

Supplementary Material

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Impact of Mental Disorders on Clinical Outcomes of Physical Diseases: An Umbrella Review of the Evidence

eTable 1 Characteristics of systematic reviews with meta-analysis studying the association between neurotic, stress-related and somatoform disorders and outcomes of physical diseases.....	2
eTable 2 Characteristics of systematic reviews with meta-analysis studying the association between mood affective disorders and outcomes of physical diseases.....	4
eTable 3 Characteristics of systematic reviews with meta-analysis studying the association between other mental disorders and outcomes of physical diseases.....	11
eTable 4 Level of evidence for the association of neurotic, stress-related and somatoform disorders and secondary outcomes of physical diseases	13
eTable 5 Level of evidence for the association between mood affective disorders and secondary outcomes of physical diseases	14
eTable 6 Level of evidence for the association between mental and behavioural disorders due to psychoactive substance use, schizophrenia, schizotypal and delusional disorders, organic, including symptomatic, mental disorders and secondary outcomes of physical diseases	16
eTable 7 Subgroup analyses for associations of mental disorders and outcomes of physical diseases supported by convincing and highly suggestive (I and II) class of evidence	17
eMethods 1. Search strategy	24
eResults 1. ROBIS assessments for Phase 2 across the four domains and for Phase 3.....	28
eResults 2. Findings from other subgroup analyses.....	28
References	30

Supplementary Tables

eTable 1 Characteristics of systematic reviews with meta-analysis studying the association between neurotic, stress-related and somatoform disorders and outcomes of physical diseases

Study (No of associations)	Mental disorder	Disorder definition (standard diagnostic criteria, established diagnostic research criteria, validated assessment instrument with cut-offs)	Physical disease	Outcome (s) (Metric)	No of prospectiv e studies (Sample size/ follow-up, range (y))	Mean age of partici pants (range)	%Male (range)	ROBIS Phase 2				ROBIS Phase 3
								Domain 1: Study eligibility criteria	Domain 2: Identificatio n and selection of studies	Domain 3: Data collection and study appraisal	Domain 4: Synthesis and findings	Risk of bias in the review
Neurotic, stress-related and somatoform disorders and cardiovascular diseases												
Li, 2020 ¹ (2)	Anxiety disorder	DSM-IV and validated assessment instruments (HADS- A≥8, GAD-7≥10, HARS ≥18)	Acute coronary syndrome	All-cause mortality; Major cardiac events (RR)	8 (6,073/ 1-10y)	59-67	67-81	Low risk	High risk	Low risk	Low risk	Low risk
Emdin, 2016 ² (2)	Anxiety disorder	DSM-III-R, DSM-III, DSM-IV, and validated assessment instruments (Zung SAS≥50)	Cardiovascular diseases	Cardiovascular mortality; Major cardiac events (RR)	6 (156,418/ 3-23y)	41-81	0-100	High risk	Low risk	High risk	Low risk	Low risk
Celano, 2015 ³ (2)	Anxiety disorder	DSM-IV and validated assessment instruments (HADS- A≥8, HARS≥18,Zung SAS≥44)	Coronary artery disease	All-cause mortality; Major cardiac events (OR)	13 (9,644/ 11-8y)	59-67	70-82	Low risk	Low risk	Low risk	High risk	Low risk
Roest, 2010 ⁴ (1)	Anxiety disorder	Validated assessment instruments (HADS- A≥8)	Myocardial infarction	Major cardiac events (OR)	3 (1,213/ 1-5y)	60-63	46-81	High risk	Low risk	High risk	High risk	Low risk
Taggart Wasson, 2018 ⁵ (1)	Post- traumatic stress disorder	Validated assessment instruments (IES ≥33)	Myocardial infarction	Medication nonadherence (RR)	2 (213/ 0.3-3y)	53-61	41-58	Low risk	Low risk	Low risk	Low risk	Low risk
Neurotic, stress-related and somatoform disorders and other physical diseases												
Atlantis, 2013 ⁶ (1)	Anxiety disorder	Validated assessment instruments (HADS- A≥8)	Chronic obstructive pulmonary disease	All-cause mortality (RR)	3 (2,099/ 1-5y)	57-69	43-69	High risk	High risk	High risk	High risk	High risk

Study (No of associations)	Mental disorder	Disorder definition (standard diagnostic criteria, established diagnostic research criteria, validated assessment instrument with cut-offs)	Physical disease	Outcome (s) (Metric)	No of prospectiv e studies (Sample size/ follow-up, range (y))	Mean age of participa nts (range)	%Male (range)	ROBIS Phase 2				ROBIS Phase 3
								Domain 1: Study eligibility criteria	Domain 2: Identificatio n and selection of studies	Domain 3: Data collection and study appraisal	Domain 4: Synthesis and findings	Risk of bias in the review
Guo, 2021 ⁷ (1)	Anxiety disorder	DSM-IV-R and validated assessment instruments (MDS- UPDRS-A≥2)	Parkinson's disease	Cognitive impairment (RR)	2 (243/ < 5y)	62-66	52-63	High risk	Low risk	Unclear risk	Low risk	Low risk
Li, 2016 ⁸ (1)	Anxiety disorder	Validated assessment instruments (HARS≥17)	Neurological diseases with mild cognitive impairment	Alzheimer's disease progression (RR)	2 (448/ 3-5.5y)	67-84	15-56	Low risk	High risk	Low risk	Low risk	Low risk
Wang, 2020 ⁹ (2)	Anxiety disorder	Validated assessment instruments (HADS- A≥10)	Breast cancer	All-cause mortality; Cancer recurrence (HR)	3 (2,874/ 8-13y)	52-60	0	Low risk	Low risk	Low risk	Low risk	Low risk

DSM— Diagnostic and statistical manual of mental disorders, GAD-7—General anxiety disorder-7, HADS-A—Hospital anxiety and depression scale (anxiety subscale), HARS—Hamilton anxiety rating scale, HR—Hazard ratio, IES— Impact of event scale, MDS-UPDRS-A— Movement disorder society-Unified Parkinson's disease rating scale (anxiety subscale), OR—Odds ratio, ROBIS— Risk of bias assessment tool for systematic reviews, RR—Risk ratio, Zung SAS— Zung self-rating anxiety scale.

eTable 2 Characteristics of systematic reviews with meta-analysis studying the association between mood affective disorders and outcomes of physical diseases

Study (No of associations)	Mental disorder	Disorder definition (standard diagnostic criteria, established diagnostic research criteria, validated assessment instrument with cut- offs)	Physical disease	Outcome (s) (Metric)	No of prospective studies (Sample size/ follow-up, range (y))	Mean age of partici- pant, range)	%Male (range)	ROBIS Phase 2				ROBIS Phase 3
								Domain 1: Study eligibility criteria	Domain 2: Identificatio n and selection of studies	Domain 3: Data collection and study appraisal	Domain 4: Synthesis and findings	Risk of bias in the review
Mood affective disorders and cardiovascular diseases (including stroke)												
Correll, 2017 ¹⁰ (1)	Bipolar disorder	ICD-8,9,10, RDC	Cardiovascular diseases	Cardiovascular mortality (RR)	6 (1,309,529/ 4-20y)	37-72	42-100	Low risk	Low risk	Unclear risk	Low risk	Low risk
Yuan, 2022 ¹¹ (1)	Bipolar disorder	ICD-9,10	Stroke	Stroke mortality (HR)	2 (10,715,313/ 7-20y)	NR	46-100	Low risk	Low risk	Unclear risk	Low risk	Low risk
Correll, 2017 ¹⁰ (1)	Depressive disorders	DSM-IV, ICD-9,10	Cardiovascular diseases	Cardiovascular mortality (RR)	5 (650,556/ 3-20y)	44-72	34-100	Low risk	Low risk	Unclear risk	Low risk	Low risk
Barth, 2004 ¹² (1)	Depressive disorders	Validated assessment instruments (BDI≥10, HADS- D≥8, Zung SDS≥50)	Coronary artery disease*	All-cause mortality (HR)	6 (7,486/ 1-15y)	53-64	31-85	High risk	Low risk	Unclear risk	High risk	High risk
Nicholson, 2006 ¹³ (1)		DSM-IV, RCD, DIS for DSM-IV, and validated assessment instruments (BDI≥10, CES- D≥16, Zung SDS≥40)		All-cause mortality (RR)	10 (6,727/ 0.33-15y)	59-71	48-73	High risk	High risk	High risk	High risk	Unclear risk
Wu, 2016 ¹⁴ (2)	Depressive disorders	ICD-8, DSM-III, IV and validated assessment instruments (CES- D≥16, HADS-D≥11, MMPI-2 D≥22, Zung SDS≥45)	Coronary artery disease	Cardiovascular mortality; Myocardial infarction (HR)	12 (161,318/ 4.2-24y)	>18-99	29-100	Low risk	Low risk	High risk	Low risk	Low risk
Shi, 2017 ¹⁵ (2)	Depressive disorders	DIS for DSM-IV and validated	Coronary artery disease	Ventricular tachycardia/	8 (3,805/ < 5y)	58-64	60-82	Low risk	Low risk	Low risk	Low risk	Low risk

Study (No of associations)	Mental disorder	Disorder definition (standard diagnostic criteria, established diagnostic research criteria, validated assessment instrument with cut- offs)	Physical disease	Outcome (s) (Metric)	No of prospective studies (Sample size/ follow-up, range (y))	Mean age of particip ants, range)	%Male (range)	ROBIS Phase 2				ROBIS Phase 3
								Domain 1: Study eligibility criteria	Domain 2: Identificatio n and selection of studies	Domain 3: Data collection and study appraisal	Domain 4: Synthesis and findings	Risk of bias in the review
		assessment instruments (BDI≥10, CES- D≥16, Zung SDS≥50)		fibrillation; Atrial fibrillation recurrence (HR)								
Flaherty, 2017 ¹⁶	Depressive disorders	Validated assessment instruments (BDI≥10, CES- D≥16)	Coronary artery bypass graft	All-cause mortality (HR)	2 (1,126/ >5y)	62-63	67	High risk	Low risk	Low risk	High risk	High risk
Gathright, 2017 ¹⁷ (1)	Depressive disorders	Validated assessment instruments (BDI≥10, CES- D≥16, HADS-D≥10, PHQ-9≥10,	Heart failure*	All-cause mortality (HR)	9 (3,376/ 1-12y)	57-79	40-85	Low risk	Low risk	Unclear risk	High risk	High risk
Sokoreli, 2016 ¹⁸ (1)		Validated assessment instruments (BDI≥10, CES- D≥24)			4 (8,108/ 1-3y)	62-73	48-65	Low risk	Low risk	High risk	High risk	High risk
Rutledge, 2016 ¹⁹ (1)	Depressive disorders	DIS for DSM-IV and validated assessment instruments (PRIME-MD positive followed by CEG; HADS-D≥8, Zung SDS≥50)	Heart failure	Major cardiac events (RR)	6 (1,088/ 0.5-3y)	53-66	51-72	Low risk	Low risk	Unclear risk	High risk	High risk
Meijer, 2011 ²⁰ (3)	Depressive disorders	CIDI, SCID/DCPR, DIS for DSM-IV, and validated assessment instruments (BDI≥10,	Myocardial infarction	All-cause mortality; Cardiovascular mortality; Major cardiac events (OR)	27 (15,319/ 1-5y)	59-65	55-84	Low risk	Low risk	High risk	High risk	Unclear risk

Study (No of associations)	Mental disorder	Disorder definition (standard diagnostic criteria, established diagnostic research criteria, validated assessment instrument with cut- offs)	Physical disease	Outcome (s) (Metric)	No of prospective studies (Sample size/ follow-up, range (y))	Mean age of particip ants, range)	%Male (range)	ROBIS Phase 2				ROBIS Phase 3
								Domain 1: Study eligibility criteria	Domain 2: Identificatio n and selection of studies	Domain 3: Data collection and study appraisal	Domain 4: Synthesis and findings	Risk of bias in the review
		HADS-D≥10, MADRS≥14, Zung SDS ≥40)										
Zhang, 2019 ²¹ (1)	Depressive disorders	MINI and validated assessment instruments (BDI≥31, HADS- D≥8, Zung SDS≥ 60)	Percutaneous coronary intervention	Major cardiac events (RR)	7 (3,375/ 1-10y)	57-64	63-78	Low risk	Low risk	High risk	Low risk	Low risk
Song, 2020 ²² (1)	Depressive disorders	MINI and validated assessment instruments (HADS- D≥8, CES-D≥16)	Percutaneous coronary intervention	All-cause mortality (RR)	5 (3,209/ 2-10y)	58-75	63-77	Low risk	High risk	Low risk	Low risk	Low risk
Blöchl, 2019 ²³ (1)	Depressive disorders	Validated assessment instruments (BDI≥10, HDRS≥7)	Stroke	Poor functional outcome (OR)	4 (2,663/ 0.6-2y)	61-73	44-65	Low risk	Unclear risk	High risk	Low risk	High risk
Bartoli, 2018 ²⁴ (1)	Depressive disorders	ICD-10, CIDI and validated assessment instruments (HDRS≥7, PHQ- 9≥10)	Stroke*	All-cause mortality (RR)	5 (1,254/ 1-10y)	60-68	54-60	Low risk	Low risk	Low risk	Unclear risk	Low risk
Cai, 2019 ²⁵ (1)		ICD-8, DSM-III-R, IV and validated assessment instruments (CES- D≥16, HADS≥11, HDRS≥7)		All-cause mortality (HR)	8 (79,962/ 1-15y)	39-72	42-98	Low risk	Unclear risk	Low risk	Low risk	Unclear risk
Pan, 2011 ²⁶ (1)	Depressive disorders	RCD and validated assessment instruments (CES-D≥16, Zung SDS≥ 60, HLEQ	Stroke	Stroke mortality (HR)	4 (35,193/ 5-29y)	46->65	43-100	Low risk	Low risk	Low risk	Low risk	Low risk

Study (No of associations)	Mental disorder	Disorder definition (standard diagnostic criteria, established diagnostic research criteria, validated assessment instrument with cut- offs)	Physical disease	Outcome (s) (Metric)	No of prospective studies (Sample size/ follow-up, range (y))	Mean age of particip ants, range)	%Male (range)	ROBIS Phase 2				ROBIS Phase 3
								Domain 1: Study eligibility criteria	Domain 2: Identificatio n and selection of studies	Domain 3: Data collection and study appraisal	Domain 4: Synthesis and findings	Risk of bias in the review
		related to DSM-IV MDD)										
Wu, 2019 ²⁷ (1)	Depressive disorders	DSM-IV, and validated assessment instruments (BDI≥14, HADS- D≥8, Zung SDS≥50)	Stroke	Stroke recurrence (RR)	5 (3,547/ 1-12y)	53-82	51-66	Low risk	High risk	Low risk	Low risk	Low risk
Mood affective disorders and chronic respiratory diseases												
Courtwright, 2016 ²⁸ (1)	Depressive disorders	DSM-IV and validated assessment instruments (BDI≥14)	Lung transplant	Posttransplant mortality (HR)	2 (356/ >5y)	49-52	49	Low risk	High risk	Low risk	Low risk	Low risk
Atlantis, 2013 ⁶ (1)	Depressive disorders	ICD-10 and validated assessment instruments (BDI≥15, HADS- D≥8, CES-D≥16, Yesavage DI≥11)	Chronic obstructive pulmonary disease	All-cause mortality (RR)	6 (1,368/ 1-7y)	61-72	33-92	High risk	High risk	High risk	High risk	High risk
Mood affective disorders and endocrine system diseases												
Chow, 2022 ²⁹ (1)	Depressive disorders	ICD-9,10, and validated assessment instruments (HADS- D≥8, PHQ-9≥10)	Diabetes mellitus	Dementia (HR)	5 (1,945,584/ 5-10.6y)	56-68	51-59	Low risk	Low risk	Low risk	Low risk	Low risk
Farooqi, 2019 ³⁰ (3)	Depressive disorders	ICD-9, DSM-III, IV, MINI and validated assessment instruments (PHQ- 9≥10)	Diabetes mellitus*	Coronary artery disease; Stroke; Cardiovascular mortality (HR)	7 (952,363/ 4-20.8y)	41-65	48-67	High risk	Low risk	Low risk	Low risk	Low risk
van Dooren, 2013 ³¹ (1)		Validated assessment instruments		Cardiovascular mortality (HR)	2 (1,045/ 6-8y)	63-65	38-70	Low risk	Low risk	Low risk	High risk	Unclear risk

Study (No of associations)	Mental disorder	Disorder definition (standard diagnostic criteria, established diagnostic research criteria, validated assessment instrument with cut- offs)	Physical disease	Outcome (s) (Metric)	No of prospective studies (Sample size/ follow-up, range (y)	Mean age of particip ants, range)	%Male (range)	ROBIS Phase 2				ROBIS Phase 3
		(BDI≥10, CES- D≥16)						Domain 1: Study eligibility criteria	Domain 2: Identificatio n and selection of studies	Domain 3: Data collection and study appraisal	Domain 4: Synthesis and findings	Risk of bias in the review
Hofmann, 2013 ³² (2)	Depressive disorders	ICD-9, DSM-IV, CIDI, and validated assessment instruments (BDI≥10, CES- D≥16, HADS-D≥8, PHQ-9≥10, DSQ≥8, GDS≥10)	Diabetes mellitus	All-cause mortality (HR)	12 (88,648)/ 2-10y)	52-76	38-100	Low risk	Low risk	Low risk	Unclear risk	Low risk
Farrokhi, 2014 ³³ (1)	Depressive disorders	ICD-9 and validated assessment instruments (BDI≥10, CES- D≥10, PHQ-9≥10)	Kidney failure	All-cause mortality (HR)	6 (12,600/ 1-5y)	>17-60	51-57	Low risk	Low risk	Low risk	Low risk	Low risk
Palmer, 2013 ³⁴ (1)	Depressive disorders	SCID, MINI and validated assessment instruments (BDI≥10, PHQ- 9≥10, CES-D≥10)	Chronic kidney disease	All-cause mortality (RR)	13 (17,688/ 1-6.5y)	>17-66	51-73	Low risk	Unclear risk	Low risk	Low risk	Unclear risk
Mood affective disorders and cancer												
Satin, 2009 ³⁵ (3)	Depressive disorders	DSM-II, IV, SCID and validated assessment instruments (BDI≥10 HADS- D≥8, CES-D≥16, EDS≥13)	Cancer	All-cause mortality (HR); Cancer progression (RR)	12 (4,745/ <5 y & ≥5 y)	35-70	0-83	High risk	Low risk	High risk	High risk	High risk
Shi, 2018 ³⁶ (2)	Depressive disorders	DSM-IV and validated assessment instruments (BDI≥10, HADS- D≥8)	Glioma; High- grade brain tumour	All-cause mortality (HR);Glioma mortality(RR)	5 (1,481/ < 5y)	45-54	34-55	Low risk	Low risk	High risk	Low risk	Low risk

Study (No of associations)	Mental disorder	Disorder definition (standard diagnostic criteria, established diagnostic research criteria, validated assessment instrument with cut- offs)	Physical disease	Outcome (s) (Metric)	No of prospective studies (Sample size/ follow-up, range (y))	Mean age of particip ants, range)	%Male (range)	ROBIS Phase 2				ROBIS Phase 3
								Domain 1: Study eligibility criteria	Domain 2: Identificatio n and selection of studies	Domain 3: Data collection and study appraisal	Domain 4: Synthesis and findings	Risk of bias in the review
Wang, 2020 ⁹ (3)	Depressive disorders	ICD-9 and validated assessment instruments (PSSCAN based on DSM-IV-TR≥11 HADS-D≥8, CES- D≥16)	Breast cancer	Breast cancer mortality; All- cause mortality; Cancer recurrence (HR)	8 (14,316/8- 13y)	52-72	0	Low risk	Low risk	Low risk	Low risk	Low risk
Mood affective disorders and other physical diseases												
Guo, 2021 ⁷ (1)	Depressive disorders	Validated assessment instruments (HADS- D≥11, MADRS ≥20 and Yesavage DI≥11)	Parkinson's disease	Cognitive impairment (RR)	2 (547/ < 5y)	68-69	38-63	High risk	Low risk	Unclear risk	Low risk	Low risk
Li, 2016 ⁸ (1)	Depressive disorders	DSM-IV and validated assessment instruments (GDS≥10, HDRS≥17)	Neurological diseases with mild cognitive impairment	Alzheimer's disease progression (RR)	5 (3,629/ 3-5.5y)	67-81	36-56	Low risk	High risk	Low risk	Low risk	Low risk
Murao, 2016 ³⁷ (1)	Depressive disorders	MINI and validated assessment instruments (GDS≥10, CES- D≥16)	Neurological diseases with mild cognitive impairment	Dementia progression (RR)	3 (7,216/ < 5y)	65-84	15-77	Low risk	Low risk	Low risk	Low risk	Low risk
Ruiz-Grosso, 2020 ³⁸ (2)	Depressive disorders	Validated assessment instruments (CES- D≥16, PHQ-9≥10)	Tuberculosis	Tuberculosis mortality; Negative outcomes during treatment (OR)	2 (900/ < 5y)	26-30	53-54	Low risk	Low risk	Low risk	Low risk	Low risk
Schoultz, 2020 ³⁹ (1)	Depressive disorders	Validated assessment instruments (HADS-D≥10)	Inflammatory bowel disease	Symptom exacerbation (HR)	2 (480/ 1-2y)	47	73	Low risk	Low risk	Low risk	Low risk	Low risk

Study (No of associations)	Mental disorder	Disorder definition (standard diagnostic criteria, established diagnostic research criteria, validated assessment instrument with cut- offs)	Physical disease	Outcome (s) (Metric)	No of prospective studies (Sample size/ follow-up, range (y))	Mean age of particip ants, range)	%Male (range)	ROBIS Phase 2				ROBIS Phase 3
								Domain 1: Study eligibility criteria	Domain 2: Identificatio n and selection of studies	Domain 3: Data collection and study appraisal	Domain 4: Synthesis and findings	Risk of bias in the review
Scott, 2018 ⁴⁰ (1)	Depressive disorders	CIDI and validated assessment instruments (BDI≥20)	Human immunodeficien cy virus infection	Pain (HR)	2 (890/ < 5y)	30-42	65-81	Low risk	Low risk	Low risk	Low risk	Low risk

BDI— Beck's depression inventory, CES— Center for epidemiologic studies depression scale, CEG — PRIME-MD Clinician evaluation guide, CIDI—composite international diagnostic interview, DIS— Diagnostic interview schedule for DSM-IV, DSM— Diagnostic and statistical manual of mental disorders, DSQ— Depression screening questionnaire, EDS—Edinburgh depression scale, GDS— Geriatric depression scale, HADS-D—Hospital anxiety and depression scale (depression subscale), HDRS— Hamilton depression rating scale, HLEQ—Health and life experiences questionnaire, HR— Hazard ratio, ICD— International classification of diseases, MADRS— Montgomery-Asberg depression rating scale, MINI— Mini international neuropsychiatric interview, MMPI-2 D— Minnesota multiphasic personality inventory-2 (depression subscale), OR—Odds ratio, PHQ-9—Patient health questionnaire-9, PRIME-MD—Primary care evaluation of mental disorders, PSSCAN— Psychological screen for cancer, ROBIS— Risk of bias assessment tool for systematic reviews, RDC—Research diagnostic criteria, RR— Risk ratio, SCID/DCPR— Structured clinical interview for DSM/Diagnostic criteria for psychosomatic research, Yesavage DI- Yesavage depression inventory, Zung SDS— Zung self-rating depression scale. *Same association but non-overlapping or minimally overlapping primary studies in those systematic reviews with meta-analysis.

eTable 3 Characteristics of systematic reviews with meta-analysis studying the association between other mental disorders and outcomes of physical diseases

Study (No of associations)	Mental disorder	Disorder definition (standard diagnostic criteria, established diagnostic research criteria, validated assessment instrument with cut-offs)	Physical disease	Outcome (s) (Metric)	No of prospective studies (Sample size/follow- up, range(y)	Mean age of participants (range)	%Male (range)	ROBIS Phase 2				ROBIS Phase 3
								Domain 1: Study eligibility criteria	Domain 2: Identification and selection of studies	Domain 3: Data collection and study appraisal	Domain 4: Synthesi s and findings	Risk of bias in the review
Mental and behavioural disorders due to psychoactive substance use and infectious diseases												
Llamosas-Falcón, 2020 ⁴¹ (2)	Alcohol use disorder	ICD-9,10	Hepatitis C virus infection	Decompensat ed liver cirrhosis; Negative course liver disease (RR)	3 (169,506/ 1-10y)	53-61	53-10	Unclear risk	High risk	Unclear risk	Unclear risk	High risk
Schizophrenia, schizotypal and delusional disorders and cardiovascular diseases and neoplasms												
Correll, 2017 ¹⁰ (1)	Schizophrenia	ICD-8,9,10	Cardiovascular diseases	Cardiovascular mortality (RR)	7 (821,483/ 4-30y)	39-72	42-100	Low risk	Low risk	Unclear risk	Low risk	Low risk
Ni, 2019 ⁴² (2)	Schizophrenia	ICD-9,10	Breast cancer; Lung cancer	Breast cancer mortality; Lung cancer mortality (RR)	2 (3,840/ 11-25y)	39	0-64	Low risk	High risk	Low risk	Low risk	Low risk
Zhuo, 2017 ⁴³ (1)	Schizophrenia	ICD-9,10	Cancer	Cancer mortality(SMR)	3 (42,102/ 11-25y)	39-72	0-100	High risk	Low risk	High risk	Unclear risk	Unclear risk
Organic, including symptomatic, mental disorders and infectious, cardiovascular diseases(including stroke), musculoskeletal system and connective tissue, and neurological disorders												
Hariyanto, 2021 ⁴⁴ (1)	Dementia	ICD-9	COVID-19*	All-cause mortality (RR)	2 (22,796)/ <5y)	55-71	60-92	Low risk	High risk	Low risk	Low risk	Low risk
Liu, 2021 ⁴⁵ (1)					2 (551/ <5y)	70-73	52-56	Low risk	Low risk	Low risk	Low risk	Low risk
Ding, 2021 ⁴⁶ (1)	Dementia	DSM-III, NINDS-AIREN, MINI	Stroke	Delirium (OR)	7 (1,389/ 0.3-10v)	56-75	46-95	Low risk	High risk	Low risk	Low risk	Low risk

Study (No of associations)	Mental disorder	Disorder definition (standard diagnostic criteria, established diagnostic research criteria, validated assessment instrument with cut-offs)	Physical disease	Outcome (s) (Metric)	No of prospective studies (Sample size/follow- up, range(y)	Mean age of participants (range)	%Male (range)	ROBIS Phase 2				ROBIS Phase 3
								Domain 1: Study eligibility criteria	Domain 2: Identification and selection of studies	Domain 3: Data collection and study appraisal	Domain 4: Synthesi s and findings	Risk of bias in the review
Liu, 2018 ⁴⁷ (2)	Delirium; Dementia	DSM-IV-TR, DSM-IV, MINI, and validated assessment instrument (CAM positive=3)	Hip fracture	All-cause mortality (HR)	7 (2,874/ <5y)	>65-85	18-27	Low risk	Low risk	Unclear risk	Low risk	Low risk
Guo, 2021 ⁷ (1)	Alzheimer's disease	Validated assessment instruments (DRS-II≤128, MDS-2 ≥1.5)	Parkinson's disease	Cognitive impairment (RR)	2 (159/ 2- 8y)	63-69	NR	High risk	Low risk	Unclear risk	Low risk	Low risk

CAM- Confusion assessment method for delirium (Positive means the presence of acute onset or fluctuating course and inattention, and either disorganized thinking or altered level of consciousness), COVID-19— coronavirus disease 2019, DRS-II—Dementia Rating Scale-II, DSM— Diagnostic and statistical manual of mental disorders, HR— Hazard ratio, ICD— International classification of diseases, MDS-2—Resident Assessment Instrument—Minimum Data Set- 2.0, MINI— Mini international neuropsychiatric interview, NINDS-AIREN-National Institute of Neurological Disorders and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences Criteria, OR—Odds ratio, ROBIS— Risk of a bias assessment tool for systematic reviews, RR— Risk ratio, SMR—standardized mortality ratio. *Same association but non-overlapping or minimally overlapping primary studies in those systematic reviews with meta-analysis.

eTable 4 Level of evidence for the association of neurotic, stress-related and somatoform disorders and secondary outcomes of physical diseases

Study	Mental disorder	Physical disease	Outcome	k	Random-effects measure, ES (95% CI)	N cases	p random effects	I ² %	PI (95% CI)	SSE/ESB	LS	eOR	CE	CES
Neurotic, stress-related and somatoform disorders and cardiovascular diseases														
Roest, 2010 ⁴	Anxiety disorder	Myocardial infarction	Major cardiac events	3	OR, 1.71 [1.25, 2.34]	149	7.0e-04	0.00	[0.23,12.86]	No/No	Yes	1.71	IV	III
Li, 2020 ¹	Anxiety disorder	Acute coronary syndrome	Major cardiac events	4	RR, 1.46 [1.19, 1.78]	484	2.4e-04	16.34	[0.79, 2.69]	No/No	No	1.46	IV	III
Emdin, 2016 ²	Anxiety disorder	Cardiovascular diseases	Major cardiac events	3	RR, 1.64 [0.86, 3.15]	249	>0.05	67.05	[0, 2245.45]	No/No	No	1.64	NS	NS
Celano, 2015 ³	Anxiety disorder	Coronary artery disease	Major cardiac events	7	OR, 1.23 [0.76, 1.99]	1,067	>0.05	72.52	[0.25, 6.06]	No/No	No	1.23	NS	NS
Taggart Wasson, 2018 ⁵	Post-traumatic stress disorder	Myocardial infarction	Medication nonadherence	2	OR, 4.29 [0.99, 18.56]	76	>0.05	30.16	NA	NA/NA	No	4.29	NS	NS
Neurotic, stress-related and somatoform disorders and other physical diseases														
Guo, 2021 ⁷	Anxiety disorder	Parkinson's disease	Cognitive impairment	2	RR, 2.59 [1.18, 5.68]	132	1.8e-02	0.00	NA	NA/NA	Yes	2.59	IV	IV
Wang, 2020 ⁹	Anxiety disorder	Breast cancer	Cancer recurrence	3	HR, 1.16 [1.01, 1.34]	1,213	3.4e-02	0.00	[1.02, 1.39]	No/No	Yes	1.16	IV	IV
Li, 2016 ⁸	Anxiety disorder	Neurological diseases with mild cognitive impairment	Alzheimer's disease progression	2	RR, 1.06 [0.34, 3.33]	113	>0.05	91.22	NA	NA/NA	No	1.06	NS	NS

CE—Class of evidence, CES — Class of evidence after sensitivity analysis (removing the n>1000 cases criterion, C I— Confidence interval, eOR—Equivalent odds ratio, ESB — Excess significance bias, ES — Effect size, HR — Hazard ratio, k—Number of samples for each association, LS — Largest study with significant effect, N cases— Number of cases for each association, NA— Not assessable, NS—Not significant, OR—Odds ratio, RR— Risk ratio, PI— Prediction interval, SSE— Small study effect.

eTable 5 Level of evidence for the association between mood affective disorders and secondary outcomes of physical diseases

Study	Mental disorder	Physical Disorder	Outcome	k	Random-effects measure, ES (95% CI)	N cases	p random effects	I ² %	PI (95% CI)	SSE/ESB	LS	eOR	CE	CES
Mood affective disorders and cardiovascular diseases (including stroke)														
Meijer, 2011 ²⁰	Depressive disorders	Myocardial infarction	Major cardiac events	15	OR, 1.52 [1.36, 1.70]	1,958	3.3e-13	24.35	[1.15, 1.92]	No/Yes	Yes	1.52	II	II
Blöchl, 2019 ²³	Depressive disorders	Stroke	Poor functional outcome	4	OR, 2.15 [1.51, 3.07]	603	2.3e-05	28.13	[0.64, 7.26]	No/Yes	Yes	2.15	IV	III
Rutledge, 2016 ¹⁹	Depressive disorders	Heart failure	Major cardiac events	6	RR, 2.12 [1.66, 2.72]	173	2.3e-09	0.00	[1.50, 3.01]	No/Yes	Yes	2.12	IV	II
Shi, 2017 ¹⁵	Depressive disorders	Coronary artery disease	Atrial fibrillation recurrence	2	HR, 1.85 [1.51, 2.26]	33	1.6e-09	0.00	NA	NA/NA	Yes	1.85	IV	II
Wu, 2019 ²⁷	Depressive disorders	Stroke	Stroke recurrence	5	RR, 1.59 [1.29, 1.95]	464	1.0e-05	0.00	[1.14, 2.22]	Yes/Yes	Yes	1.59	IV	III
Zhang, 2019 ²¹	Depressive disorders	Percutaneous coronary intervention	Major cardiac events	7	RR, 1.57 [1.27, 1.94]	714	2.8e-05	44.15	[0.96, 2.58]	No/Yes	Yes	1.57	IV	III
Shi, 2017 ¹⁵	Depressive disorders	Coronary artery disease	Ventricular tachycardia/fibrillation	6	HR, 1.49 [1.22, 1.82]	453	7.8e-05	24.35	[1.13, 1.97]	No/Yes	Yes	1.49	IV	III
Wu, 2016 ¹⁴	Depressive disorders	Coronary artery disease	Myocardial infarction	8	HR, 1.33 [1.09, 1.63]	3,781	5.3e-03	80.91	[0.75, 2.37]	Yes/Yes	Yes	1.33	IV	IV
Mood affective disorders and endocrine system diseases														
Chow, 2022 ²⁹	Depressive disorders	Diabetes mellitus	Dementia	5	HR, 2.11 [1.77, 2.52]	95,097	8.5e-17	84.15	[1.21, 3.67]	No/No	Yes	2.11	II	II
Farooqi, 2019 ³⁰	Depressive disorders	Diabetes mellitus	Coronary artery disease	4	HR, 1.35 [1.13, 1.6]	862	6.9e-04	34.97	[0.92, 1.96]	Yes/No	Yes	1.35	IV	III
Farooqi, 2019 ³⁰	Depressive disorders	Diabetes mellitus	Stroke	2	HR, 1.96 [0.85, 4.55]	40,845	>0.05	92.17	NA	NA/NA	Yes	1.96	NS	NS
Mood affective disorders and cancer														
Satin, 2009 ³⁵	Depressive disorders	Cancer	Cancer progression	3	RR, 1.23 [0.85, 1.77]	538	>0.05	0.00	[0.11, 13.2]	No/No	No	1.23	NS	NS
Wang, 2020 ⁹	Depressive disorders	Breast cancer	Cancer recurrence	5	HR, 1.18 [0.96, 1.45]	1,722	>0.05	42.11	[0.70, 1.99]	No/No	Yes	1.18	NS	NS
Mood affective disorders and other physical diseases														

Study	Mental disorder	Physical Disorder	Outcome	k	Random-effects measure, ES (95% CI)	N cases	p random effects	I ² %	PI (95% CI)	SSE/ESB	LS	eOR	CE	CES
Ruiz-Grosso, 2020 ³⁸	Depressive disorders	Tuberculosis	Negative outcomes in treatment	2	OR, 4.21 [2.33, 7.58]	146	1.7e-06	0.00	NA	NA/NA	Yes	4.21	IV	III
Scott, 2018 ⁴⁰	Depressive disorders	Human immunodeficiency virus infection	Pain	2	HR, 2.26 [1.47, 3.46]	131	1.9e-04	39.93	NA	NA/NA	No	2.26	IV	III
Schoultz, 2020 ³⁹	Depressive disorders	Inflammatory bowel disease	Symptom exacerbation	2	HR, 1.05 [1.01, 1.10]	156	2.1e-02	0.00	NA	NA/NA	No	1.05	IV	IV
Murao, 2016 ³⁷	Depressive disorders	Mild cognitive impairment	Dementia progression	3	RR, 1.48 [0.77, 2.84]	58	>0.05	83.95	[0, 2925.66]	No/No	No	1.48	NS	NS
Li, 2016 ⁸	Depressive disorders	Mild cognitive impairment	Alzheimer's disease progression	5	RR, 1.31 [0.77, 2.22]	1,121	>0.05	83.74	[0.20, 8.33]	No/No	Yes	1.31	NS	NS
Guo, 2021 ⁷	Depressive disorders	Parkinson's disease	Cognitive impairment	2	RR, 0.43 [0.11, 1.65]	205	>0.05	84.2	NA	NA/NA	No	0.43	NS	NS

CE—Class of evidence, CES — Class of evidence after sensitivity analysis (removing the n>1000 cases criterion, CI — Confidence interval, eOR—Equivalent odds ratio, ESB — Excess significance bias, ES — Effect size, HR — Hazard ratio, k—Number of samples for each association, LS — Largest study with significant effect, N cases— Number of cases for each association, NA— Not assessable, NS—Not significant, OR—Odds ratio, RR— Risk ratio, PI— Prediction interval, SSE— Small study effect.

eTable 6 Level of evidence for the association between mental and behavioural disorders due to psychoactive substance use, schizophrenia, schizotypal and delusional disorders, organic, including symptomatic, mental disorders and secondary outcomes of physical diseases

Study	Mental disorder	Physical Disorder	Outcome	k	Random-effects measure, ES (95% CI)	N cases	p random effects	I ² %	PI (95% CI)	SSE/ESB	LS	eOR	CE	CES
Mental and behavioural disorders due to psychoactive substance use and infectious diseases														
Llamosas -Falcón, 2020 ⁴¹	Alcohol use disorder	Hepatitis C virus infection	Decompensated liver cirrhosis	2	RR, 3.15 [2.87, 3.46]	6,113	7.9e-131	0.00	NA	NA/NA	Yes	3.15	II	II
Llamosas -Falcón, 2020 ⁴¹	Alcohol use disorder	Hepatitis C virus infection	Negative course liver disease	3	RR, 3.83 [1.24, 11.85]	6,218	2.0e-02	87.37	[0.00,36211 21.27]	No/Yes	Yes	3.83	IV	IV
Schizophrenia, schizotypal and delusional disorders and cardiovascular diseases and cancer														
No secondary outcomes														
Organic, including symptomatic, mental disorders and infectious, cardiovascular diseases, musculoskeletal system and connective tissue, and neurological disorders														
Ding, 2021 ⁴⁶	Dementia	Stroke	Delirium	7	OR, 5.90 [3.95, 8.83]	284	5.7e-18	0.00	[3.48,10.01]	No/No	Yes	5.90	IV	I
Guo, 2021 ⁷	Alzheimer's disease	Parkinson's disease	Cognitive impairment	2	RR, 0.09 [0.00, 6.26]	22	>0.05	94.36	NA	NA/NA	No	0.09	NS	NS

CE—Class of evidence, CES — Class of evidence after sensitivity analysis (removing the n>1000 cases criterion, CI — Confidence interval, eOR—Equivalent odds ratio, ESB — Excess significance bias, ES — Effect size, HR — Hazard ratio, k—Number of samples for each association, LS — Largest study with significant effect, N cases— Number of cases for each association, NA— Not assessable, NS—Not significant, OR—Odds ratio, RR— Risk ratio, PI— Prediction interval, SMR—standardized mortality ratio, SSE— Small study effect.

eTable 7 Subgroup analyses for associations of mental disorders and outcomes of physical diseases supported by convincing and highly suggestive (I and II) class of evidence

Subgroup	k	Random-effects measure, ES (95% CI)	N cases	p random effects	I ² %	PI (95% CI)	SSE/ES B	LS	eOR	CE/ CES
Mood affective disorders and cardiovascular diseases (including stroke)										
Depressive disorders / Heart failure/ All-cause mortality ¹⁸										
a) Diagnostic method										
Standard diagnostic criteria		No data available or only one study								
Research criteria		No data available or only one study								
Validated assessment instruments with cut-offs that map onto discrete categories	3	HR, 1.43 [1.22, 1.67]	896	1.2e-05	0.00	[0.51, 4.00]	No/No	Yes	1.43	I/IV
b) Timing of mental diagnosis										
Diagnosis of mental disorder before the diagnosis of physical disease		No data available or only one study								
Diagnosis of mental disorder after the diagnosis of physical disease	3	HR, 1.43 [1.22, 1.67]	896	1.2e-05	0.00	[0.51, 4.00]	No/No	Yes	1.43	I/IV
c) Follow-up duration										
>5 years		No data available or only one study								
≤5 years	4	HR, 1.44 [1.26, 1.65]	1,377	1.4e-07	0.00	[1.07, 1.94]	No/No	Yes	1.44	I/I
d) Type of estimates										
Adjusted estimates	4	HR, 1.44 [1.26, 1.65]	1,377	1.4e-07	0.00	[1.07, 1.94]	No/No	Yes	1.44	I/I
Unadjusted estimates		No data available or only one study								
e) Age of participants										
<50 years old		No data available or only one study								
≥50 years old	4	HR, 1.44 [1.26, 1.65]	1,377	1.4e-07	0.00	[1.07, 1.94]	No/No	Yes	1.44	I/I
f) Exposure to psychiatric medications										
Yes	2	HR, 1.43 [1.19, 1.71]	794	1.1e-04	0.00	NA	NA/NA	Yes	1.43	I/IV
No		No data available or only one study								
g) Sex										
Majority of male	3	HR, 1.43 [1.22, 1.67]	896	1.2e-05	0.00	[0.51, 4.00]	No/No	Yes	1.43	I/IV
Majority of female		No data available or only one study								
Depressive disorders /Myocardial infraction/Major cardiac events ²⁰										
a) Diagnostic method										

Subgroup	k	Random-effects measure, ES (95% CI)	N cases	p random effects	I ² %	PI (95% CI)	SSE/ES B	LS	eOR	CE/ CES
Standard diagnostic criteria		No data available or only one study								
Research criteria	4	OR, 1.69 [0.38, 7.44]	142	>0.05	69.66	[0.00, 980.31]	No/No	No	1.69	II/NS
Validated assessment instruments with cut-offs that map onto discrete categories	11	OR, 1.51 [1.35, 1.7]	1,816	3.0e-12	0.00	[1.32, 1.73]	No/Yes	Yes	1.51	II/II
<i>b) Timing of mental diagnosis</i>										
Diagnosis of mental disorder before the diagnosis of physical disease		No data available or only one study								
Diagnosis of mental disorder after the diagnosis of physical disease	15	OR, 1.52 [1.36, 1.7]	1,958	3.3e-13	24.35	[1.34, 1.72]	No/Yes	Yes	1.52	II/II
<i>c) Follow-up duration</i>										
>5 years		No data available or only one study								
≤5 years	15	OR, 1.52 [1.36, 1.7]	1,958	3.3e-13	24.35	[1.34, 1.72]	No/Yes	Yes	1.52	II/II
<i>d) Type of estimates</i>										
Adjusted estimates		No data available or only one study								
Unadjusted estimates	15	OR, 1.52 [1.36, 1.7]	1,958	3.3e-13	24.35	[1.34, 1.72]	No/Yes	Yes	1.52	II/II
<i>e) Age of participants</i>										
<50 years old		No data available or only one study								
≥50 years old	13	OR, 1.53 [1.33, 1.76]	1,337	1.8e-09	29.6	[1.31, 1.8]	No/No	Yes	1.53	II/I
<i>f) Exposure to psychiatric medications</i>										
Yes		No data available or only one study								
No		No data available or only one study								
<i>g) Sex</i>										
Majority of male	13	OR, 1.53 [1.33, 1.76]	1,337	1.8e-09	29.6	[1.31, 1.8]	No/No	Yes	1.53	II/I
Majority of female		No data available or only one study								
Mood affective disorders and endocrine system diseases										
Depressive disorders/ Kidney failure/All-cause mortality ³³										
<i>a) Diagnostic method</i>										
Standard diagnostic criteria		No data available or only one study								
Research criteria		No data available or only one study								
Validated assessment instruments with cut-offs that map onto discrete categories	5	HR, 1.41 [1.30, 1.53]	221	1.4e-16	29.65	[1.24, 1.62]	No/Yes	Yes	1.41	II/IV
<i>b) Timing of mental diagnosis</i>										

Subgroup	k	Random-effects measure, ES (95% CI)	N cases	p random effects	I ² %	PI (95% CI)	SSE/ES B	LS	eOR	CE/ CES
Diagnosis of mental disorder before the diagnosis of physical disease	2	HR, 1.41 [1.31, 1.52]	1,613	1.8e-18	0.00	NA	NA/NA	Yes	1.41	II/II
Diagnosis of mental disorder after the diagnosis of physical disease	4	HR, 1.71 [1.16, 2.5]	221	6.4e-03	46.86	[0.42, 7.00]	Yes/Yes	Yes	1.71	II/IV
<i>c) Follow-up duration</i>										
>5 years	2	HR, 1.92 [1.2, 3.06]	83	6.3e-03	0.00	NA	NA/NA	Yes	1.92	II/IV
≤5 years	4	HR, 1.40 [1.30, 1.50]	1,751	1.9e-21	16.31	[1.20, 1.62]	No/Yes	Yes	1.40	II/IV
<i>d) Type of estimates</i>										
Adjusted estimates	6	HR, 1.41 [1.31, 1.51]	1,834	1.0e-22	12.85	[1.28, 1.55]	Yes/Yes	Yes	1.41	II/II
Unadjusted estimates	No data available or only one study									
<i>e) Age of participants</i>										
<50 years old	No data available or only one study									
≥50 years old	3	HR, 1.91 [1.03, 3.55]	165	4.1e-02	61.19	[0, 1623.27]	Yes/Yes	Yes	1.91	II/IV
<i>f) Exposure to psychiatric medications</i>										
Yes	No data available or only one study									
No	No data available or only one study									
<i>g) Sex</i>										
Majority of male	3	HR, 1.92 [1.08, 3.42]	1,664	2.7e-02	56.91	[0.00, 959.04]	No/Yes	Yes	1.92	II/IV
Majority of female	No data available or only one study									
Depressive disorders/Diabetes mellitus/All-cause mortality ³²										
<i>a) Diagnostic method</i>										
Standard diagnostic criteria	6	HR, 1.54 [1.09, 2.18]	3,725	1.4e-02	85.18	[0.48, 4.99]	No/Yes	No	1.54	II/IV
Research criteria	No data available or only one study									
Validated assessment instruments with cut-offs that map onto discrete categories	6	HR, 2.57 [1.82, 3.64]	1,872	9.9e-08	88.08	[0.81, 8.19]	No/No	Yes	2.57	II/II
<i>b) Timing of mental diagnosis</i>										
Diagnosis of mental disorder before the diagnosis of physical disease	No data available or only one study									
Diagnosis of mental disorder after the diagnosis of physical disease	2	HR, 2.57 [0.73, 9.03]	783	>0.05	96.65	NA	NA/NA	Yes	2.57	II/NS
<i>c) Follow-up duration</i>										
>5 years	5	HR, 2.81 [1.82, 4.34]	1,828	3.2e-06	92.39	[0.53, 14.85]	No/No	Yes	2.81	II/III

Subgroup	k	Random-effects measure, ES (95% CI)	N cases	p random effects	I ² %	PI (95% CI)	SSE/ES B	LS	eOR	CE/ CES
≤5 years	2	HR, 2.79 [1.71, 4.54]	280	3.8e-05	0.00	NA	NA/NA	Yes	2.79	II/IV
<i>d) Type of estimates</i>										
Adjusted estimates	7	HR, 2.84 [2.00, 4.03]	2,108	4.7e-09	88.81	[0.88, 9.15]	No/No	Yes	2.84	II/II
Unadjusted estimates		No data available or only one study								
<i>e) Age of participants</i>										
<50 years old		No data available or only one study								
≥50 years old	4	HR, 2.91 [2.27, 3.73]	1,312	2.7e-17	64.63	[1.07, 7.96]	No/No	Yes	2.91	II/II
<i>f) Exposure to psychiatric medications</i>										
Yes		No data available or only one study								
No		No data available or only one study								
<i>g) Sex</i>										
Majority of male	4	HR, 2.46 [1.46, 4.13]	1,305	7.0e-04	89.37	[0.24, 25.3]	No/Yes	Yes	2.46	I/III
Majority of female	3	HR, 3.49 [2.51, 4.86]	803	1.4e-13	57.37	[0.1, 124.03]	No/No	Yes	3.49	I/IV
Depressive disorders/Diabetes mellitus /Dementia²⁹										
<i>a) Diagnostic method</i>										
Standard diagnostic criteria	3	HR, 1.99 [1.62, 2.45]	94,793	3.8e-11	90.16	[0.19, 21.4]	No/No	Yes	1.99	II/II
Research criteria		No data available or only one study								
Validated assessment instruments with cut-offs that map onto discrete categories	2	HR, 2.63 [1.90, 3.64]	304	6.0e-09	0.00	NA	NA/NA	Yes	2.63	II/IV
<i>b) Timing of mental diagnosis</i>										
Diagnosis of mental disorder before the diagnosis of physical disease	3	HR, 1.99 [1.62, 2.45]	94,793	3.8e-11	90.16	[0.19, 21.4]	No/No	Yes	1.99	II/II
Diagnosis of mental disorder after the diagnosis of physical disease	2	HR, 2.63 [1.90, 3.64]	304	6.0e-09	0.00	NA	NA/NA	Yes	2.63	II/IV
<i>c) Follow-up duration</i>										
>5 years	5	HR, 2.11 [1.77, 2.52]	95,097	8.5e-17	84.15	[1.21, 3.67]	No/No	Yes	2.11	II/II
≤5 years		No data available or only one study								
<i>d) Type of estimates</i>										
Adjusted estimates	5	HR, 2.11 [1.77, 2.52]	95,097	8.5e-17	84.15	[1.21, 3.67]	No/No	Yes	2.11	II/II
Unadjusted estimates		No data available or only one study								
<i>e) Age of participants</i>										
<50 years old		No data available or only one study								

Subgroup	k	Random-effects measure, ES (95% CI)	N cases	p random effects	I ² %	PI (95% CI)	SSE/ES B	LS	eOR	CE/ CES
≥50 years old	5	HR, 2.11 [1.77, 2.52]	95,097	8.5e-17	84.15	[1.21, 3.67]	No/No	Yes	2.11	II/II
<i>f) Exposure to psychiatric medications</i>										
Yes		No data available or only one study								
No		No data available or only one study								
<i>g) Sex</i>										
Majority of male	5	HR, 2.11 [1.77, 2.52]	95,097	8.5e-17	84.15	[1.21, 3.67]	No/No	Yes	2.11	II/II
Majority of female		No data available or only one study								
Mental and behavioural disorders due to psychoactive substance use and infectious diseases										
Alcohol use disorder/ Hepatitis C virus infection/ Decompensated liver cirrhosis⁴¹										
<i>a) Diagnostic method</i>										
Standard diagnostic criteria	2	OR, 3.15 [2.87, 3.46]	6,113	7.9e-131	0.00	NA	NA/NA	Yes	3.15	II/II
Research criteria		No data available or only one study								
Validated assessment instruments with cut-offs that map onto discrete categories		No data available or only one study								
<i>b) Timing of mental diagnosis</i>										
Diagnosis of mental disorder before the diagnosis of physical disease		No data available or only one study								
Diagnosis of mental disorder after the diagnosis of physical disease	2	OR, 3.15 [2.87, 3.46]	6,113	7.9e-131	0.00	NA	NA/NA	Yes	3.15	II/II
<i>c) Follow-up duration</i>										
>5 years		No data available or only one study								
≤5 years		No data available or only one study								
<i>d) Type of estimates</i>										
Adjusted estimates	2	OR, 3.15 [2.87, 3.46]	6,113	7.9e-131	0.00	NA	NA/NA	Yes	3.15	II/II
Unadjusted estimates		No data available or only one study								
<i>e) Age of participants</i>										
<50 years old		No data available or only one study								
≥50 years old		No data available or only one study								
<i>f) Exposure to psychiatric medications</i>										
Yes		No data available or only one study								
No		No data available or only one study								
<i>g) Sex</i>										

Subgroup	k	Random-effects measure, ES (95% CI)	N cases	p random effects	I ² %	PI (95% CI)	SSE/ES B	LS	eOR	CE/ CES
Majority of male		No data available or only one study								
Majority of female		No data available or only one study								
Schizophrenia, schizotypal and delusional disorders and cardiovascular diseases and cancer										
Schizophrenia/ Cardiovascular diseases/ Cardiovascular mortality ¹⁰										
a) Diagnostic method										
Standard diagnostic criteria	6	RR, 1.54 [1.35, 1.76]	8,356	1.1e-10	39.62	[1.15, 2.07]	No/No	No	1.54	I/I
Research criteria		No data available or only one study								
Validated assessment instruments with cut-offs that map onto discrete categories		No data available or only one study								
b) Timing of mental diagnosis										
Diagnosis of mental disorder before the diagnosis of physical disease	7	RR, 1.54 [1.36, 1.75]	9,097	2.2e-11	27.82	[1.19, 2.00]	No/No	No	1.54	I/I
Diagnosis of mental disorder after the diagnosis of physical disease		No data available or only one study								
c) Follow-up duration										
>5 years	3	RR, 1.91 [1.22, 2.98]	7,338	4.4e-03	55.45	[0.02, 210.9]	No/No	Yes	1.91	I/IV
≤5 years	4	RR, 1.46 [1.29, 1.66]	1,759	1.3e-09	0.00	[1.05, 2.04]	No/No	No	1.46	I/I
d) Type of estimates										
Adjusted estimates	5	RR, 1.78 [1.22, 2.61]	2,299	2.8e-03	49.05	[0.59, 5.40]	No/No	No	1.78	I/IV
Unadjusted estimates		No data available or only one study								
e) Age of participants										
<50 years old	2	RR, 1.56 [1.32, 1.84]	646	1.5e-07	0.00	NA	NA/NA	Yes	1.56	I/IV
≥50 years old	3	RR, 1.43 [1.27, 1.61]	7,391	5.0e-09	0.00	[0.66, 3.11]	No/No	No	1.43	I/III
f) Exposure to psychiatric medications										
Yes	4	RR, 1.92 [1.31, 2.81]	1,039	8.8e-04	41.35	[0.47, 7.75]	No/No	No	1.92	I/III
No		No data available or only one study								
g) Sex										
Majority of male	4	RR, 1.53 [1.34, 1.74]	8,156	2.2e-10	60.39	[0.98, 2.38]	No/No	Yes	1.53	I/I
Majority of female	2	RR, 1.89 [0.97, 3.70]	200	>0.05	0.00	NA	NA/NA	No	1.89	I/NS
Schizophrenia/Cancer/Cancer mortality ⁴³										
a) Diagnostic method										
Standard diagnostic criteria	3	SMR, 1.74 [1.41, 2.15]	6,145	2.9e-07	66.53	[0.17, 17.56]	No/No	Yes	1.74	II/II

Subgroup	k	Random-effects measure, ES (95% CI)	N cases	p random effects	I ² %	PI (95% CI)	SSE/ES B	LS	eOR	CE/ CES
Research criteria		No data available or only one study								
Validated assessment instruments with cut-offs that map onto discrete categories		No data available or only one study								
<i>b) Timing of mental diagnosis</i>										
Diagnosis of mental disorder before the diagnosis of physical disease	3	SMR, 1.74 [1.41, 2.15]	6,145	2.9e-07	66.53	[0.17, 17.56]	No/No	Yes	1.74	II/II
Diagnosis of mental disorder after the diagnosis of physical disease		No data available or only one study								
<i>c) Follow-up duration</i>										
>5 years	3	SMR, 1.74 [1.41, 2.15]	6,145	2.9e-07	66.53	[0.17, 17.56]	No/No	Yes	1.74	II/II
≤5 years		No data available or only one study								
<i>d) Type of estimates</i>										
Adjusted estimates		No data available or only one study								
Unadjusted estimates		No data available or only one study								
<i>e) Age of participants</i>										
<50 years old		No data available or only one study								
≥50 years old		No data available or only one study								
<i>f) Exposure to psychiatric medications</i>										
Yes	2	SMR, 1.52 [1.25, 1.85]	108	3.5e-05	0.00	NA	NA/NA	Yes	1.52	II/IV
No		No data available or only one study								
<i>g) Sex</i>										
Majority of male	3	SMR, 1.80 [1.47, 2.22]	6141	2.8e-08	60.13	[0.19, 16.78]	No/No	Yes	1.80	II/II
Majority of female		No data available or only one study								

CE—Class of evidence, CES — Class of evidence after subgroup analysis, CI — Confidence interval, eOR—Equivalent odds ratio, ESB — Excess significance bias, ES — Effect size, HR — Hazard ratio, k—Number of samples for each association, LS — Largest study with significant effect, N cases— Number of cases for each association, NA— Not assessable, NS—Not significant, OR—Odds ratio, RR— Risk ratio, PI— Prediction interval, SMR—standardized mortality ratio, SSE— Small study effect.

eMethods 1. Search strategy

PubMed: (Somatic disease OR Cardiovascular Diseases OR coronary disease OR Coronary Heart Disease OR Heart Failure OR Myocardial Failure OR myocardial infarction OR Rheumatic Heart Disease OR stroke OR CAD OR abnormal heart rhythms OR arrhythmia OR sudden cardiac death OR cerebrovascular disease OR cerebrovascular diseases OR cerebro vascular disease OR cerebro vascular diseases OR cerebral vascular disease OR cerebral vascular diseases OR hypertension OR hypertensive OR myocarditis OR angina OR transient ischemic attack OR transient ischemic attacks OR transient ischaemic attack OR peripheral artery disease OR peripheral artery diseases OR hypertrophic cardiomyopathy OR chronic respiratory diseases OR pulmonary hypertension OR pneumonia OR asthma OR asthmatic OR chronic obstructive pulmonary disease OR chronic obstructive pulmonary diseases OR COPD OR obstructive sleep apnea syndrome OR neurocognitive disorder OR neurocognitive disorders OR Lewy Bodies OR Huntington Neurodegenerative Diseases OR multiple sclerosis OR Alzheimer Disease OR autoimmune encephalopathy OR paraneoplastic encephalitis OR peripheral neuropathy OR dementia OR Parkinson disease OR Amyotrophic Lateral Sclerosis OR ALS OR epilepsy OR epileptic OR seizure OR seizures OR Obesity OR obese OR overweight OR over weight OR dyslipidemia OR Cushing OR hidradenitis suppurativa OR metabolic syndrome OR chronic renal failure OR myeloproliferative disorder OR myeloproliferative disorders OR diabetes mellitus OR diabetes OR diabetic OR thyroid disorder OR thyroid disorders OR sarcoidosis OR liver disease OR liver diseases OR functional gastrointestinal disorder OR functional gastrointestinal disorders OR ulcerative colitis OR Crohn disease OR gastroesophageal reflux disease OR gastroesophageal reflux diseases OR GERD OR chronic pancreatitis OR chronic kidney disease OR kidney disease OR kidney diseases OR acute kidney injury OR acute kidney injuries OR dialysis OR benign prostatic hyperplasia OR kidney stone OR kidney stones OR Neoplasm OR Neoplasms OR cancer OR cancers OR tumor OR tumors OR liver disease cirrhosis OR Irritable bowel syndrome OR vitiligo OR acne OR melanoma OR systemic lupus OR atopic eczema OR celiac disease OR ankylosing spondylitis OR Bechterew OR psoriasis OR rheumatoid arthritis OR RA OR inflammatory bowel disease OR Graves disease OR osteoporosis OR fracture OR fractures OR lymphoma OR anemia OR anemias OR anaemia OR anaemias OR HIV/AIDS OR infectious OR infection OR virus infection OR musculoskeletal disorders OR low back pain OR fibromyalgia OR osteoarthritis OR arthritis OR chronic pain) AND ("Mental Disorders"[Mesh] OR mental disorder OR mental disorders OR psychiatric disorder OR psychiatric disorders OR psychopathological disorder OR psychopathological disorders OR psychopathological condition OR psychopathological conditions OR ADHD OR attention-deficit hyperactivity disorder OR attention deficit OR hyperkinetic disorder OR hyperkinetic syndrome OR Autism OR autistic OR Asperger OR neurodevelopmental disorder OR neurodevelopmental disorders OR Intellectual Disability OR Intellectual Disabilities OR mental retardation OR learning disability OR Schizophrenia OR schizophrenic OR psychotic disorder OR psychotic disorders OR psychosis OR Schizotypal OR Delusional Disorder OR Brief Psychotic Disorder OR Schizophreniform Disorder OR Schizoaffective disorder OR Bipolar disorder OR bipolar disorders OR Depression OR depressive OR mood OR Anxiety OR anxious OR panic disorder OR agoraphobia OR Obsessive-compulsive disorder OR Obsessive compulsive disorder OR OCD OR PTSD OR Trauma-related disorder OR Trauma-related disorders OR Stress-related disorder OR Stress-related disorders OR Substance-related disorder OR Substance-related disorders OR addictive disorder OR addiction disorders OR drug abuse OR eating disorder OR eating disorders OR anorexia OR bulimia OR binge-eating OR binge eating OR sleep disorder OR sleep disorders OR sleep disturbance OR sleep disturbances OR insomnia OR Body Dysmorphic Disorder OR Trichotillomania OR Hair-Pulling Disorder OR Excoriation Disorder OR Skin-Picking Disorder OR dissociative disorder OR dissociative disorders Dissociative Identity Disorder OR Restless Legs Syndrome OR Gender Dysphoria OR Personality disorder OR Personality disorders OR Antisocial Personality Disorder OR Paranoid Personality Disorder OR Schizoid Personality Disorder OR Schizotypal Personality Disorder OR Borderline Personality Disorder OR Histrionic Personality Disorder OR Narcissistic Personality Disorder OR Avoidant Personality Disorder OR Dependent Personality Disorder OR Obsessive-Compulsive Personality Disorder) AND ("Mortality"[Mesh] OR "mortality*" [tiab] OR "mortality rate*" [tiab] OR "death"[MeSH Terms] OR "death*" [tiab] OR "death rate*" [tiab] OR "crude death rate*" [tiab] OR "age-specific death rate*" [tiab] OR "survival"[MeSH Terms] OR "survival*" [tiab] OR

"prognosis"[MeSH Terms] OR "prognosis"[tiab] OR disability [tiab] OR disease-specific symptom severity [tiab] OR "disability-adjusted life years") AND ("Systematic Review"[Publication Type:NoExp] OR "Systematic Reviews as Topic"[mesh:noexp] OR "meta-analysis as topic"[MESH:NOEXP] OR "Meta-Analysis"[Publication Type:NoExp] OR "meta analyses"[ot] OR "meta analyses"[Title/Abstract] OR "meta analysis"[Title/Abstract] OR "meta analysis"[Title/Abstract] OR "meta analytic"[ot] OR "meta analytic"[Title/Abstract] OR "meta analytical"[ot] OR "meta analytical"[Title/Abstract] OR "meta analytics"[Title/Abstract] OR "meta analyze"[ot] OR "meta analyze"[Title/Abstract] OR ("meta"[ot] AND "analyzed"[ot]) OR "meta analyzed"[Title/Abstract] OR "meta regression"[Title/Abstract] OR "metaanalyses"[ot] OR "metaanalyses"[Title/Abstract] OR "metaanalysis"[ot] OR "metaanalysis"[Title/Abstract] OR "metaanalytic"[Title/Abstract] OR "metaanalyze"[Title/Abstract] OR "metaanalyzed"[Title/Abstract])

EMBASE: #1 somatic AND ('disease/exp OR disease) OR 'cardiovascular disease' OR 'coronary artery disease' OR 'ischemic heart disease' OR 'heart failure' OR 'heart infarction' OR 'rheumatic heart disease' OR 'cerebrovascular accident' OR 'heart arrhythmia' OR 'sudden cardiac death' OR 'cerebrovascular disease' OR 'hypertension' OR 'myocarditis' OR 'angina pectoris' OR 'transient ischemic attack' OR 'peripheral occlusive artery disease' OR 'hypertrophic cardiomyopathy' OR 'chronic respiratory tract disease' OR 'pulmonary hypertension' OR 'pneumonia' OR 'asthma' OR 'chronic obstructive lung disease' OR 'sleep disordered breathing' OR 'disorders of higher cerebral function' OR 'lewy body' OR 'parkinson disease' OR 'huntington chorea' OR 'multiple sclerosis' OR 'alzheimer disease' OR 'autoimmune encephalitis' OR 'paraneoplastic encephalitis' OR 'peripheral neuropathy' OR 'dementia' OR 'amyotrophic lateral sclerosis' OR 'epilepsy' OR 'seizure' OR 'obesity' OR 'dyslipidemia' OR 'cushing syndrome' OR 'suppurative hidradenitis' OR 'metabolic disorder' OR 'chronic kidney failure' OR 'myeloproliferative disorder' OR 'diabetes mellitus' OR 'non insulin dependent diabetes mellitus' OR 'insulin dependent diabetes mellitus' OR 'thyroid disease' OR 'sarcoidosis' OR 'liver disease' OR 'digestive system function disorder' OR 'ulcerative colitis' OR 'crohn disease' OR 'pancreas disease' OR 'dialysis' OR 'prostate hypertrophy' OR 'nephrolithiasis' OR 'neoplasm' OR 'malignant neoplasm' OR 'liver cirrhosis' OR 'irritable colon' OR 'vitiligo' OR 'acne' OR 'melanoma' OR 'systemic lupus erythematosus' OR 'atopic dermatitis' OR 'celiac disease' OR 'ankylosing spondylitis' OR 'inflammatory bowel disease' OR 'graves disease' OR 'osteoporosis' OR 'fracture' OR 'lymphoma' OR 'anemia' OR 'human immunodeficiency virus' OR 'infection' OR 'virus infection' OR 'musculoskeletal disorders' OR 'chronic pain' OR 'low back pain' OR 'fibromyalgia' OR 'osteoarthritis' OR 'arthritis'

#2 'mental disease' OR 'attention deficit hyperactivity disorder' OR 'hyperkinetic disorder' OR 'autism' OR 'asperger syndrome' OR 'schizophrenia' OR 'psychosis' OR 'bipolar disorder' OR 'depression' OR 'dysthymia' OR 'mood disorder' OR 'anxiety disorder' OR 'anxiety' OR 'obsessive compulsive disorder' OR 'posttraumatic stress disorder' OR 'stress related disorder' OR 'drug dependence' OR 'addiction' OR 'eating disorder' OR 'anorexia' OR 'bulimia' OR 'binge eating disorder' OR 'sleep disorder' OR 'insomnia' OR 'personality disorder' OR 'borderline state' OR 'body dysmorphic disorder' OR 'antisocial personality disorder' OR 'paranoid personality disorder' OR 'schizoidism' OR 'histrionic personality disorder' OR 'narcissism' OR 'avoidant personality disorder' OR 'compulsive personality disorder'

#3 'mortality ' OR 'mortality rate' OR 'mortality risk' OR 'survival' ' OR 'incidence' OR 'survival rate' OR 'death' OR 'prognosis' OR 'function' OR 'disability' OR 'symptom severity' OR 'quality of life' OR 'disability-adjusted life year'

#4 'systematic review' OR 'systematic review (topic)' OR 'meta analysis' OR 'meta analysis (topic)'

#1 AND #2 AND #3 AND #4 AND ([systematic review]/lim OR [meta analysis]/lim)

APA PsycInfo: (somatic disease or cardiovascular diseases or coronary disease or coronary heart disease or heart failure or myocardial failure or myocardial infarction or rheumatic heart disease or stroke or cad or abnormal heart rhythms or arrhythmia or sudden cardiac death or cerebrovascular disease or cerebrovascular diseases or cerebro vascular disease or cerebro vascular diseases or cerebral vascular disease or cerebral vascular diseases or hypertension or hypertensive or

myocarditis or angina or transient ischemic attack or transient ischemic attacks or transient ischaemic attack or peripheral artery disease or peripheral artery diseases or hypertrophic cardiomyopathy or chronic respiratory diseases or pulmonary hypertension or pneumonia or asthma or asthmatic or chronic obstructive pulmonary disease or chronic obstructive pulmonary diseases or copd or obstructive sleep apnea syndrome or neurocognitive disorder or neurocognitive disorders or lewy bodies or huntington neurodegenerative diseases or multiple sclerosis or alzheimer disease or autoimmune encephalopathy or paraneoplastic encephalitis or peripheral neuropathy or dementia or parkinson disease or amyotrophic lateral sclerosis or als or epilepsy or epileptic or seizure or seizures or obesity or obese or overweight or over weight or dyslipidemia or cushing or hidradenitis suppurativa or metabolic syndrome or chronic renal failure or myeloproliferative disorder or myeloproliferative disorders or diabetes mellitus or diabetes or diabetic or thyroid disorder or thyroid disorders or sarcoidosis or liver disease or liver diseases or functional gastrointestinal disorder or functional gastrointestinal disorders or ulcerative colitis or crohn disease or gastroesophageal reflux disease or gastroesophageal reflux diseases or gerd or chronic pancreatitis or chronic kidney disease or kidney disease or kidney diseases or acute kidney injury or acute kidney injuries or dialysis or benign prostatic hyperplasia or kidney stone or kidney stones or neoplasm or neoplasms or cancer or cancers or tumor or tumors or liver disease cirrhosis or irritable bowel syndrome or vitiligo or acne or melanoma or systemic lupus or atopic eczema or celiac disease or ankylosing spondylitis or bechterew or psoriasis or rheumatoid arthritis or ra or inflammatory bowel disease or graves disease or osteoporosis or fracture or fractures or lymphoma or anemia or anemias or anaemia or anaemias or hiv/aids or infectious or infection or virus infection or musculoskeletal disorders or low back pain or fibromyalgia or osteoarthritis or arthritis or chronic pain) AND (mental health or mental illness or mental disorder or psychiatric illness) AND (survival or mortality or cancer or rejection or infection or hospitalization for health or treatment outcome) AND (meta-analysis or systematic review)

Expanders - Apply related words; Also search within the full text of the articles; Apply equivalent subjects

JB I database of systematic reviews and implementation reports: (Somatic disease OR Cardiovascular Diseases OR coronary disease OR Coronary Heart Disease OR Heart Failure OR Myocardial Failure OR myocardial infarction OR Rheumatic Heart Disease OR stroke OR CAD OR abnormal heart rhythms OR arrhythmia OR sudden cardiac death OR cerebrovascular disease OR cerebrovascular diseases OR cerebro vascular disease OR cerebro vascular diseases OR cerebral vascular disease OR cerebral vascular diseases OR hypertension OR hypertensive OR myocarditis OR angina OR transient ischemic attack OR transient ischemic attacks OR transient ischaemic attack OR peripheral artery disease OR peripheral artery diseases OR hypertrophic cardiomyopathy OR chronic respiratory diseases OR pulmonary hypertension OR pneumonia OR asthma OR asthmatic OR chronic obstructive pulmonary disease OR chronic obstructive pulmonary diseases OR COPD OR obstructive sleep apnea syndrome OR neurocognitive disorder OR neurocognitive disorders OR Lewy Bodies OR Huntington Neurodegenerative Diseases OR multiple sclerosis OR Alzheimer Disease OR autoimmune encephalopathy OR paraneoplastic encephalitis OR peripheral neuropathy OR dementia OR Parkinson disease OR Amyotrophic Lateral Sclerosis OR ALS OR epilepsy OR epileptic OR seizure OR seizures OR Obesity OR obese OR overweight OR over weight OR dyslipidemia OR Cushing OR hidradenitis suppurativa OR metabolic syndrome OR chronic renal failure OR myeloproliferative disorder OR myeloproliferative disorders OR diabetes mellitus OR diabetes OR diabetic OR thyroid disorder OR thyroid disorders OR sarcoidosis OR liver disease OR liver diseases OR functional gastrointestinal disorder OR functional gastrointestinal disorders OR ulcerative colitis OR Crohn disease OR gastroesophageal reflux disease OR gastroesophageal reflux diseases OR GERD OR chronic pancreatitis OR chronic kidney disease OR kidney disease OR kidney diseases OR acute kidney injury OR acute kidney injuries OR dialysis OR benign prostatic hyperplasia OR kidney stone OR kidney stones OR Neoplasm OR Neoplasms OR cancer OR cancers OR tumor OR tumors OR liver disease cirrhosis OR Irritable bowel syndrome OR vitiligo OR acne OR melanoma OR systemic lupus OR atopic eczema OR celiac disease OR ankylosing spondylitis OR Bechterew OR psoriasis OR rheumatoid arthritis OR RA OR inflammatory bowel disease OR Graves disease OR osteoporosis OR fracture OR fractures OR lymphoma OR anemia OR anemias OR anaemia OR anaemias OR HIV/AIDS OR infectious OR infection OR virus infection OR musculoskeletal disorders OR low back pain OR fibromyalgia OR osteoarthritis OR arthritis OR chronic pain) AND (mental

disorder OR mental disorders OR psychiatric disorder OR psychiatric disorders OR
 psychopathological disorder OR psychopathological disorders OR psychopathological condition OR
 psychopathological conditions OR ADHD OR attention-deficit hyperactivity disorder OR attention
 deficit OR hyperkinetic disorder OR hyperkinetic syndrome OR Autism OR autistic OR Asperger OR
 neurodevelopmental disorder OR neurodevelopmental disorders OR Intellectual Disability OR
 Intellectual Disabilities OR mental retardation OR learning disability OR Schizophrenia OR
 schizophrenic OR psychotic disorder OR psychotic disorders OR psychosis OR Schizotypal OR
 Delusional Disorder OR Brief Psychotic Disorder OR Schizophreniform Disorder OR Schizoaffective
 disorder OR Bipolar disorder OR bipolar disorders OR Depression OR depressive OR mood OR
 Anxiety OR anxious OR panic disorder OR agoraphobia OR Obsessive-compulsive disorder OR
 Obsessive compulsive disorder OR OCD OR PTSD OR Trauma-related disorder OR Trauma-related
 disorders OR Stress-related disorder OR Stress-related disorders OR Substance-related disorder OR
 Substance-related disorders OR addictive disorder OR addiction disorders OR drug abuse OR eating
 disorder OR eating disorders OR anorexia OR bulimia OR binge-eating OR binge eating OR sleep
 disorder OR sleep disorders OR sleep disturbance OR sleep disturbances OR insomnia OR Body
 Dysmorphic Disorder OR Trichotillomania OR Hair-Pulling Disorder OR Excoriation Disorder OR Skin-
 Picking Disorder OR dissociative disorder OR dissociative disorders Dissociative Identity Disorder OR
 Restless Legs Syndrome OR Gender Dysphoria OR Personality disorder OR Personality disorders
 OR Antisocial Personality Disorder OR Paranoid Personality Disorder OR Schizoid Personality
 Disorder OR Schizotypal Personality Disorder OR Borderline Personality Disorder OR Histrionic
 Personality Disorder OR Narcissistic Personality Disorder OR Avoidant Personality Disorder OR
 Dependent Personality Disorder OR Obsessive-Compulsive Personality Disorder) AND (mortality OR
 survival OR death* OR prognosis OR function OR disability OR disease-specific symptom severity,
 OR quality of life OR HRQOL OR disability-adjusted life years)

eResults 1. ROBIS assessments for Phase 2 across the four domains and for Phase 3

In phase 2 and in Domain 1: Study eligibility criteria, 35 (74.5%) of the systematic reviews with meta-analysis were evaluated as low risk, 11 (23.4%) as high risk, and one (2.1%) as unclear risk of bias. In Domain 2: Identification and selection of studies, 34 (72.3%) were evaluated as low risk, 10 (21.3%) as high risk, and three (6.4%) as unclear risk of bias. In Domain 3: Data collection and study appraisal, 26 (55.3%) were evaluated as low risk, 13 (27.6%) as high risk of bias, and eight (17.1%) as unclear risk. In Domain 4: Synthesis and findings, 31 (66%) were evaluated as low risk, 12 (25.5%) as high risk, and four (8.5%) as unclear risk of bias. In Phase 3, 32 (68.1%) systematic reviews with meta-analysis were evaluated as low risk, nine (19.1%) were evaluated as high risk, and six (12.8%) were evaluated as low unclear risk of bias.

eResults 2. Findings from other subgroup analyses

When restricting the analyses to studies formulating a diagnosis of mental disorder before the diagnosis of physical disease (NB: the clinical outcomes always followed the diagnosis of psychiatric disorders), the level of evidence of class I and II associations remained unchanged. When restricting the analyses to studies formulating a diagnosis of mental disorder after the diagnosis of physical disease, the class I and II associations between depression and all-cause mortality in patients with heart failure, kidney failure, and diabetes mellitus, as well as between depression and dementia in patients with diabetes mellitus were downgraded to weak evidence (class IV, number of primary studies, k, ranging from 2 to 4) or to non-significant level (NS, k=2 studies).

When restricting the analyses to follow-up duration >5 years, the class I association between schizophrenia and cardiovascular mortality in cardiovascular diseases and the class II associations between depression and all-cause mortality in kidney failure and diabetes mellitus were downgraded to suggestive or weak evidence (class III and IV, k ranging from 2 to 5). When restricting the analyses to follow-up duration ≤5 years, only the class II association between depression and all-cause mortality in diabetes mellitus was downgraded to weak (class IV, k=2 studies) evidence. There was no change in the level of evidence for the remaining associations.

When restricting the analyses to adjusted estimates, only the class I association between schizophrenia and cardiovascular mortality in cardiovascular diseases was downgraded to weak (class IV, k=5) evidence. There was no change in the level of evidence for the remaining

associations, as most of the included associations were preferably adjusted. When restricting to unadjusted estimates, there was no change in the level of evidence.

When restricting the analyses to age of participants <50 years old, the class I association between schizophrenia and cardiovascular mortality in cardiovascular diseases was downgraded to weak (class IV, k=2) evidence. When restricting the analyses to an age of participants ≥ 50 years old, the class I association between schizophrenia and cardiovascular mortality in cardiovascular diseases and the class II association between depression and all-cause mortality in kidney failure were downgraded to suggestive (class III) or weak evidence (class IV, k=3 studies per association)

When restricting the analyses to studies including in their samples a majority of males, the class I association between schizophrenia and cardiovascular mortality in cardiovascular diseases and between depression and all-cause mortality in heart failure were downgraded to highly suggestive (class II) or weak (class IV) evidence (k ranging from 3 to 4). The class II associations between depression and all-cause mortality in kidney failure and diabetes mellitus were downgraded to suggestive or weak evidence (class III and IV, k ranging from 3 to 4). When restricting the analyses to studies including in their samples a majority of females, the class II association between depression and all-cause mortality in diabetes mellitus was downgraded to weak evidence (class IV, k=3 studies).

However, it is important to note that all these subgroup analyses were conducted in a very small number of primary studies and are, therefore, highly underpowered.

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