

## Supplementary information

Elena Dragioti, Joaquim Radua, Marco Solmi, Corentin J. Gosling, Dominic Oliver, Filippo Lascialfari, Muhammad Ahmed, Samuele Cortese, Andrés Estradé, Gonzalo Arrondo, Mary Gouva, Michele Fornaro, Agapi Batiridou, Konstantina Dimou, Dimitrios Tsartsalis, Andre F. Carvalho, Jae Il Shin, Michael Berk, Silvia Stringhini, Christoph U. Correll, Paolo Fusar-Poli.

### **Impact of mental disorders on clinical outcomes of physical diseases: an umbrella review assessing population attributable fraction and generalized impact fraction “in press” in World Psychiatry, 2022**

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## 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 <sup>1</sup> (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 <sup>2</sup> (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 <sup>3</sup> (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 <sup>4</sup> (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 <sup>5</sup> (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 <sup>6</sup> (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 <sup>7</sup> (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 <sup>8</sup> (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 <sup>9</sup> (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- 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
Mood affective disorders and cardiovascular diseases (including stroke)												
Correll, 2017 <sup>10</sup> (1)	Bipolar disorder	ICD-8,9,10, RDC	Cardiovascular diseases	Cardiovascular mortality (RR)	6 (11,309,529/ 4-20y)	37-72	42-100	Low risk	Low risk	Unclear risk	Low risk	Low risk
Yuan, 2022 <sup>11</sup> (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 <sup>10</sup> (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 <sup>12</sup> (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 <sup>13</sup> (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 <sup>14</sup> (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 <sup>15</sup> (2)	Depressive disorders	DIS for DSM-IV and validated	Coronary artery disease	Ventricular tachycardia/	8 (3,805/ < 5v)	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 <sup>16</sup>	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 <sup>17</sup> (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 <sup>18</sup> (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 <sup>19</sup> (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 (1,058/ 0.5-3y)	53-66	51-72	Low risk	Low risk	Unclear risk	High risk	High risk
Meijer, 2011 <sup>20</sup> (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 (15,474/ 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  Risk of bias in the review
								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	
		HADS-D≥10, MADRS≥14, Zung SDS ≥40)										
Zhang, 2019 <sup>21</sup> (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 <sup>22</sup> (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 <sup>23</sup> (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 <sup>24</sup> (1)	Depressive disorders	ICD-10, CIDI and validated assessment instruments (HDRS≥7, PHQ- 9≥10)	Stroke*	All-cause mortality (RR)	5 (1,154/ 1-10y)	60-68	54-60	Low risk	Low risk	Low risk	Unclear risk	Low risk
Cai, 2019 <sup>25</sup> (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 <sup>26</sup> (1)	Depressive disorders	RCD and validated assessment instruments (CES-D≥16, Zung SDS≥ 60, HLEQ related to DSM-IV	Stroke	Stroke mortality (HR)	4 (35,183/ 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
		MDD)										
Wu, 2019 <sup>27</sup> (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 <sup>28</sup> (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 <sup>6</sup> (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 <sup>29</sup> (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 <sup>30</sup> (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 <sup>31</sup> (1)		Validated assessment instruments (BDI≥10, CES-		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  Risk of bias in the review
								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	
		D≥16)										
Hofmann, 2013 <sup>32</sup> (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 (88,548)/ 2-10y)	52-76	38-100	Low risk	Low risk	Low risk	Unclear risk	Low risk
Farrokhi, 2014 <sup>33</sup> (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 <sup>34</sup> (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 <sup>35</sup> (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 (4,728/ <5 y & ≥5 y)	35-70	0-83	High risk	Low risk	High risk	High risk	High risk
Shi, 2018 <sup>36</sup> (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 (1,953/ < 5y)	45-54	34-55	Low risk	Low risk	High risk	Low risk	Low risk
Wang, 2020 <sup>9</sup>	Depressive	ICD-9 and validated	Breast cancer	Breast cancer	8 (12,133/8-	52-72	0	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  Risk of bias in the review
								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	
(3)	disorders	assessment instruments (PSSCAN based on DSM-IV-TR≥11 HADS-D≥8, CES- D≥16)		mortality; All- cause mortality; Cancer recurrence (HR)	13y)							
Mood affective disorders and other physical diseases												
Guo, 2021 <sup>7</sup> (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 <sup>8</sup> (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 <sup>37</sup> (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 <sup>38</sup> (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 <sup>39</sup> (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
Scott, 2018 <sup>40</sup>	Depressive	CIDI and validated	Human	Pain (HR)	2 (890/	30-42	65-81	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
(1)	disorders	assessment instruments (BDI≥20)	immunodeficien cy virus infection		< 5y)							

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 <sup>41</sup> (2)	Alcohol use disorder	ICD-9,10	Hepatitis C virus infection	Decompensat ed liver cirrhosis; Negative course liver disease (RR)	3 (169,509/ 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 <sup>10</sup> (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 <sup>42</sup> (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 <sup>43</sup> (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 <sup>44</sup> (1)	Dementia	ICD-9	COVID-19*	All-cause mortality (RR)	2 (22,786)/ <5y)	55-71	60-92	Low risk	High risk	Low risk	Low risk	Low risk
Liu, 2021 <sup>45</sup> (1)					2 (551/ <5y)	70-73	52-56	Low risk	Low risk	Low risk	Low risk	Low risk
Ding, 2021 <sup>46</sup> (1)	Dementia	DSM-III, NINDS-AIREN, MINI	Stroke	Delirium (OR)	7 (1,389/ 0.3-10y)	56-75	46-95	Low risk	High risk	Low risk	Low risk	Low risk
Liu, 2018 <sup>47</sup>	Delirium;	DSM-IV-TR,	Hip fracture	All-cause	7 (2,874/	>65-85	18-27	Low risk	Low risk	Unclear	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	
(2)	Dementia	DSM-IV, MINI, and validated assessment instrument (CAM positive=3)		mortality (HR)	<5y)					risk		
Guo, 2021 <sup>7</sup> (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 <sup>2</sup> %	PI (95% CI)	SSE/ESB	LS	eOR	CE	CES
Neurotic, stress-related and somatoform disorders and cardiovascular diseases														
Roest, 2010 <sup>4</sup>	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 <sup>1</sup>	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 <sup>2</sup>	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 <sup>3</sup>	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 <sup>5</sup>	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 <sup>7</sup>	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 <sup>9</sup>	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 <sup>8</sup>	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 <sup>2</sup> %	PI (95% CI)	SSE/ESB	LS	eOR	CE	CES
Mood affective disorders and cardiovascular diseases (including stroke)														
Meijer, 2011 <sup>20</sup>	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 <sup>23</sup>	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 <sup>19</sup>	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 <sup>15</sup>	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 <sup>27</sup>	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 <sup>21</sup>	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 <sup>15</sup>	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 <sup>14</sup>	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 <sup>29</sup>	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 <sup>30</sup>	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 <sup>30</sup>	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 <sup>35</sup>	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,	Depressive	Breast cancer	Cancer	5	HR, 1.18	1,722	>0.05	42.11	[0.70, 1.99]	No/No	Yes	1.18	NS	NS

Study	Mental disorder	Physical Disorder	Outcome	k	Random-effects measure, ES (95% CI)	N cases	p random effects	I <sup>2</sup> %	PI (95% CI)	SSE/ESB	LS	eOR	CE	CES
2020 <sup>9</sup>	disorders		recurrence		[0.96, 1.45]									
Mood affective disorders and other physical diseases														
Ruiz-Grosso, 2020 <sup>38</sup>	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 <sup>40</sup>	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 <sup>39</sup>	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 <sup>37</sup>	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 <sup>8</sup>	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 <sup>7</sup>	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 <sup>2</sup> %	PI (95% CI)	SSE/ESB	LS	eOR	CE	CES
Mental and behavioural disorders due to psychoactive substance use and infectious diseases														
Llamosas-Falcón, 2020 <sup>41</sup>	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 <sup>41</sup>	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 <sup>46</sup>	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 <sup>7</sup>	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 <sup>2</sup> %	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 <sup>18</sup>										
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 <sup>20</sup>										
a) Diagnostic method										

Subgroup	k	Random-effects measure, ES (95% CI)	N cases	p random effects	I <sup>2</sup> %	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, 1.70]	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, 1.70]	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, 1.70]	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 <sup>33</sup>										
<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 <sup>2</sup> %	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, 2.50]	221	6.4e-03	46.86	[0.42, 7.00]	Yes/Yes	Yes	1.71	II/IV
c) Follow-up duration										
>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
d) Type of estimates										
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									
e) Age of participants										
<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
f) Exposure to psychiatric medications										
Yes	No data available or only one study									
No	No data available or only one study									
g) Sex										
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 <sup>32</sup>										
a) Diagnostic method										
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
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	2	HR, 2.57 [0.73, 9.03]	783	>0.05	96.65	NA	NA/NA	Yes	2.57	II/NS
c) Follow-up duration										
>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 <sup>2</sup> %	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
<b>Depressive disorders/Diabetes mellitus /Dementia<sup>29</sup></b>										
<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								

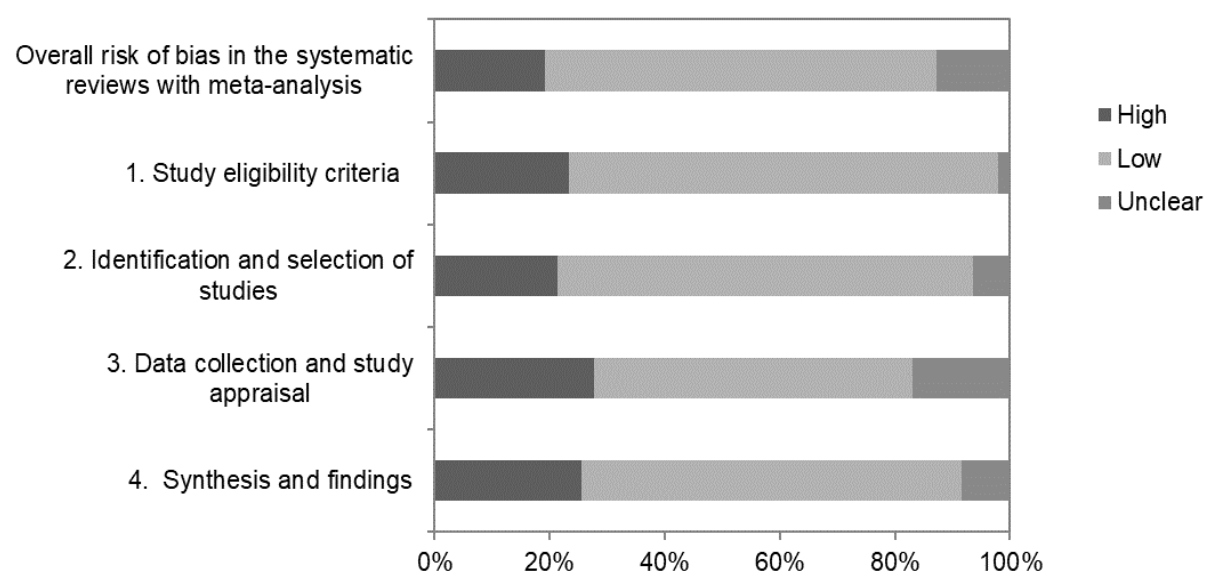
Subgroup	k	Random-effects measure, ES (95% CI)	N cases	p random effects	I <sup>2</sup> %	PI (95% CI)	SSE/ES B	LS	eOR	CE/ CES
≥50 years old	5	HR, 2.11 [1.77, 2.52]	95,097	8.5e-17	84.15	[1.21, 3.67]	No/No	Yes	2.11	II/II
<i>f) Exposure to psychiatric medications</i>										
Yes		No data available or only 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								
<b>Mental and behavioural disorders due to psychoactive substance use and infectious diseases</b>										
<b>Alcohol use disorder/ Hepatitis C virus infection/ Decompensated liver cirrhosis<sup>41</sup></b>										
<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 <sup>2</sup> %	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 <sup>10</sup>										
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 <sup>43</sup>										
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 <sup>2</sup> %	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								

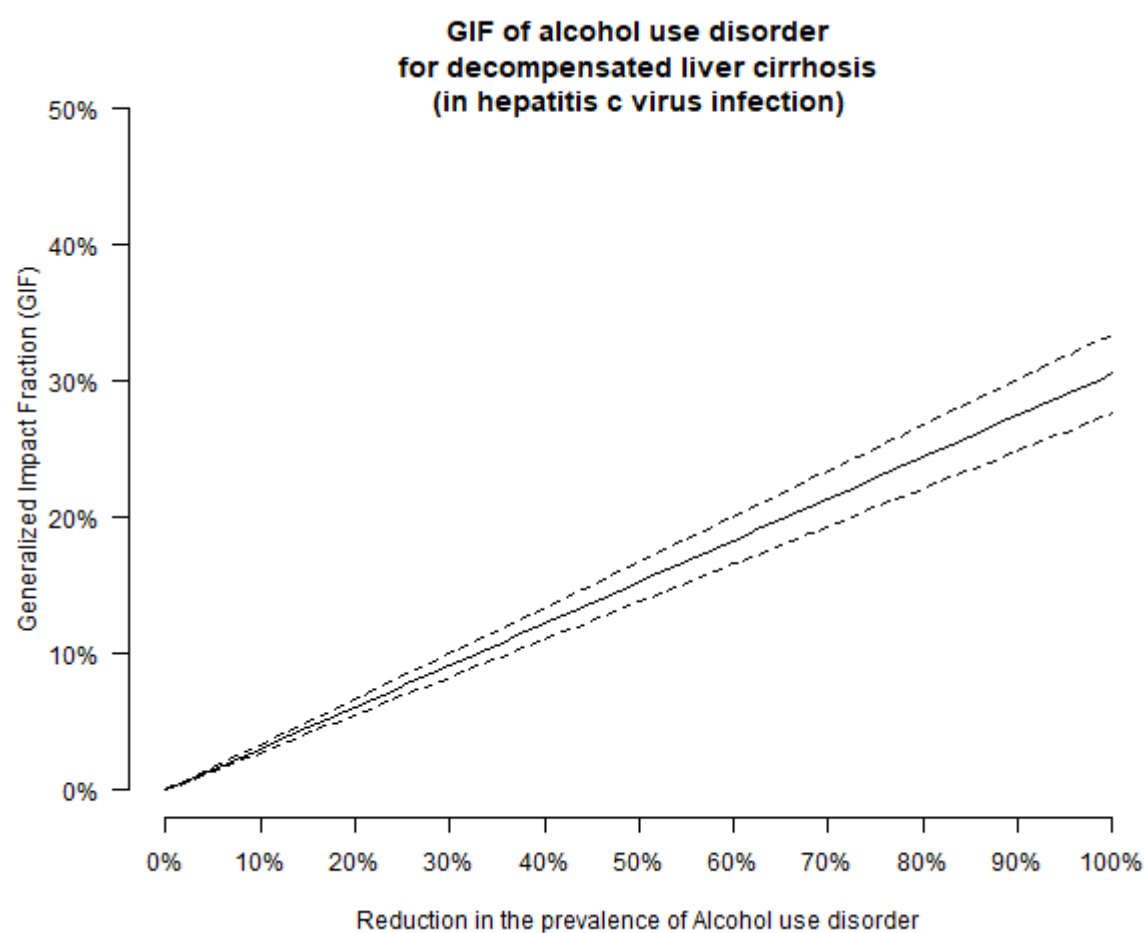
CE—Class of evidence, CES — Class of evidence after subgroup analysis, CI — Confidence interval, eOR—Equivalent odds ratio, ESB — Excess significance bias, ES — Effect size, HR — Hazard ratio, k—Number of samples for each association, LS — Largest study with significant effect, N cases— Number of cases 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.

**eFigure 1.** Graphical summary of the ROBIS assessment in the 47 systematic reviews with meta-analyses included in the current umbrella review

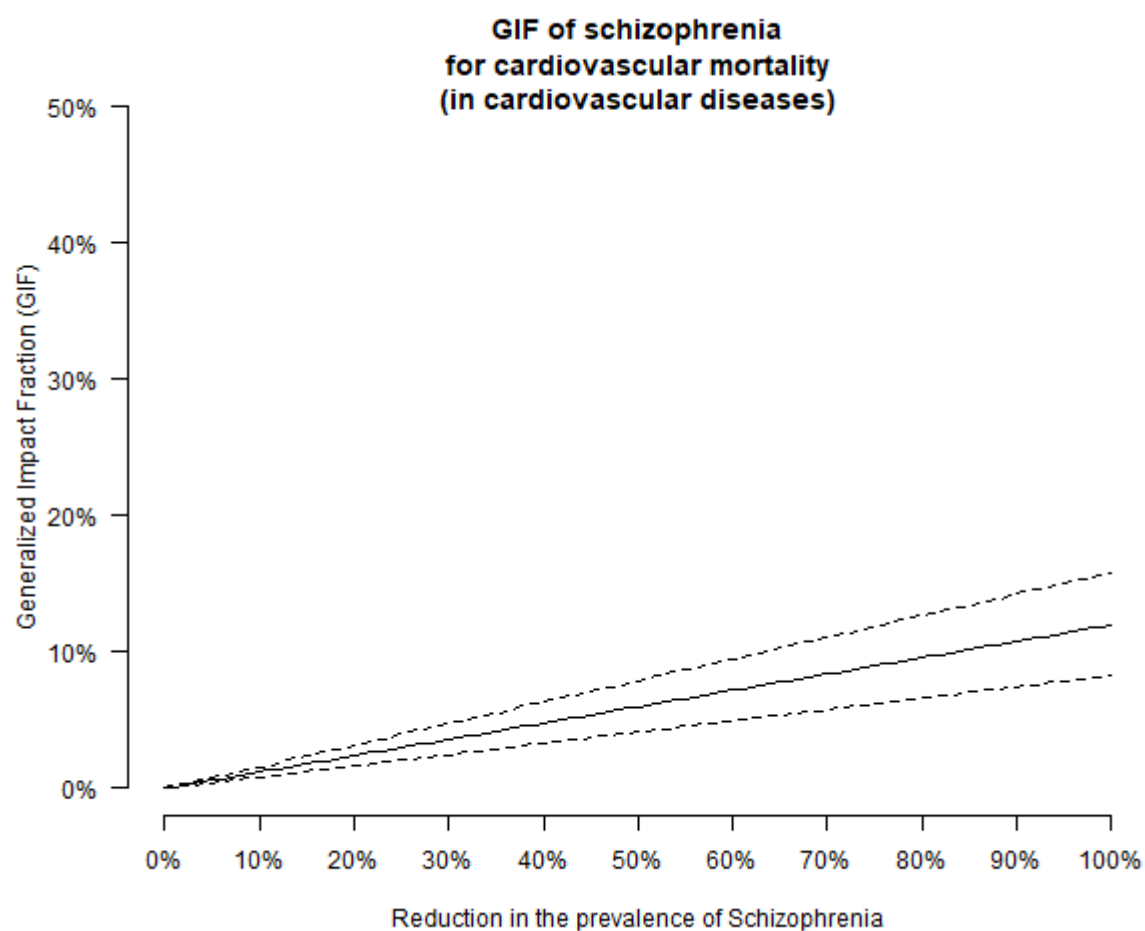




**eFigure 2.** The meta-analytic Generalized Impact Fraction (GIF) for alcohol use disorder



**eFigure 3.** The meta-analytic Generalized Impact Fraction (GIF) for schizophrenia



## 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 to research criteria, the class II association between depressive disorders and major cardiac events in patients with myocardial infarction was downgraded to a non-significant level.

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  $\leq 5$  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 to unadjusted estimates, there was no change in the level of evidence.

When restricting the analyses to an age of participants  $\geq 50$  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 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.

### **Declaration of Interest**

CU Correll has been a consultant and/or advisor to or has received honoraria from: AbbVie, Acadia, Alkermes, Allergan, Angelini, Aristo, Boehringer-Ingelheim, Cardio Diagnostics, Cerevel, CNX Therapeutics, Compass Pathways, Darnitsa, Gedeon Richter, Hikma, Holmusk, IntraCellular Therapies, Janssen/J&J, Karuna, LB Pharma, Lundbeck, MedAvante-ProPhase, MedInCell, Merck, Mindpax, Mitsubishi Tanabe Pharma, Mylan, Neurocrine, Newron, Noven, Otsuka, Pharmabrain, PPD Biotech, Recordati, Relmada, Reviva, Rovi, Seqirus, SK Life Science, Sunovion, Sun Pharma, Supernus, Takeda, Teva, and Viatris. He provided expert testimony for Janssen and Otsuka. He served on a Data Safety Monitoring Board for Lundbeck, Relmada, Reviva, Rovi, Supernus, and Teva. He has received grant support from Janssen and Takeda. He received royalties from UpToDate and is also a stock option holder of Cardio Diagnostics, Mindpax, LB Pharma and Quantics. MS received honoraria/has been a consultant for Angelini, Lundbeck, Otsuka. The other authors have no conflict of interest to declare.



## References

1. Li J, Ji F, Song J, et al. Anxiety and clinical outcomes of patients with acute coronary syndrome: a meta-analysis. *BMJ Open*. 2020;10(7):e034135.
2. Emdin CA, Odutayo A, Wong CX, Tran J, Hsiao AJ, Hunn BH. Meta-Analysis of Anxiety as a Risk Factor for Cardiovascular Disease. *Am J Cardiol*. 2016;118(4):511-519.
3. Celano CM, Millstein RA, Bedoya CA, Healy BC, Roest AM, Huffman JC. Association between anxiety and mortality in patients with coronary artery disease: A meta-analysis. *Am Heart J*. 2015;170(6):1105-1115.
4. Roest AM, Martens EJ, Denollet J, de Jonge P. Prognostic association of anxiety post myocardial infarction with mortality and new cardiac events: a meta-analysis. *Psychosom Med*. 2010;72(6):563-569.
5. Taggart Wasson L, Shaffer JA, Edmondson D, et al. Posttraumatic stress disorder and nonadherence to medications prescribed for chronic medical conditions: A meta-analysis. *J Psychiatr Res*. 2018;102:102-109.
6. Atlantis E, Fahey P, Cochrane B, Smith S. Bidirectional associations between clinically relevant depression or anxiety and COPD: a systematic review and meta-analysis. *Chest*. 2013;144(3):766-777.
7. Guo Y, Liu FT, Hou XH, et al. Predictors of cognitive impairment in Parkinson's disease: a systematic review and meta-analysis of prospective cohort studies. *J Neurol*. 2021;268(8):2713-2722.
8. Li JQ, Tan L, Wang HF, et al. Risk factors for predicting progression from mild cognitive impairment to Alzheimer's disease: a systematic review and meta-analysis of cohort studies. *J Neurol Neurosurg Psychiatry*. 2016;87(5):476-484.
9. Wang X, Wang N, Zhong L, et al. Prognostic value of depression and anxiety on breast cancer recurrence and mortality: a systematic review and meta-analysis of 282,203 patients. *Mol Psychiatry*. 2020;25(12):3186-3197.
10. Correll CU, Solmi M, Veronese N, et al. Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: a large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls. *World Psychiatry*. 2017;16(2):163-180.
11. Yuan M, Xiao ZL, Zhou HY, et al. Bipolar disorder and the risk for stroke incidence and mortality: a meta-analysis. *Neurol Sci*. 2022;43(1):467-476.
12. Barth J, Schumacher M, Herrmann-Lingen C. Depression as a risk factor for mortality in patients with coronary heart disease: a meta-analysis. *Psychosom Med*. 2004;66(6):802-813.
13. Nicholson A, Kuper H, Hemingway H. Depression as an aetiologic and prognostic factor in coronary heart disease: a meta-analysis of 6362 events among 146 538 participants in 54 observational studies. *Eur Heart J*. 2006;27(23):2763-2774.
14. Wu Q, Kling JM. Depression and the Risk of Myocardial Infarction and Coronary Death: A Meta-Analysis of Prospective Cohort Studies. *Medicine (Baltimore)*. 2016;95(6):e2815.
15. Shi S, Liu T, Liang J, Hu D, Yang B. Depression and Risk of Sudden Cardiac Death and Arrhythmias: A Meta-Analysis. *Psychosom Med*. 2017;79(2):153-161.
16. Flaherty LB, Wood T, Cheng A, Khan AR. Pre-existing psychological depression confers increased risk of adverse cardiovascular outcomes following cardiac surgery: A systematic review and meta-analysis. *J Thorac Cardiovasc Surg*. 2017;154(5):1578-1586 e1571.
17. Gathright EC, Goldstein CM, Josephson RA, Hughes JW. Depression increases the risk of mortality in patients with heart failure: A meta-analysis. *J Psychosom Res*. 2017;94:82-89.
18. Sokoreli I, de Vries JGG, Pauws SC, Steyerberg EW. Depression and anxiety as predictors of mortality among heart failure patients: systematic review and meta-analysis. *Heart Fail Rev*. 2016;21(1):49-63.

19. Rutledge T, Reis VA, Linke SE, Greenberg BH, Mills PJ. Depression in heart failure a meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes. *J Am Coll Cardiol*. 2006;48(8):1527-1537.
20. Meijer A, Conradi HJ, Bos EH, Thombs BD, van Melle JP, de Jonge P. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: a meta-analysis of 25 years of research. *Gen Hosp Psychiatry*. 2011;33(3):203-216.
21. Zhang WY, Nan N, Song XT, Tian JF, Yang XY. Impact of depression on clinical outcomes following percutaneous coronary intervention: a systematic review and meta-analysis. *BMJ Open*. 2019;9(8):e026445.
22. Song X, Song J, Shao M, et al. Depression predicts the risk of adverse events after percutaneous coronary intervention: A meta-analysis. *J Affect Disord*. 2020;266:158-164.
23. Blochl M, Meissner S, Nestler S. Does depression after stroke negatively influence physical disability? A systematic review and meta-analysis of longitudinal studies. *J Affect Disord*. 2019;247:45-56.
24. Bartoli F, Di Brita C, Crocamo C, Clerici M, Carra G. Early Post-stroke Depression and Mortality: Meta-Analysis and Meta-Regression. *Front Psychiatry*. 2018;9:530.
25. Cai W, Mueller C, Li YJ, Shen WD, Stewart R. Post stroke depression and risk of stroke recurrence and mortality: A systematic review and meta-analysis. *Ageing Res Rev*. 2019;50:102-109.
26. Pan A, Sun Q, Okereke OI, Rexrode KM, Hu FB. Depression and risk of stroke morbidity and mortality: a meta-analysis and systematic review. *JAMA*. 2011;306(11):1241-1249.
27. Wu QE, Zhou AM, Han YP, et al. Poststroke depression and risk of recurrent stroke: A meta-analysis of prospective studies. *Medicine (Baltimore)*. 2019;98(42):e17235.
28. Courtwright AM, Salomon S, Lehmann LS, Wolfe DJ, Goldberg HJ. The Effect of Pretransplant Depression and Anxiety on Survival Following Lung Transplant: A Meta-analysis. *Psychosomatics*. 2016;57(3):238-245.
29. Chow YY, Verdonchot M, McEvoy CT, Peeters G. Associations between depression and cognition, mild cognitive impairment and dementia in persons with diabetes mellitus: A systematic review and meta-analysis. *Diabetes Res Clin Pract*. 2022;185:109227.
30. Farooqi A, Khunti K, Abner S, Gillies C, Morriss R, Seidu S. Comorbid depression and risk of cardiac events and cardiac mortality in people with diabetes: A systematic review and meta-analysis. *Diabetes Res Clin Pract*. 2019;156:107816.
31. van Dooren FE, Nefs G, Schram MT, Verhey FR, Denollet J, Pouwer F. Depression and risk of mortality in people with diabetes mellitus: a systematic review and meta-analysis. *PLoS One*. 2013;8(3):e57058.
32. Hofmann M, Kohler B, Leichsenring F, Kruse J. Depression as a risk factor for mortality in individuals with diabetes: a meta-analysis of prospective studies. *PLoS One*. 2013;8(11):e79809.
33. Farrokhi F, Abedi N, Beyene J, Kurdyak P, Jassal SV. Association between depression and mortality in patients receiving long-term dialysis: a systematic review and meta-analysis. *Am J Kidney Dis*. 2014;63(4):623-635.
34. Palmer SC, Vecchio M, Craig JC, et al. Association between depression and death in people with CKD: a meta-analysis of cohort studies. *Am J Kidney Dis*. 2013;62(3):493-505.
35. Satin JR, Linden W, Phillips MJ. Depression as a predictor of disease progression and mortality in cancer patients: a meta-analysis. *Cancer*. 2009;115(22):5349-5361.
36. Shi C, Lamba N, Zheng LJ, et al. Depression and survival of glioma patients: A systematic review and meta-analysis. *Clin Neurol Neurosurg*. 2018;172:8-19.
37. Mourao RJ, Mansur G, Malloy-Diniz LF, Castro Costa E, Diniz BS. Depressive symptoms increase the risk of progression to dementia in subjects with mild cognitive impairment: systematic review and meta-analysis. *Int J Geriatr Psychiatry*. 2016;31(8):905-911.

38. Ruiz-Grosso P, Cachay R, de la Flor A, Schwalb A, Ugarte-Gil C. Association between tuberculosis and depression on negative outcomes of tuberculosis treatment: A systematic review and meta-analysis. *PLoS One*. 2020;15(1):e0227472.
39. Schoultz M, Beattie M, Gorely T, Leung J. Assessment of causal link between psychological factors and symptom exacerbation in inflammatory bowel disease: a systematic review utilising Bradford Hill criteria and meta-analysis of prospective cohort studies. *Syst Rev*. 2020;9(1):169.
40. Scott W, Arkuter C, Kioskli K, et al. Psychosocial factors associated with persistent pain in people with HIV: a systematic review with meta-analysis. *Pain*. 2018;159(12):2461-2476.
41. Llamosas-Falcon L, Shield KD, Gelovany M, Manthey J, Rehm J. Alcohol use disorders and the risk of progression of liver disease in people with hepatitis C virus infection - a systematic review. *Subst Abuse Treat Prev Policy*. 2020;15(1):45.
42. Ni L, Wu J, Long Y, et al. Mortality of site-specific cancer in patients with schizophrenia: a systematic review and meta-analysis. *BMC Psychiatry*. 2019;19(1):323.
43. Zhuo C, Tao R, Jiang R, Lin X, Shao M. Cancer mortality in patients with schizophrenia: systematic review and meta-analysis. *Br J Psychiatry*. 2017;211(1):7-13.
44. Hariyanto TI, Putri C, Arisa J, Situmeang RFV, Kurniawan A. Dementia and outcomes from coronavirus disease 2019 (COVID-19) pneumonia: A systematic review and meta-analysis. *Arch Gerontol Geriatr*. 2021;93:104299.
45. Liu L, Ni SY, Yan W, et al. Mental and neurological disorders and risk of COVID-19 susceptibility, illness severity and mortality: A systematic review, meta-analysis and call for action. *EClinicalMedicine*. 2021;40:101111.
46. Ding G, Hua S, Chen J, Yang S, Xie R. Does cognitive decline/dementia increase Delirium risk after stroke? *Psychogeriatrics*. 2021;21(4):605-611.
47. Liu Y, Wang Z, Xiao W. Risk factors for mortality in elderly patients with hip fractures: a meta-analysis of 18 studies. *Aging Clin Exp Res*. 2018;30(4):323-330.