson et al. 1989).

Of patients reporting to a gastroenterologist 13–52% suffer from a functional abdominal syndrome (Hill and Blendis 1967; Fahrländer 1972; Almy 1973; Ferguson et al. 1977; Fielding 1977; Whitehead and Bosmjian 1982). In early (Bockus et al. 1929; Almy 1951) as well as in recent publications on functional GI syndromes (Chaudhary and Truelove 1961; Craig and Brown 1984; Kellow et al. 1992) it has been noted that psychosocial distress appeared to bring forth functional abdominal symptoms. For instance, Talley et al. (1995) reported that a history of self-reported sexual, physical, emotional or verbal abuse is more frequent in outpatients with irritable bowel syndrome than patients with organic gastroenterological disease.

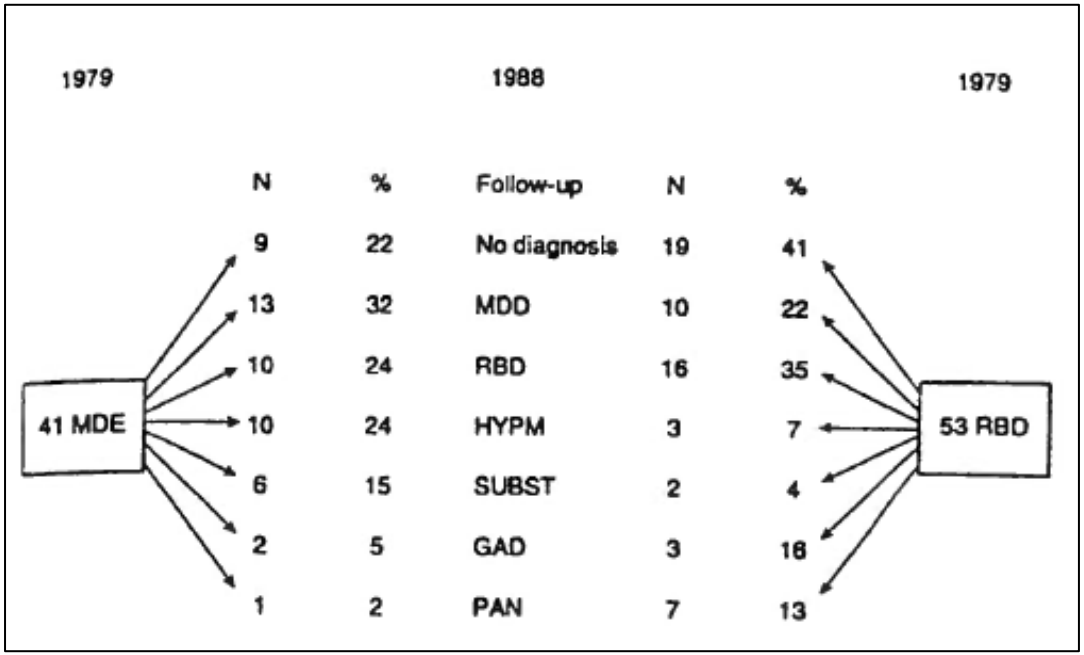
Hochstrasser B and Angst J. Eur Arch Psychiatry Clin Neurosci. 1996;246(5):261-72.

Longitudinal patterns of comorbidity of mood disorders

British Journal of Psychiatry (1996), **168** (suppl. 30), 31–37

Comorbidity of Mood Disorders: A Longitudinal Prospective Study

JULES ANGST



EPA Epidemiology and Social Psychiatry Section Conference - Beaune 1998

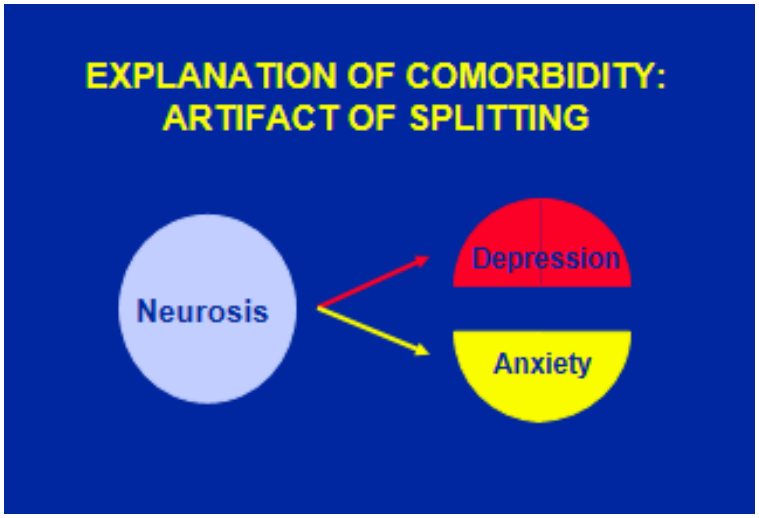
COMORBIDITY OF MOOD AND ANXIETY DISORDERS

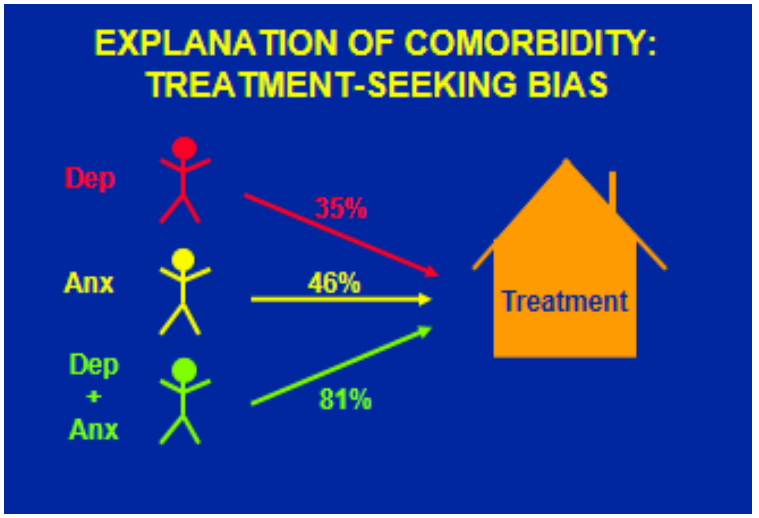
M. PREISIG
B. FENTON
LAUSANNE, SWITZERLAND

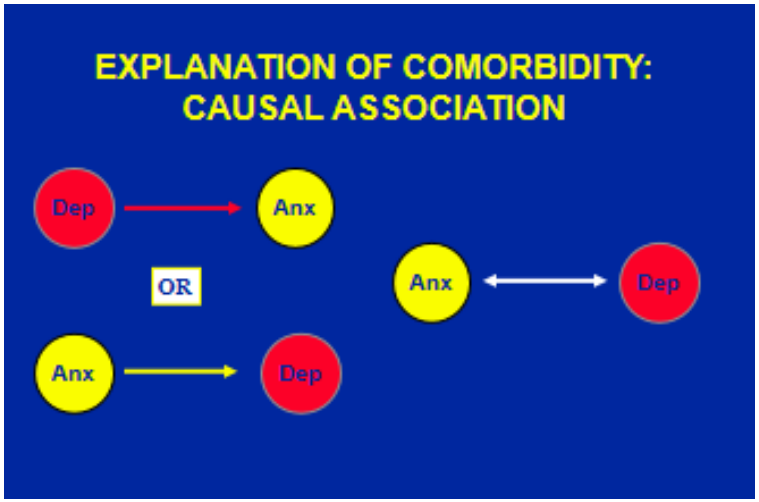


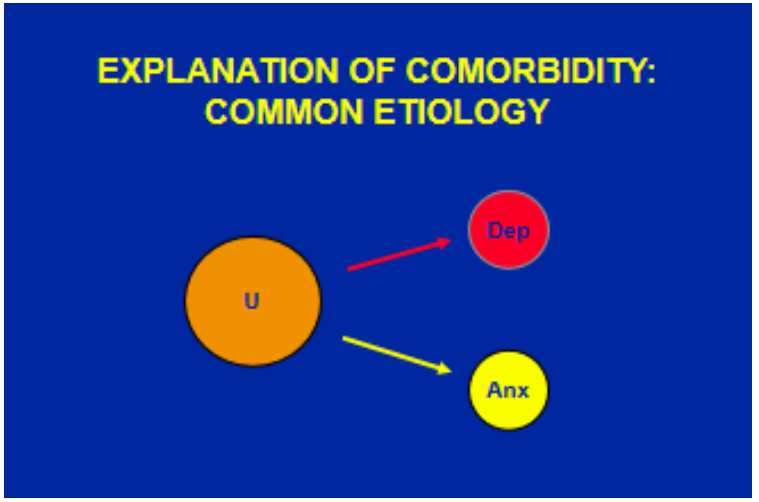
Hôtel-Dieu

Mechanisms underlying comorbidity



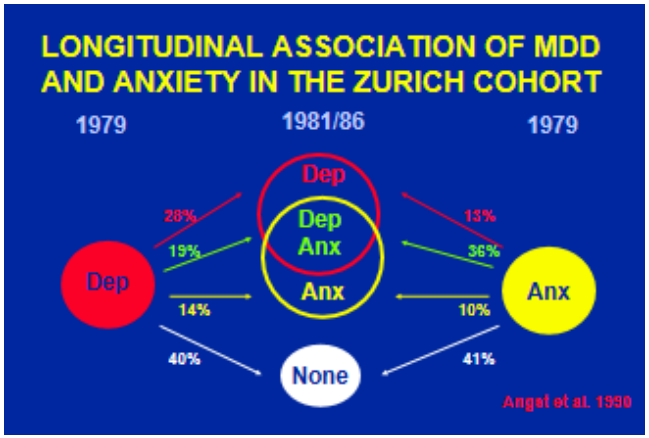




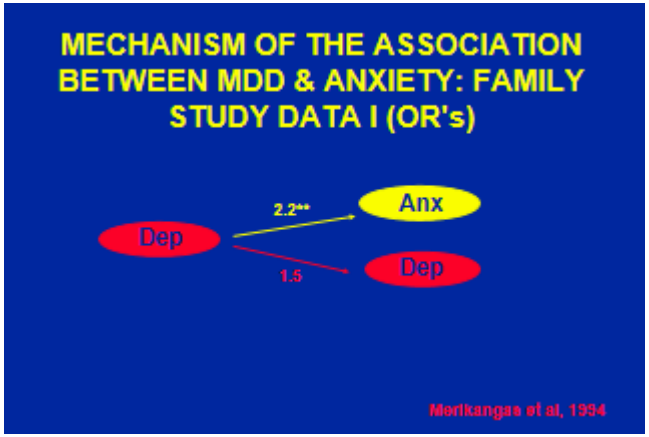


Approaches to investigate mechanisms of comorbidity

- **Longitudinal studies**: What is first?
  → does not prove causality



- **Family studies**:
  → Distinction between shared factors vs. causality



- **Mendelian Randomization Studies**: use single-nucleotide polymorphisms (SNPs) as instrumental variables for an exposure to infer the causal effect of this exposure on an outcome

Zurich Cohort Study data to the clinical impact of the comorbidity of depression and anxiety

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ACTA PSYCHIATRICA SCANDINAVICA
ISSN 0001-690X

Clinical significance and comorbidity of subthreshold depression and anxiety in the community

Preisig M, Merikangas KR, Angst J. Clinical significance and comorbidity of subthreshold depression and anxiety in the community. Acta Psychiatr Scand 2001: 104: 96–103. © Munksgaard 2001.

Objective: This report examines: 1) the magnitude of co-occurrence of threshold and subthreshold-level depression and anxiety in the community, and 2) the relationship between comorbidity and the diagnostic level of depression and anxiety and their clinical correlates.
Method: A community sample of 591 subjects was interviewed prospectively five times across 15 years from the ages of 20–35. The diagnostic interview allowed the assignment of diagnoses according to DSM-III criteria and operational definitions of subthreshold syndromes.
Results: 1) Comorbidity between depression and anxiety was more frequent when one syndrome reached threshold level; 2) comorbidity at both the threshold and subthreshold diagnostic levels was associated with symptom severity, disability and treatment, whereas the diagnostic level was associated with disability and suicidal attempts.
Conclusion: The systematic association between comorbidity across diagnostic threshold levels of anxiety and depression with clinical correlates suggests the importance of a more dimensional approach to their classification.

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Key words: epidemiological studies; subthreshold disorders; depressive disorder; anxiety disorder; comorbidity

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Accepted for publication April 20, 2001

Associated clinical features of comorbidity between depression and anxiety disorders

Table 2. Effects of multiple regression models of global symptom severity (SCL-90-R)§

	Comorbidity (DA, Da, Ad, da) vs. other		Threshold (DA, Da, Ad, D, A) vs. subthreshold (da, d, a)		
SCL-90-R scale	β (SE)	*p*	β (SE)	*p*	Model r^2
GSI	5.88 (0.86)	<0.0001	−0.22 (0.87)	NS	0.50
Depression[1]	4.26 (0.94)	<0.0001	−0.25 (0.92)	NS	0.48
Anxiety[2]	6.14 (1.58)	<0.0001	1.86 (1.19)	NS	0.41

§Adjusted for sex, number of assessments, and initial risk (initial SCL-90 score).
[1]Severity adjustment made for the diagnostic level of depression (threshold depression vs. subthreshold).
[2]Severity adjustment made for the diagnostic level of anxiety (threshold anxiety vs. subthreshold).

Table 3. Adjusted odds ratios§ (99.17% confidence intervals) of clinical validators of comorbidity and threshold level

Validity indicators	Comorbidity (DA, Da, Ad, da) vs. other	Threshold (DA, Da, Ad, D, A) vs. subthreshold (da, d, a)
Work impairment	3.5*** (1.8–6.8)	3.8*** (1.9–7.4)
Lifetime treatment for depression or anxiety	3.6*** (1.9–6.7)	1.5 (0.8–2.9)
History of suicide attempts	1.1 (0.5–2.5)	3.2* (1.2–8.6)

§ Adjusted for sex, number of assessments, and initial risk (initial SCL-90 score).
[1] Severity adjustment made for the diagnostic level of depression (threshold depression vs. subthreshold).
[2] Severity adjustment made for the diagnostic level of anxiety (threshold anxiety vs. subthreshold).
+ $P<0.05$; * $P<0.0083$; ** $P<0.001$; *** $P<0.0001$.

→ Comorbidity associated with greater clinical severity

Lifetime psychiatric comorbidity in people with mood disorders in the general population



City of Lausanne

Journal of Affective Disorders 167 (2014) 198–205

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Journal of Affective Disorders

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

Research report

Prevalence and correlates of DSM-5 bipolar and related disorders and hyperthymic personality in the community

Sylfa Fassassi [a,*], Caroline Vandeleur [a], Jean-Michel Aubry [b], Enrique Castelao [a], Martin Preisig [a]

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Lifetime psychiatric comorbidity in people with mood disorders in the general population

Table 3
Lifetime comorbidity of bipolar and related disorders with other DSM-IV psychiatric disorders.

	Bipolar I $N=37$		Bipolar II $N=28$		MDD $N=1557$		Others $N=1946$	
	%	OR (95%C.I.)[a]	%	OR (95%C.I.)[a]	%	OR (95%C.I.)[a]	%	OR (95%CI.)[a]
Any anxiety disorder	47.2	**6.6 (3.4,12.9)*****	40.7	**4.5 (2.1,10.0)*****	30.4	**2.8 (2.4,3.4)*****	12.2	(ref.)
Agoraphobia	14.3	**6.5 (2.4,17.8)*****	3.7	1.2 (0.2,8.8)	4.9	**1.5 (1.0,2.2)***	2.7	(ref.)
Social Phobia	25.7	**4.1 (1.9,8.9)*****	29.6	**4.7 (2.0,10.9)*****	18.0	**2.4 (1.9,3.0)*****	7.8	(ref.)
Generalized Anxiety Disorder	14.3	**17.5 (6.1,50.3)*****	7.4	**7.5 (1.6,33.9)****	3.5	**3.4 (2.0,5.7)*****	1.0	(ref.)
Panic disorder	5.6	2.7 (0.6,11.6)	3.7	1.4 (0.2,10.6)	4.3	**1.6 (1.1,2.4)***	2.2	(ref.)
Post-traumatic Stress Disorder	14.3	**7.6 (2.8,20.7)*****	11.1	**5.1 (1.5,17.5)****	7.9	**3.4 (2.4,4.9)*****	2.2	(ref.)
OCD	8.3	**15.8 (4.2,59.6)*****	3.7	6.1 (0.8,49.4)	1.9	**3.1 (1.5,6.3)****	0.6	(ref.)
Any substance use disorder	26.3	2.0 (1.0,4.4)	21.4	2.4 (0.9,6.2)	16.1	**1.6 (1.3,2.0)*****	14.2	(ref.)
Alcohol abuse	21.6	**2.6 (1.1,6.0)***	14.3	2.3 (0.8,7.2)	8.8	**1.3 (1.0,1.7)***	9.4	(ref.)
Alcohol dependence	18.9	**5.2 (2.2,12.3)*****	10.7	**3.6 (1.0,12.4)***	5.0	**1.6 (1.1,2.2)****	4.3	(ref.)
Illicit drug abuse	2.7	1.0 (0.1,7.4)	3.7	1.9 (0.3,15.1)	4.8	**2.5 (1.7,3.7)*****	2.4	(ref.)
Illicit drug dependence	2.6	1.0 (0.1,7.3)	3.6	1.8 (0.2,14.2)	3.0	1.4 (0.9,2.2)	2.5	(ref.)
Impulse-control disorder	20	**4.1 (1.7,9.7)****	3.7	0.8 (0.1,5.7)	7.1	**1.5 (1.1,2.0)****	5.5	(ref.)
ADHD	11.4	**7.2 (2.4,21.8)*****	3.7	2.5 (0.3,19.1)	3.3	**2.2 (1.4,3.5)*****	1.7	(ref.)
Disruptive Behavioral Disorder	14.3	**3.6 (1.3,9.6)***	3.7	1.0 (0.1,7.7)	4.1	1.1 (0.8,1.6)	4.2	(ref.)

OR=odd's ratios; 95% CI=95 % confidence intervals; ref=reference category.

[a] Adjusted for age and sex.

*** $p<0.001$.

** $p<0.01$.

* $p<0.05$.

Comorbidity of bipolar disorders



Bipolar and anxiety disorders

Prevalence of anxiety disorders in treated patients with bipolar disorder (%)

EBioMedicine 2 (2015) 1405–1419

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journal homepage: www.ebiomedicine.com

Research Article

A Lifetime Prevalence of Comorbidity Between Bipolar Affective Disorder and Anxiety Disorders: A Meta-analysis of 52 Interview-based Studies of Psychiatric Population

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Table 1
Summary of lifetime prevalence of comorbid anxiety disorders in bipolar I, publication bias and heterogeneity findings.

Comorbid anxiety disorders	Number of studies	Total number of cases	Lifetime prevalence (95% CI)	Cochran Q (P value)	Heterogeneity I^2 (95% CI)	Begg-Mazumdar (P value)	Egger (95% CI)	Harbord (95% CI)
Anxiety disorders	29	3064	42.7% (37.5–48.0)	575.62 (P < 0.0001)	95.1% (94.2–95.8)	0.167 (0.210)	5.1 (2.1–8.0)	4.3 (1.4–7.2)
Panic disorder	45	1537	16.8% (13.7–20.1)	775.97 (P < 0.0001)	94.2% (93.3–94.9)	0.273 (0.007)	4.0 (2.4–5.7)	2.6 (0.2–5.0)
Generalised anxiety disorder	30	892	14.4% (10.8–18.3)	478.00 (P < 0.0001)	93.9% (92.7–94.9)	0.149 (0.256)	4.0 (1.8–6.1)	1.1 (−1.6–3.9)
Posttraumatic stress disorder	25	1185	10.8% (7.3–14.9)	678.29 (P < 0.0001)	96.5% (95.9–96.9)	0.193 (0.185)	3.9 (0.6–7.2)	−1.3 (−4.4.1.7)
Obsessive compulsive disorder	43	808	10.7% (8.7–13.0)	424.42 (P < 0.0001)	90.1% (87.9–91.7)	0.229 (0.030)	3.4 (2.4–4.3)	3.7 (1.9–5.4)
Social anxiety disorder	32	921	13.3% (10.1–16.9)	553.76 (P < 0.0001)	94.4% (93.3–95.2)	0.209 (0.095)	4.0 (2.3–5.8)	2.9 (0.1–5.7)
Specific phobia	26	448	10.8% (8.2–13.7)	185.39 (P < 0.0001)	86.5% (81.7–89.6)	0.286 (0.041)	2.7 (0.9–4.4)	1.3 (−1.1–3.7)
Agoraphobia	11	251	7.8% (5.2–11.0)	101.16 (P < 0.0001)	90.1% (84.8–93)	0.381 (0.121)	3.0 (0.7–5.3)	4.7 (0.3–9.0)

Heterogeneity interpretation: Cochrane test: a P value of <.1 is considered significant for the presence of statistical heterogeneity. I^2: greater than 80% = moderate, I^2 greater than 90% = high. Publication bias interpretation: Begg–Mazumdar test: P value < 0.05 is considered significant and indicates a presence of publication bias. Egger and Harbord tests: if the intercept differs significantly from zero, this may indicate that publication bias is present.

Bipolar and anxiety disorders : Hypotheses regarding underlying mechanisms

- Mechanisms are still poorly understood.
- Bipolar disorders are typically preceded by anxiety disorders.
- Bipolar disorders with mixed episodes or rapid cycling are more frequently associated with anxiety disorders.

Bipolar and anxiety disorders : clinical consequences

- Increased risk of substance abuse
- Poor course: increased suicidal risk

Bipolar and substance use disorders

Comorbidity between bipolar and alcohol use disorders in the general population

Journal of Affective Disorders 206 (2016) 321–330

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Review article

Comorbidity of bipolar and substance use disorders in national surveys of general populations, 1990–2015: Systematic review and meta-analysis

Glenn E. Hunt [a,*], Gin S. Malhi [b], Michelle Cleary [c], Harry Man Xiong Lai [a], Thiagarajan Sitharthan [a]

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[c] School of Health Sciences, University of Tasmania, Sydney, NSW, Australia

Alcohol use and bipolar disorders

Group by Alcohol Use Disorder	Study name	Odds ratio	Lower limit	Upper limit
Abuse	NCS-R Merikangas 2007a	3.700	2.401	5.702
Abuse	NESARC-Grant 2004a	1.700	1.085	2.663
Abuse	Singapore-Subramaniam 2013a	3.600	0.419	30.916
Abuse	WHO-Merikangas 2011a	4.100	3.050	5.511
Abuse	NCS-R Merikangas 2007b	4.300	3.331	5.551
Abuse	NESARC-Grant 2004b	1.400	0.939	2.087
Abuse	Korea-KECA-Chou 2012b	2.040	0.229	18.172
Abuse	Singapore-Subramaniam 2013b	2.900	1.096	7.673
Abuse	WHO-Merikangas 2011b	7.900	6.190	10.083
Abuse		3.248	2.081	5.068
Abuse/dependence	NESARC-Grant 2004c	3.500	2.711	4.518
Abuse/dependence	Australia-Mitchell 2004d	3.400	1.396	8.279
Abuse/dependence	NESARC-Grant 2004d	3.500	2.792	4.387
Abuse/dependence	Korea-KECA-Chou 2012d	0.380	0.041	3.483
Abuse/dependence	Australia-Teesson 2010d	1.000	0.293	3.416
Abuse/dependence		3.108	2.272	4.253
Dependence	NCS-R Merikangas 2007e	4.400	2.441	7.932
Dependence	NESARC-Grant 2004e	5.200	3.938	6.866
Dependence	WHO-Merikangas 2011e	5.200	3.579	7.555
Dependence	NCS-R Merikangas 2007f	5.700	4.287	7.578
Dependence	NESARC-Grant 2004f	5.700	4.395	7.392
Dependence	Singapore-Subramaniam 2013f	1.700	0.487	5.938
Dependence	WHO-Merikangas 2011f	12.100	8.964	16.334
Dependence		5.783	4.300	7.777
Overall		4.088	3.368	4.963

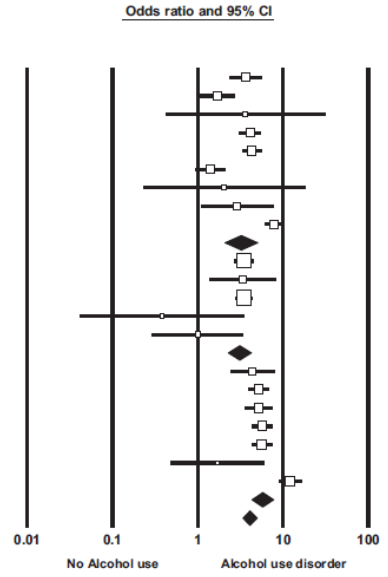

Fig. 3. Forest plot of the random effects meta-analysis of alcohol use and bipolar disorder. Comparisons are made between subgroups based on severity of alcohol use. Summary statistics are indicated by filled diamonds for studies reporting alcohol abuse (a, b), abuse/dependence (c, d) and dependence (e, f). Estimates for 12 month (a, c, e) and lifetime (b, d, f) estimates were pooled within each diagnostic group.

Relationship between alcohol consumption and mood episodes in bipolar disorder

TABLE 7–3. Relationship between Alcohol Consumption and Phase of Bipolar Illness

	DEPRESSED PHASE (%)			MANIC PHASE (%)		
Study	Increase	Decrease	No Change	Increase	Decrease	No change
Minski, 1938	100	0	0	29	0	71
Mayfield and Coleman, 1968	26	43	31	83	0	17
Winokur et al., 1969	27	0	73	42	0	47
Reich et al., 1974[a]	3	0	97[a]	50	0	50[a]
Hensel et al., 1979[b]	21	22	57	14	7	79
Bernadt and Murray, 1986	38	25	36	20	23	57

[a]No information given as to decrease or no change.
[b]Depressed phase approximated, excluding unipolar patients.

Goodwin FK and Jamison KR (2008)

Comorbidity between bipolar and illicit drug use disorders in the general population

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Review article

Comorbidity of bipolar and substance use disorders in national surveys of general populations, 1990–2015: Systematic review and meta-analysis

Glenn E. Hunt [a,*], Gin S. Malhi [b], Michelle Cleary [c], Harry Man Xiong Lai [a], Thiagarajan Sitharthan [a]

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Illicit drug use and bipolar disorders

Group by Drug Use Disorder	Study name	Odds ratio	Lower limit	Upper limit
Abuse	NCS-R Merikangas 2007a	3.500	2.355	5.201
Abuse	NESARC-Grant 2004a	3.700	2.340	5.850
Abuse	NESARC-Compton 2007a	1.400	0.895	2.189
Abuse	WHO-Merikangas 2011a	3.600	2.622	4.942
Abuse	NCS-R Merikangas 2007b	4.500	3.365	6.017
Abuse	NESARC-Grant 2004b	4.200	2.822	6.250
Abuse	NESARC-Grant 2005b	3.000	2.466	3.650
Abuse	WHO-Merikangas 2011b	9.200	6.998	12.096
Abuse		3.733	2.628	5.303
Abuse/dependence	NESARC-Grant 2004c	4.100	2.824	5.952
Abuse/dependence	NESARC-Compton 2007c	2.400	1.697	3.394
Abuse/dependence	Australia-Mitchell 2004d	5.200	2.479	10.908
Abuse/dependence	NESARC-Grant 2004d	7.400	5.411	10.120
Abuse/dependence	NESARC-Grant 2005d	5.800	5.010	6.714
Abuse/dependence		4.672	3.200	6.823
Dependence	NCS-R Merikangas 2007e	3.100	1.407	6.832
Dependence	NESARC-Grant 2004e	4.400	2.213	8.750
Dependence	NESARC-Compton 2007e	4.200	2.707	6.517
Dependence	WHO-Merikangas 2011e	4.800	2.788	8.264
Dependence	NCS-R Merikangas 2007f	5.200	3.728	7.254
Dependence	NESARC-Grant 2004f	13.900	8.902	21.704
Dependence	NESARC-Grant 2005f	10.500	8.607	12.810
Dependence	NEMESIS-Ravelli 1998f	25.700	12.277	53.799
Dependence	WHO-Merikangas 2011f	18.200	13.198	25.097
Dependence		7.869	5.207	11.891
Overall		4.956	3.984	6.167

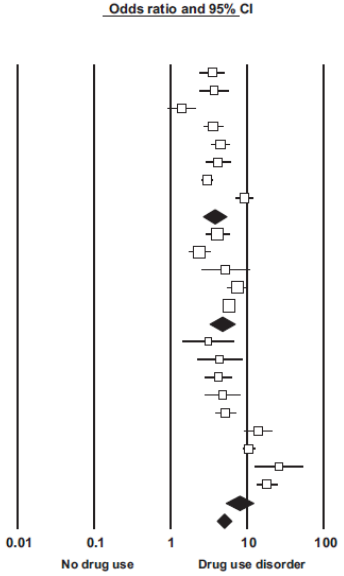

Fig. 4. Forest plot of the random effects meta-analysis of illicit drug use and bipolar disorder. Comparisons are made between subgroups based on severity of illicit drug use. Summary statistics are indicated by filled diamonds for studies reporting illicit drug abuse (a, b), abuse/dependence (c, d) and dependence (e, f). Estimates for 12 month (a, c, e) and lifetime (b, d, f) estimates were pooled within each diagnostic group.

Comorbid substance use disorders in patients with a bipolar disorder (%)

Journal of Affective Disorders 206 (2016) 331–349

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Review article

Prevalence of comorbid bipolar and substance use disorders in clinical settings, 1990–2015: Systematic review and meta-analysis

Glenn E. Hunt [a,*], Gin S. Malhi [b], Michelle Cleary [c], Harry Man Xiong Lai [a], Thiagarajan Sitharthan [a]

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[b] Discipline of Psychiatry and CADE Clinic, Royal North Shore Hospital, University of Sydney, NSW, Australia
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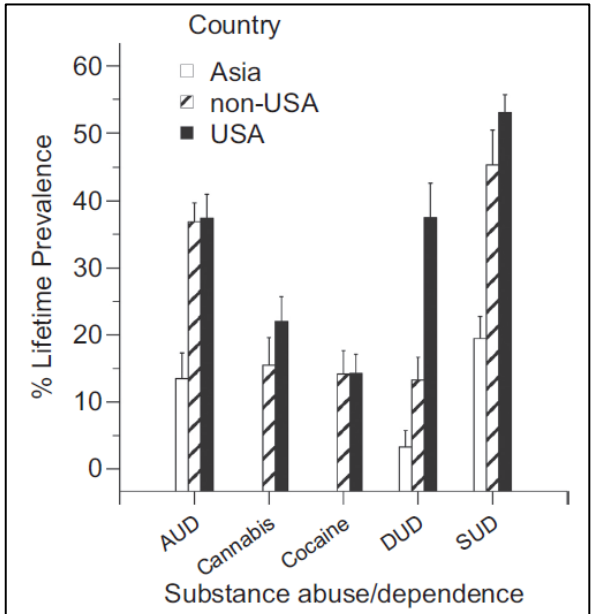

Fig. 3. Prevalence of lifetime SUDs based on country of origin for subjects with BD-I or BD. Comparisons were made between Asian countries (open bars), non-USA (Europe and other countries) (striped bars) and USA (filled bars). Data displayed are weighted means (±SEM). Lifetime data for cannabis or cocaine use disorders were not reported for Asia.

Bipolar and substance use disorders: Hypotheses regarding underlying mechanisms

- Self-medication hypothesis
- Triggering of bipolar disorder through psychoactive substances

Bipolar and substance use disorders: Clinical consequences

- Increased severity of psychopathology
- Poor course:
  - mixt episodes
  - rapid cycling
  - impulsivity
  - perturbed sleep rhythm
  - increased suicidal risk
- Decreased adherence to treatment
- Decreased treatment efficacy

Bipolar disorders and physical illness

Asian Journal of Psychiatry 99 (2024) 104138

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Comorbid physical health outcomes in patients with bipolar disorder: An umbrella review of systematic reviews and meta-analyses

Jiseung Kang [a,b,1], Hyeri Lee [c,d,1], Jaeyu Park [c,d], Hyeon Jin Kim [c,d], Rosie Kwon [c,d], Sunyoung Kim [e], Guillaume Fond [f], Laurent Boyer [f], Masoud Rahmati [f,g,h], Lee Smith [i], Christa J. Nehs [a,b], Yejun Son [c,j], Soeun Kim [c,j], Hayeon Lee [c,k], Jinseok Lee [k], Min Seo Kim [l,m,*], Tae Kim [n,**], Dong Keon Yon [c,d,j,o,***,2]

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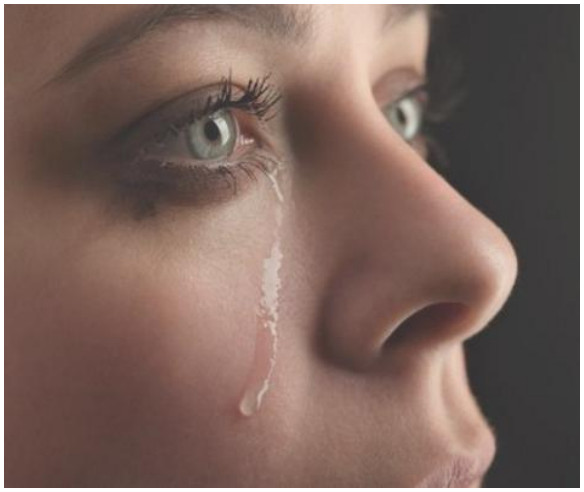
Results of umbrella review

	eOR (95% CI)	Direction	CE*
1. Neurological outcomes			
Dementia	**2.96 (1.69 to 5.17)**	Association	III
Parkinson's disease	**3.35 (1.72 to 6.53)**	Association	III
2. Respiratory outcomes			
Asthma	**1.86 (1.42 to 2.42)**	Association	IV
3. Infectious outcomes			
Toxoplasmosis (Toxoplasma gondii infection)	**1.69 (1.21 to 2.37)**	Association	IV
4. Cardiovascular outcomes			
Hypertension	**1.28 (1.02 to 1.60)**	Association	I
Myocardial infarction	1.09 (0.89 to 1.34)	No association	NS
Stroke incidence	2.12 (0.74 to 6.02)	No association	III
Stroke mortality	1.54 (0.83 to 2.87)	No association	IV
5. Oncological outcomes			
Overall cancer	1.24 (0.98 to 1.59)	No association	IV
Breast cancer	**1.33 (1.15 to 1.55)**	Association	IV
6. Gastrointestinal outcomes			
Irritable bowel syndrome	1.55 (0.75 to 3.22)	No association	IV
7. Metabolic outcomes			
Obesity	**1.64 (1.30 to 1.99)**	Association	III
Type 2 diabetes mellitus	**1.98 (1.55 to 2.52)**	Association	IV
8. Pain			
All types of pain	0.76 (0.50 to 1.03)	No association	III

Comorbidity of depressive disorders



Depression and anxiety disorders

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REVIEW

ADAA ANXIETY AND DEPRESSION ASSOCIATION OF AMERICA WILEY

Co-morbidity between mood and anxiety disorders: A systematic review and meta-analysis

Sukanta Saha[1,2] | Carmen C. W. Lim[1,2] | Danielle L. Cannon[2] | Lucinda Burton[2] | Monique Bremner[2] | Peter Cosgrove[2] | Yan Huo[3] | John J. McGrath[1,2,4]

Depression and anxiety disorders

TABLE 3 Pooled estimates for broadly defined depressive disorder (DEP) and anxiety disorders

Broadly defined depressive disorder	Anxiety disorder type	Crude estimates				Adjusted estimates			
		n	Pooled OR (95% CI)	I^2	*p* value	*n*	Pooled aOR (95% CI)	I^2	*p* value
I. Lifetime estimates									
DEP	ANX	17	4.4 (3.1–6.2)	97.2%	<.001	3	3.2 (2.2–4.7)	97.9%	<.001
DEP	Agoraphobia	11	4.0 (3.0–5.2)	80.8%	<.001	1	-[a]	-	-
DEP	OCD	14	5.6 (4.4–7.2)	61.3%	<.001	8	4.8 (3.8–6.2)	9.4%	.25
DEP	GAD	11	9.0 (5.6–14.5)	96.7%	<.001	4	5.8 (3.6–9.5)	62.7%	.08
DEP	Panic disorder	15	7.6 (5.2–11.1)	92.1%	<.001	11	7.4 (4.4–12.4)	87.4%	<.001
DEP	PTSD	5	6.1 (2.7–13.7)	94.5%	<.001	1	-[a]	-	-
DEP	Social phobia	13	4.6 (3.8–5.6)	76.2%	<.001	8	3.7 (3.1–4.4)	53.4%	.06
DEP	Specific phobia	14	3.3 (2.7–4.0)	85.5%	<.001	7	2.4 (1.6–3.5)	90.4%	<.001
II. Period prevalence estimates									
DEP	ANX	23	9.4 (6.3–14.3)	96.5%	<.001	11	6.6 (4.7–9.1)	94.2%	<.001
DEP	Agoraphobia	10	6.6 (3.6–11.8)	90.7%	<.001	5	5.6 (3.3–9.4)	82.1%	<.001
DEP	OCD	10	7.7 (4.8–12.2)	65.2%	.01	5	4.4 (2.2–8.9)	74.2%	.01
DEP	GAD	22	13.8 (9.9–19.3)	93.5%	<.001	12	11.7 (5.2–26.3)	99.5%	<.001
DEP	Panic disorder	13	9.9 (6.8–14.3)	83.6%	<.001	7	6.2 (3.2–11.9)	94.7%	<.001
DEP	PTSD	6	14.7 (8.2–26.4)	86.9%	<.001	6	4.1 (1.4–11.4)	97.8%	<.001
DEP	Social phobia	9	8.8 (5.4–14.2)	90.4%	<.001	6	6.6 (9.2–13.0)	96.3%	<.001
DEP	Specific phobia	8	3.7 (2.7–5.0)	80.4%	<.001	3	2.9 (2.3–3.7)	46.3%	.16

Abbreviations: ANX, broadly defined anxiety disorder; GAD, generalized anxiety disorder; OCD, obsessive-compulsive disorder; PTSD, posttraumatic stress disorder.

[a]Estimates were not pooled if the number of studies are less than 3 for that disorder pair.

Depression and substance use disorders

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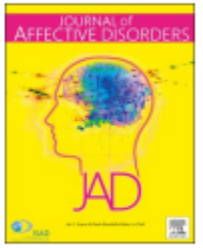

Review article

Prevalence of comorbid substance use in major depressive disorder in community and clinical settings, 1990–2019: Systematic review and meta-analysis

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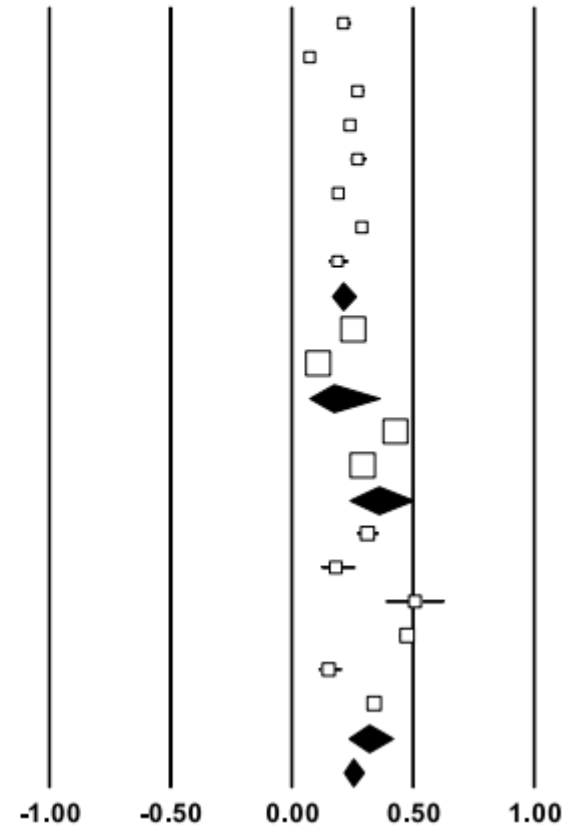
Depression and substance use disorders

Journal of Affective Disorders 266 (2020) 288–304

Substance use and major depression

Group by population	Study name	Statistics for each study: Event rate	Lower limit	Upper limit	Events/Total: Total
1-Epidemiology	1 NSMHWB	0.213	0.182	0.247	131 / 615
1-Epidemiology	4 CCHS	0.074	0.061	0.088	109 / 1479
1-Epidemiology	6 ECA	0.272	0.245	0.300	270 / 994
1-Epidemiology	10. NCS	0.240	0.219	0.262	367 / 1530
1-Epidemiology	10b. NCS-R	0.272	0.238	0.308	169 / 622
1-Epidemiology	12a. NESARC	0.192	0.178	0.206	593 / 3090
1-Epidemiology	14b. NSDUH	0.289	0.283	0.295	6370 / 22044
1-Epidemiology	15. OHS	0.189	0.151	0.235	63 / 333
1-Epidemiology		0.208	0.164	0.260	
2-Case registry	16. Denmark	0.254	0.252	0.256	49984 / 197057
2-Case registry	17. Norway	0.109	0.107	0.111	9725 / 89033
2-Case registry		0.170	0.070	0.357	
3-Cohort	19. MIDAS	0.428	0.384	0.473	205 / 479
3-Cohort	22. STAR*D	0.292	0.276	0.309	829 / 2835
3-Cohort		0.356	0.236	0.497	
4-Clinical	Abraham-99	0.312	0.267	0.361	117 / 375
4-Clinical	Minnai-06	0.182	0.120	0.265	20 / 110
4-Clinical	Mueser-00	0.508	0.385	0.631	31 / 61
4-Clinical	Pages-97	0.476	0.443	0.509	424 / 891
4-Clinical	Sanderson-90	0.152	0.109	0.209	30 / 197
4-Clinical	Watkins-06	0.340	0.312	0.369	361 / 1061
4-Clinical		0.315	0.232	0.413	
Overall		0.250	0.212	0.293	



Associations between major depressive disorder (MDD) and physical diseases

SPECIAL ARTICLE

Comorbidity between major depressive disorder and physical diseases: a comprehensive review of epidemiology, mechanisms and management

Michael Berk[1], Ole Köhler-Forsberg[2,3], Megan Turner[1], Brenda W.J.H. Penninx[4], Anna Wrobel[1], Joseph Firth[5,6], Amy Loughman[1], Nicola J. Reavley[7], John J. McGrath[8-10], Natalie C. Momen[11], Oleguer Plana-Ripoll[8,11], Adrienne O'Neil[1], Dan Siskind[9,12,13], Lana J. Williams[1], Andre F. Carvalho[1], Lianne Schmaal[14,15], Adam J. Walker[1], Olivia Dean[1], Ken Walder[1], Lesley Berk[1], Seetal Dodd[1,14], Alison R. Yung[1], Wolfgang Marx[1]

[1]Institute for Mental and Physical Health and Clinical Translation (IMPACT), School of Medicine, Deakin University, Geelong, VIC, Australia; [2]Psychosis Research Unit, Aarhus University Hospital - Psychiatry, Aarhus, Denmark; [3]Department of Clinical Medicine, Aarhus University, Aarhus, Denmark; [4]Department of Psychiatry and Amsterdam Public Health, Amsterdam UMC, Vrije Universiteit, Amsterdam, The Netherlands; [5]Division of Psychology and Mental Health, University of Manchester, Manchester Academic Health Science Centre, Manchester, UK; [6]Greater Manchester Mental Health NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK; [7]Centre for Mental Health, Melbourne School of Population and Global Health, University of Melbourne, Melbourne, VIC, Australia; [8]National Centre for Register-Based Research, Aarhus University, Aarhus, Denmark; [9]Queensland Centre for Mental Health Research, Park Centre for Mental Health, Brisbane, QLD, Australia; [10]Queensland Brain Institute, University of Queensland, Brisbane, QLD, Australia; [11]Department of Clinical Epidemiology, Aarhus University and Aarhus University Hospital, Aarhus, Denmark; [12]Metro South Addiction and Mental Health Service, Brisbane, QLD, Australia; [13]Faculty of Medicine, University of Queensland, Brisbane, QLD, Australia; [14]Centre for Youth Mental Health, University of Melbourne, Parkville, VIC, Australia; [15]Orygen, Parkville, VIC, Australia

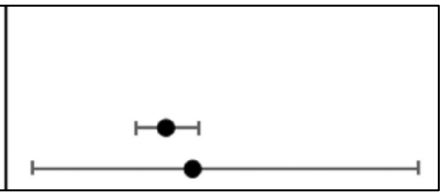
Populations with common physical diseases – such as cardiovascular diseases, cancer and neurodegenerative disorders – experience substantially higher rates of major depressive disorder (MDD) than the general population. On the other hand, people living with MDD have a greater risk for many physical diseases. This high level of comorbidity is associated with worse outcomes, reduced adherence to treatment, increased mortality, and greater health care utilization and costs. Comorbidity can also result in a range of clinical challenges, such as a more complicated therapeutic alliance, issues pertaining to adaptive health behaviors, drug-drug interactions and adverse events induced by medications used for physical and mental disorders. Potential explanations for the high prevalence of the above comorbidity involve shared genetic and biological pathways. These latter include inflammation, the gut microbiome, mitochondrial function and energy metabolism, hypothalamic-pituitary-adrenal axis dysregulation, and brain structure and function. Furthermore, MDD and physical diseases have in common several antecedents related to social factors (e.g., socioeconomic status), lifestyle variables (e.g., physical activity, diet, sleep), and stressful live events (e.g., childhood trauma). Pharmacotherapies and psychotherapies are effective treatments for comorbid MDD, and the introduction of lifestyle interventions as well as collaborative care models and digital technologies provide promising strategies for improving management. This paper aims to provide a detailed overview of the epidemiology of the comorbidity of MDD and specific physical diseases, including prevalence and bidirectional risk; of shared biological pathways potentially implicated in the pathogenesis of MDD and common physical diseases; of socio-environmental factors that serve as both shared risk and protective factors; and of management of MDD and physical diseases, including prevention and treatment. We conclude with future directions and emerging research related to optimal care of people with comorbid MDD and physical diseases.

Key words: Depression, physical diseases, comorbidity, cardiovascular diseases, cancer, inflammation, lifestyle factors, childhood trauma, collaborative care, digital technologies

(World Psychiatry 2023;22:366–387)

Risk of mortality among individuals with MDD

	ES	95% CI
Mortality		
All-cause	1.48	1.39-1.58
Coronary heart disease	1.56	1.08-2.24



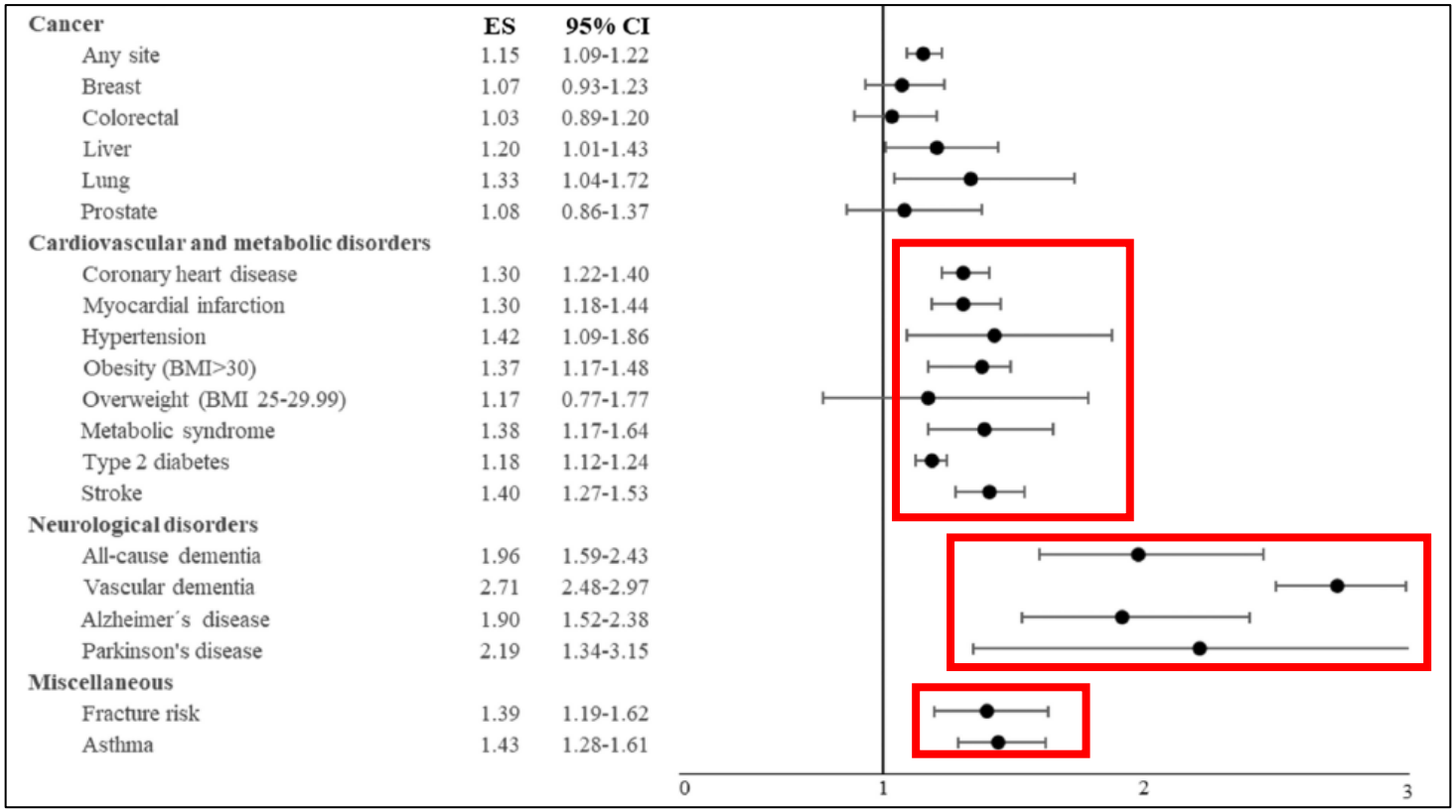
Berk et al (2023) World Psychiatry 22:366–387

Loss of years of life according to Danish registers

- Men: 8.27 years
- Women: 6.40 years

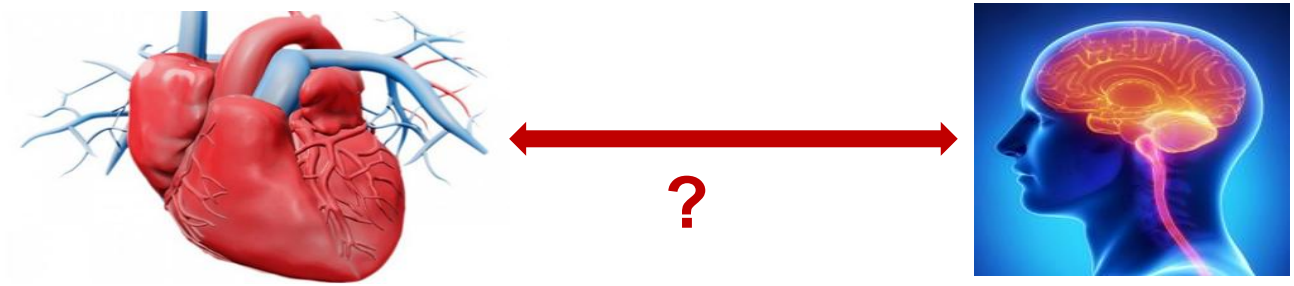
Weye N et al (2020) jamanetworkopen: Jun 1;3(6):e206646

Risk of physical diseases among individuals with MDD



Berk et al (2023) World Psychiatry 22:366–387

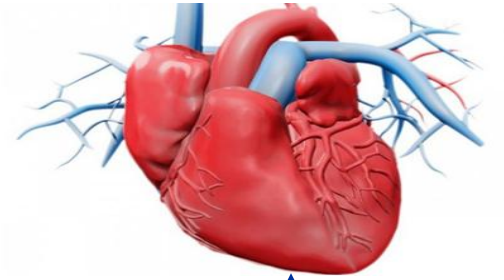
How to explain the links between MDD and physical health?



Example: Comorbidity between MDD and cardiovascular diseases (CVD)

Hypothesis 1: Causality MDD → CVD

MDD increases vulnerability to cardiovascular risk factors (CVRF) and CVD





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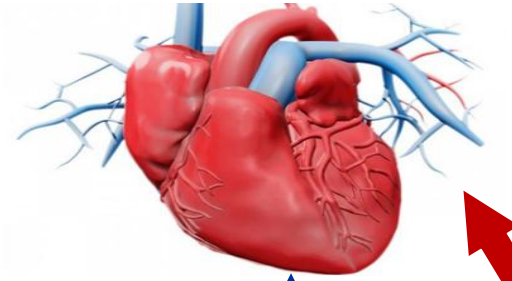
Cardiovascular risk factors

Hypothesis 1: Causality MDD → CVD

MDD increases vulnerability to CVRF and CVD





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Cardiovascular risk factors

Other potential mediators



Socioeconomic level




Behavior



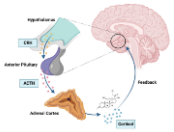
Immune system



Stress



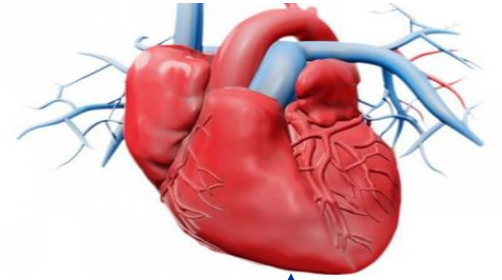
Gut microbiota



HPA-axis

Hypothesis 1: Causality CVD → MDD

CVRF/CVD increase vulnerability to MDD





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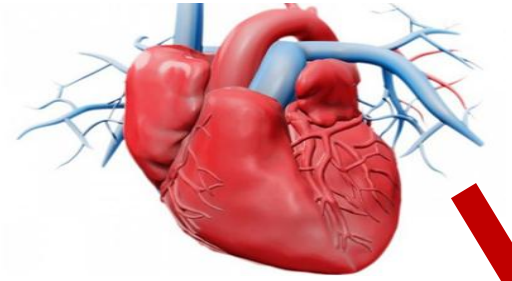
Cardiovascular risk factors

Hypothesis 1: Causality CVD → MDD

CVRF/CVD increase vulnerability to MDD





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Cardiovascular risk factors

Other potential mediators



Socioeconomic level




Behavior



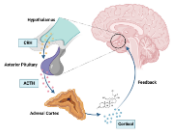
Immune system



Stress



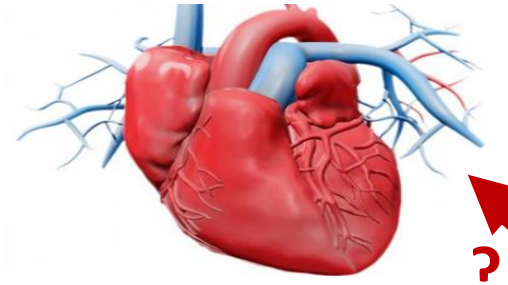
Gut microbiota



HPA-axis

Hypothesis 2: Shared underlying liability

CVRF/CVD and mental disorders share common pathogenic processes









Potential common processes



Socioeconomic level



Behavior



Stress



Genes



Immune system

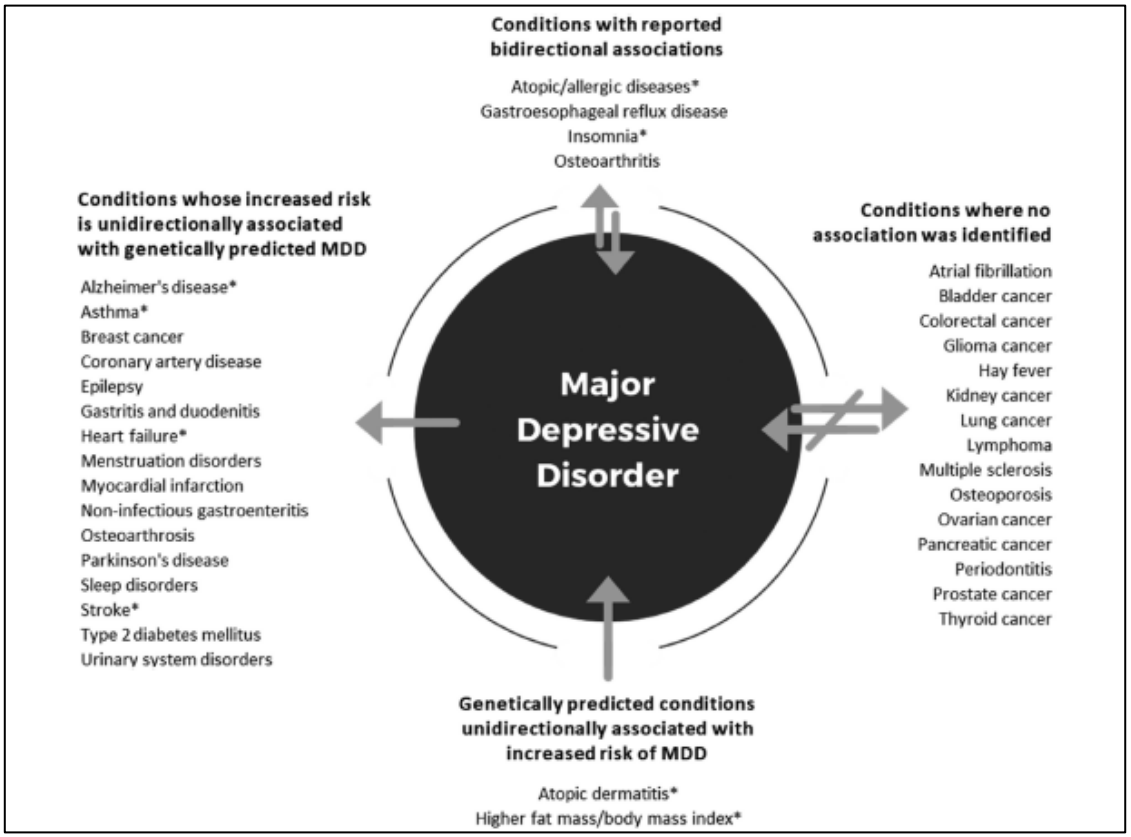


Gut microbiota



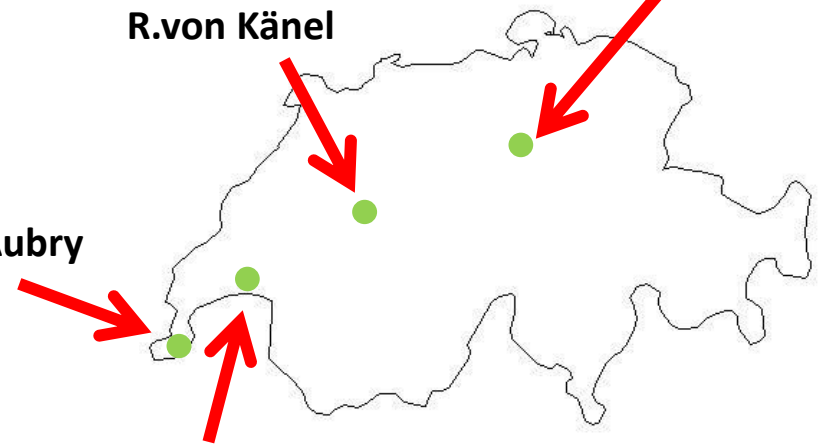
HPA-axis

Associations between MDD and physical diseases according to Mendelian randomization studies



Berk et al (2023) World Psychiatry 22:366–387

Cardiovascular diseases and psychiatric disorders in the general population: a prospective follow-up study (CoLaus|PsyCoLaus)



Zürich
T. Lüscher, V. Ajdacic-Gross, C. Hock

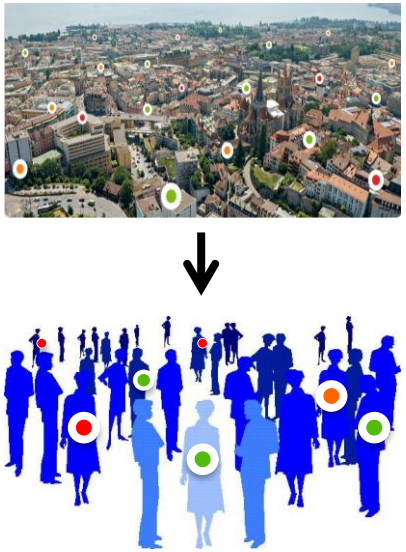
Bern
R.von Känel

Geneva
J.M. Gaspoz, J.M. Aubry

Lausanne
M. Preisig, P. Vollenweider, G. Waeber, F. Paccaud

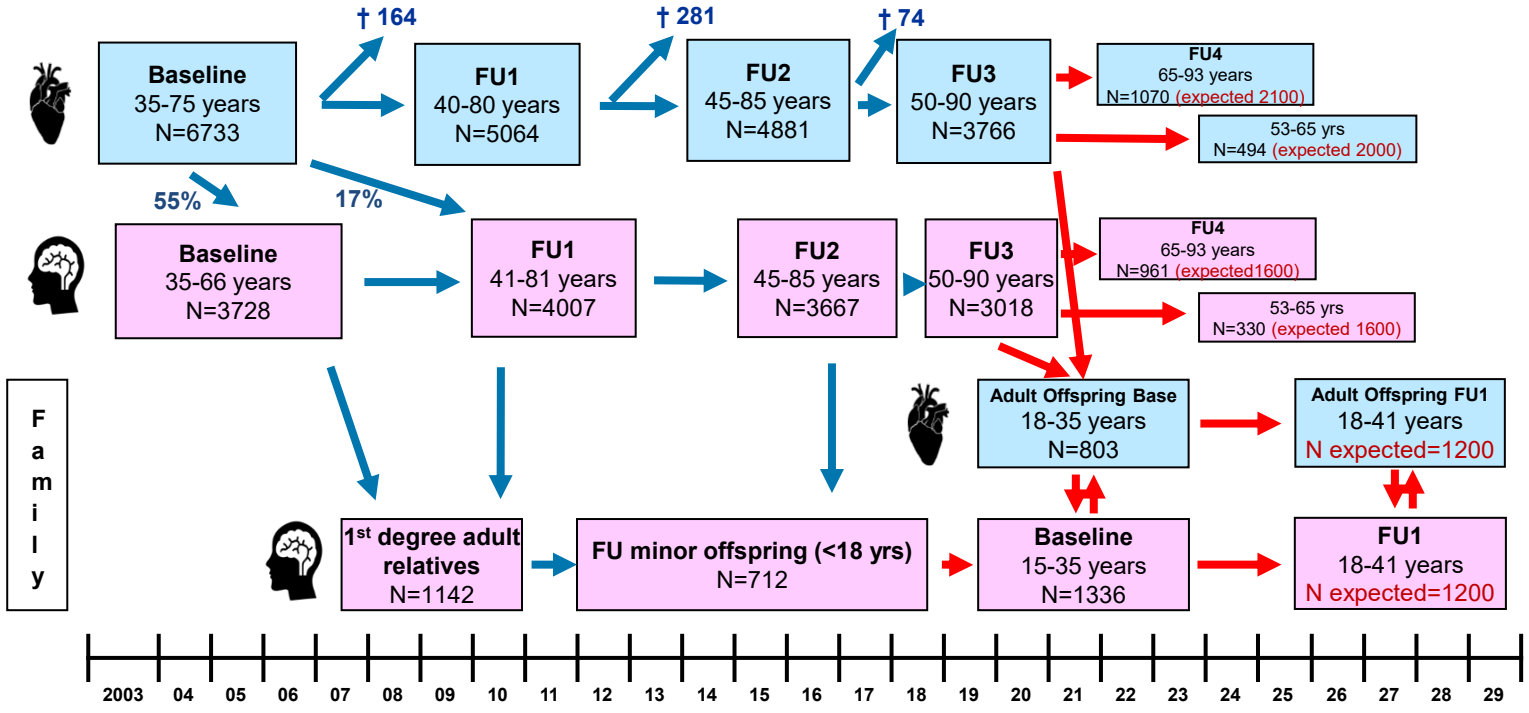
Supported by:
- 9 grants from the Swiss National Science Foundation
- 2 grants from GlaxoSmithKline.

CoLaus¦PsyCoLaus
Recruitment



- Recruitment 2003-2006
- Age: 35-75 years
- Representative sample of the population of Lausanne
- 6734 participants

CoLaus¦PsyCoLaus
Physical and psychiatric evaluations

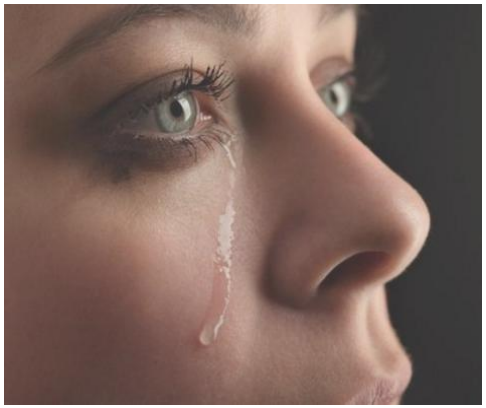


Associations of subtypes with metabolic markers






Major finding



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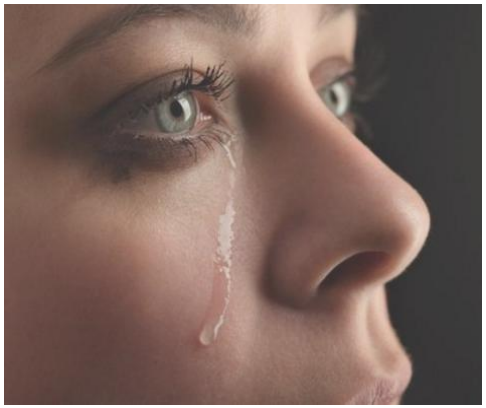




Atypique



Mélancolique

Subtyping according to the DSM-IV/DSM-5

Melancholic



A. One of the following:

1. Loss of pleasure in activities

2) Lack of reactivity to positive events

B. Three of the following:

1. Distinct quality of depressed mood

2) Depression worse in the morning

3) Early morning awakening

4) Psychomotor agitation or retardation

5) Anorexia or weight loss

6) Inappropriate guilt

Atypical



A. Mood reactivity to positive events

B. Two of the following:

1) Weight gain or increase in appetite

2) Hypersomnia

3) Leaden paralysis

4) Long-standing pattern of interpersonal rejection sensitivity

Prospective associations between DSM-IV MDD subtypes and metabolic markers



Aurélie Lasserre

colaus psycolaus



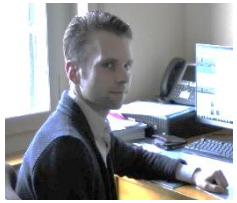
Atypical MDD
β = 2.41***
Melancholic MDD
β = 1.43**

Lasserre (2014) JAMA Psychiatry 71:880-88



*p<.05; **p<.01; ***p<.001

Prospective associations between DSM-IV MDD subtypes and metabolic markers



Dominique Rudaz



Atypical MDD
β = 2.41***
Melancholic MDD
β = 1.43**
Lasserre (2014) JAMA Psychiatry 71:880-88

Atypical MDD
β = 1.7**
Rudaz (2017) J Affect Disord 222:195-203



NESARC (age: 47 years; 3-year FU)

ORIGINAL ARTICLE

Cardiovascular Risk Factors as Differential Predictors of Incident Atypical and Typical Major Depressive Disorder in US Adults

Jay S. Patel, MS, Jessica Berntson, MS, Brittanny M. Polanka, MS, and Jesse C. Stewart, PhD

Psychosomatic Medicine, V 80 • 508-514 508 July/August 2018

	Atypical	Typical
BMI	1.32***	1.06
Hypertension	0.57***	1.09

n= 22'915
Atypical defined by presence of hyperphagia/weight gain or hypersomnia

*p<.05; **p<.01; ***p<.001

Prospective associations between DSM-IV MDD subtypes and metabolic markers



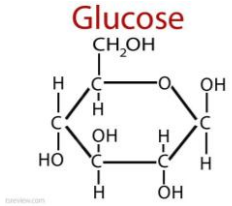
Aurélie Lasserre

colaus psycolaus



Atypical MDD
β = 2.41***
Melancholic MDD
β = 1.43**
Lasserre (2014) JAMA Psychiatry 71:880-88

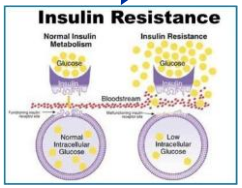
Atypical MDD
β = 1.7**
Rudaz (2017) J Affect Disord 222:195-203





Atypical MDD
β = 131**
(after adjustment for waist gain)

β = 0.25**



HOMA-IR

Atypical MDD
OR =2.49*

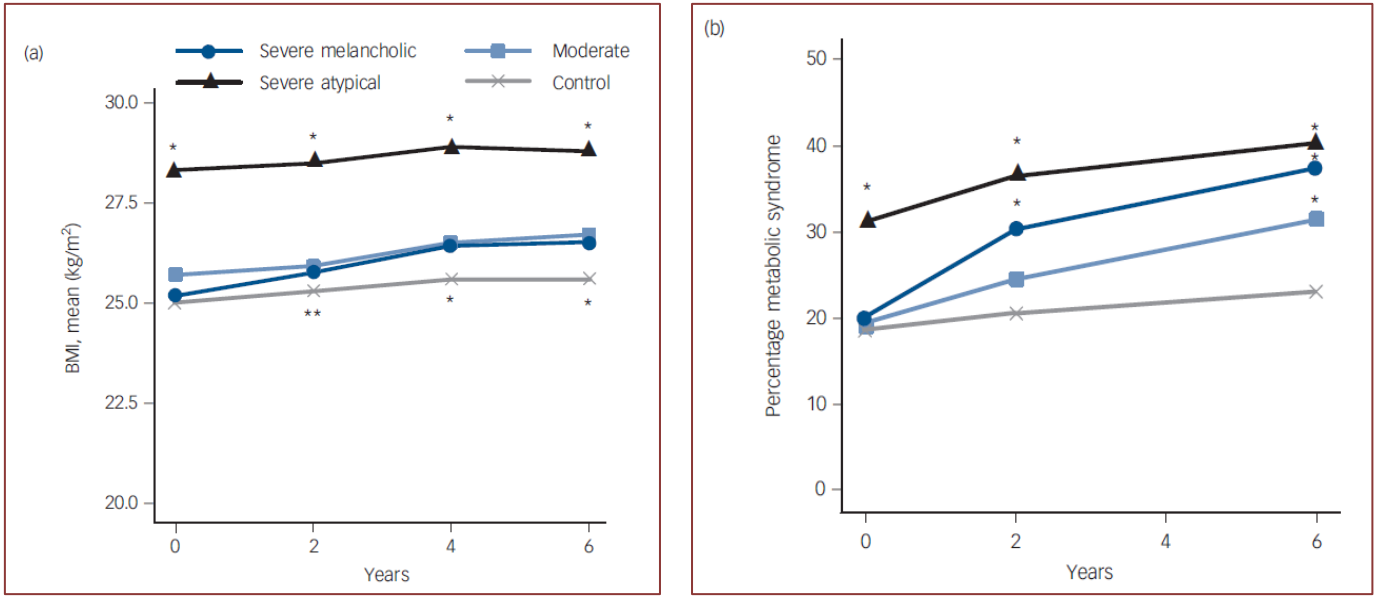


Lasserre (2017) Mol Psychiatry 22:932-39

*p<.05; **p<.01; ***p<.001

Prospective associations between DSM-IV MDD subtypes and metabolic markers

NESDA: 6-year follow-up



Lamers F, 2016, British J Psychiatry 208: 62-68

Prospective associations between DSM-IV MDD subtypes and metabolic markers



Lasserre (2014) JAMA Psychiatry 71:880-88

Rudaz (2017) J Affect Disord 222:195-203

colaus psycolaus



Are these associations causal?

Prospective associations between DSM-IV MDD subtypes and metabolic markers



Giorgio Pistis



Lasserre (2014) JAMA Psychiatry 71:880-88

Rudaz (2017) J Affect Disord 222:195-203



Mendelian Randomization using the data of CoLaus¦PsyCoLaus and NESDA

The polygenic risk score of BMI:

- was not associated with atypical MDD
- was associated with the atypical symptom increase in appetite

➢ Evidence for causality between BMI and the risk of having increased appetite during depression

Pistis et al. Translational Psychiatry (2021) 11:96

Cross-sectional associations between depression subtypes and obesity



Received: 4 June 2019 | Revised: 17 August 2019 | Accepted: 16 September 2019

DOI: 10.1111/obr.12966

OBESITY COMORBIDITY

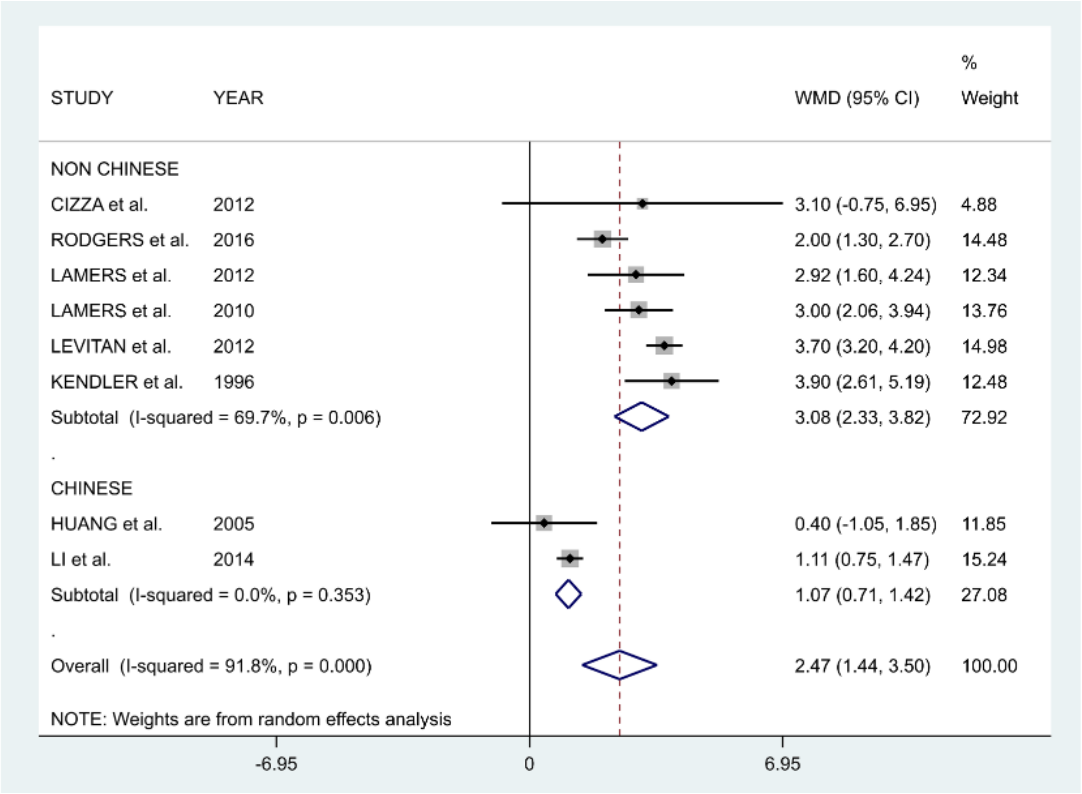
WILEY obesityreviews

Depression subtypes and obesity in adults: A systematic review and meta-analysis

Daniela Alves Silva[1,2] | Evandro da Silva Freire Coutinho[3] | Lara Onofre Ferriani[1] | Maria Carmen Viana[1,4]

Obesity Reviews. 2019;1–13.

Cross-sectional studies comparing the BMI among adults with atypical and melancholic subtypes of depression



Alves Silva D, 2019, Obesity Reviews: 1-13

Depression Heterogeneity and Its Biological Underpinnings: Toward Immunometabolic Depression

Yuri Milaneschi, Femke Lamers, Michael Berk, and Brenda W.J.H. Penninx

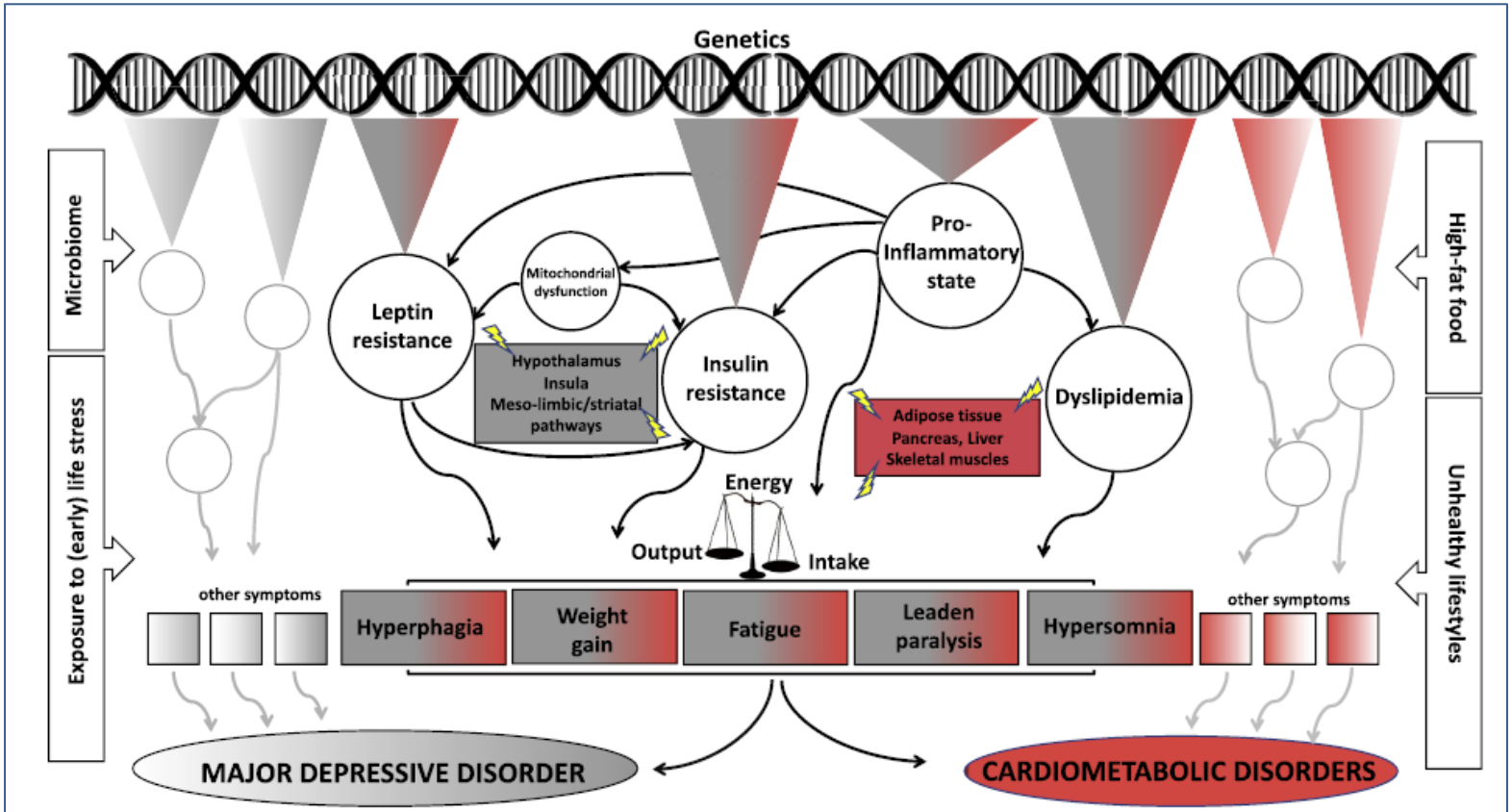
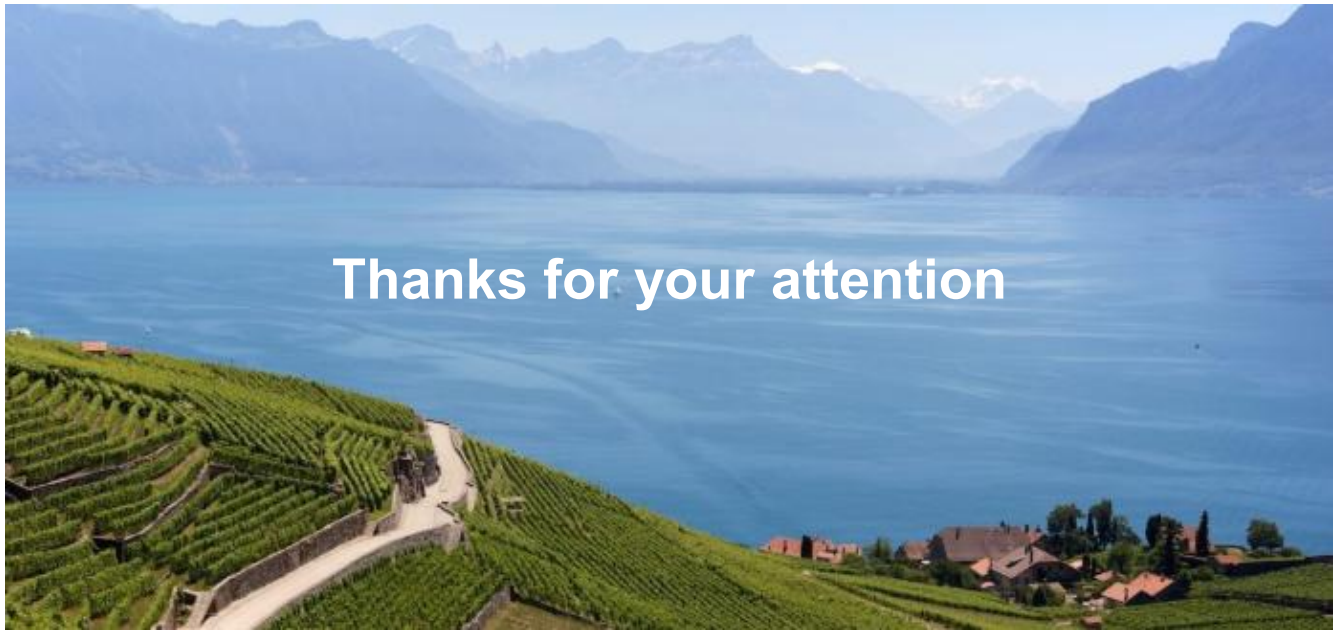


Figure 1. Immunometabolic depression: a watershed model.

Milaneschi Y, 2020, Biol Psychiatry 88: 369-380

Consequences of psychiatric and physical comorbidity

- **General**: more complicated therapeutic alliance and decreased adherence to treatment;
- **Psychiatric comorbidity**: increased clinical severity, poor course, lower treatment response;
- **Physical comorbidity**: higher risk of drug-drug interactions and adverse events induced by medications used for physical and mental diseases.


Thanks for your attention