

Cardiorespiratory fitness and risk of mental disorders and dementia: a systematic review and meta-analysis

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Cardiorespiratory fitness (CRF) is a strong indicator of overall physical health, but its relevance for mental and neurocognitive health across the life course remains unclear. Here we synthesize evidence from cohort studies examining the associations between CRF and the risk of mental and neurocognitive disorders across all age groups in the general population. Twenty-seven studies comprising 4,007,638 individuals were included. Compared with low CRF, high CRF was associated with a reduced risk of depression (hazard ratio (HR) = 0.64; 95% confidence interval (CI), 0.56–0.74), all-cause dementia (HR = 0.61; 95% CI: 0.55–0.68) and psychotic disorders (HR = 0.71; 95% CI: 0.65–0.77) in adults. A one metabolic equivalent of task (1 MET; 3.5 ml kg⁻¹ min⁻¹) higher level of CRF was associated with lower risks of depression (HR = 0.95; 95% CI: 0.92–0.98) and all-cause dementia (HR = 0.81; 95% CI: 0.67–0.98). Overall certainty of evidence ranged from very low to moderate. These findings suggest that CRF may be a useful marker for identifying adults at increased risk of depression, dementia and psychotic disorders, highlighting the need for further large-scale longitudinal studies.

Mental and neurocognitive disorders are among the leading causes of disability burden worldwide¹, affecting over 1.15 billion individuals in 2021². In addition, subthreshold symptoms can substantially impair quality of life and are associated with an increased risk of progression to a clinical diagnosis³. The etiology of mental and neurocognitive disorders involves a complex interaction of genetic, neurological, psychosocial, environmental and lifestyle factors, thus posing a challenge for the development of primary prevention strategies^{4,5}.

Cardiorespiratory fitness (CRF) is a pivotal indicator of overall physical health, representing the ability of multiple physiological systems to efficiently deliver and use oxygen during sustained physical activity⁶. Genetics account for nearly half of the variation in CRF⁷, with

the remaining influence being predominantly shaped by regular physical activity patterns⁸. Since early meta-analyses examining CRF utility as a predictor of health outcomes⁹, a substantial corpus of evidence from cohort studies has consistently highlighted the value of CRF in identifying individuals at heightened risk of mortality¹⁰ and cardiovascular diseases¹¹. Consequently, CRF has been recognized as an important, readily measurable risk factor^{12,13}, and its integration as a clinical vital sign has been specifically proposed for cardiovascular disease risk assessment¹⁴, providing precise insights that facilitate the development of physical activity recommendations and exercise prescriptions¹⁵.

A 2024 overview of meta-analyses of cohort studies indicates that CRF is a strong and consistent predictor of mortality and future chronic

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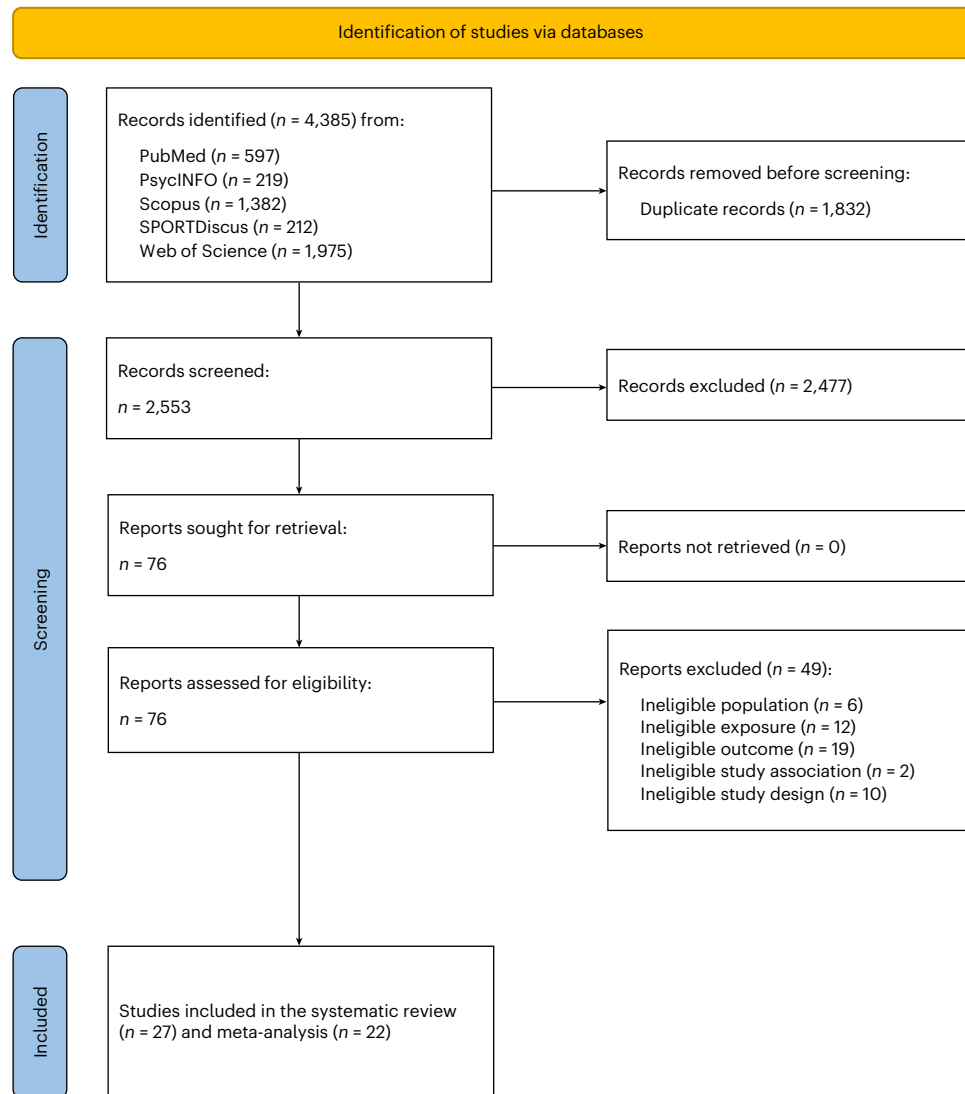


Fig. 1 | Flow diagram of the study selection process. Inclusion criteria were as follows: (1) general populations without mental or neurocognitive disorders at baseline, across all age groups, (2) CRF levels, (3) mental and neurocognitive

health outcomes assessed either as clinical diagnoses or symptom severity measures, and (4) prospective or retrospective cohort studies published in peer-reviewed journals.

conditions such as stroke and type 2 diabetes mellitus among adults in the general population¹⁶. However, this study revealed the need for further evidence across additional health outcomes. CRF has been hypothesized to influence mental and neurocognitive health through various physiological and psychological mechanisms, including enhanced neuroplasticity, increased cerebral blood flow, reduced systemic inflammation and improved stress regulation¹⁷. So far, few meta-analyses have examined the associations between CRF and mental or neurocognitive disorders^{18,19}. Each synthesized fewer than five primary studies, limiting the certainty of the available evidence and underscoring the need for additional high-quality research¹⁶. Furthermore, both meta-analyses were limited to adult populations and focused on anxiety, depression and all-cause dementia^{18,19}. The recent surge in research on the determinants of mental and neurocognitive disorders underscores the urgent need to update this body of research^{4,5}. From both clinical and public health perspectives, it is also important to clarify the role of CRF in the prevention of mental and neurocognitive health conditions across the lifespan, including less prevalent mental disorders such as neurodevelopmental and psychotic disorders. Accordingly, this Analysis synthesizes the available evidence from cohort studies on the associations between CRF levels and the risk of mental and neurocognitive disorders across all ages in the general population.

Results

Study selection

A total of 2,553 studies were considered for this title–abstract review; of these, 76 were fully assessed for eligibility and 49 were finally excluded (Supplementary Table 1), leaving a total of 27 cohort studies^{20–46} in the systematic review (Fig. 1).

Study characteristics

Supplementary Tables 2 and 3 summarize the main characteristics of the studies included. The studies were published between 2009²⁸ and 2025²². The follow-up period ranged from 4 (ref. 26) to 29 years⁴⁶. The studies included a total of 4,007,638 individuals (30.5% female participants) in nine different countries, including Finland^{32,34,45}, Germany⁴¹, Italy²⁶, the Netherlands³⁵, Norway^{27,29,31}, Sweden^{24,25,30,34,39,42,43,46}, Taiwan⁴⁴, the United Kingdom^{20,22,33} and the United States^{21,23,28,36–38,40}. The participants across studies were predominantly white (either of European ancestry or non-Hispanic in US cohorts). The mean age at baseline ranged from 10.6 (ref. 44) to 72.5 years²⁶, comprising children under 12 years⁴⁴ and adults aged 18–64 years^{20–43,45,46} and 65 years or older²⁶.

The CRF levels were estimated using direct^{32,41,45} or indirect^{20–31,33–40,42–44,46} measures through maximal or submaximal tests.

Table 1 | Summary of the available cohort evidence on the associations between CRF and mental and neurocognitive disorders in the general population

Mental and neurocognitive disorders	Cohort evidence in the general population ^a			References
	<18 years	18–64 years	≥65 years	
Anxiety disorders	✓	✓✓✓✓	†	24,29,33,41,44
Depressive disorders	✓	✓✓✓✓✓ ✓✓✓✓	✓†	23–26,28,29,33,35,37,40–42,44
Neurocognitive disorders (all-cause dementia)	—	✓✓✓✓✓ ✓✓✓✓✓	†††††	20–22,27,30–32,34,36,38,46
Neurodevelopmental disorders ^b	✓	—	—	44
Bipolar and related disorders	—	✓	—	43
Obsessive-compulsive and related disorders	—	✓	—	43
Schizophrenia spectrum and other psychotic disorders	—	✓✓	†	43,45
Somatic symptom and related disorders	—	✓	—	43
Trauma- and stressor-related disorders	—	✓	—	43
Sleep-wake disorders ^c	—	✓	—	39
Other mental disorders ^d	—	—	—	NA
Total number of outcome-specific associations	3	32	1	20–46

^aCohort studies were classified according to the age range (<18 years, 18–64 years and ≥65 years) of the study population, based on the mean age of the total sample at baseline. Check marks (✓) indicate cohort studies that examined associations between CRF and risk of mental or neurocognitive disorders. Dashes (—) indicate that no cohort studies examined associations between CRF and risk of mental or neurocognitive disorders. Dagger symbols (†) indicate studies in which the mean age at baseline was between 18 and 64 years and extended beyond 65 years during follow-up. ^bAttention-deficit/hyperactivity disorder. ^cSleep apnea (obstructive, central and mixed). ^dDisruptive, impulse-control and conduct disorders; dissociative disorders; elimination disorders; feeding and eating disorders; medication-induced movement disorders and other adverse effects of medication; other neurocognitive (that is, delirium) and neurodevelopmental (that is, autism spectrum disorders, communication disorders, intellectual developmental disorders, motor disorders, and specific learning disorders) disorders; personality disorders; paraphilic disorders; sexual dysfunctions; and substance-related and addictive disorders. NA, not applicable.

The included studies provided data for CRF categories by standardizing the cutoff point for high and low levels according to participant's age and sex^{22,23,26–33,35,36,38,40,42,43,45}. Alternatively, data on age and sex were only adjusted in the estimate risk model²⁵. Six studies were conducted exclusively among male participants^{30,32,39,42,43,45}, and five studies disclosed data regarding study associations by sex^{20,26,28,37,40,44}. The metrics used were distance²⁶ or duration^{40,44} of field-based tests, metabolic equivalent of task (MET)^{20–23,28,33,34,36,37}, peak workload^{30,35,39,42,43,46} and maximum oxygen consumption (VO_{2max})^{24,25,27,29,31,32,41,45}. Cohort studies employed a single baseline assessment of CRF levels, with subsequent repeated measurements^{24,27,28,31,36,37}. Analysis of CRF was performed as a continuous variable^{20–23,25,27–29,34–39,41,45} or as a comparison between categories^{22,23,25–33,35,36,38,40,42–46}.

Mental and neurocognitive disorders, whether clinical diagnoses^{20–25,27,30–32,34,36,38,39,41–46} or manifestations of mild to severe symptoms^{26,28,29,33,35,37,40,41}, primarily included anxiety disorders (hereafter anxiety)^{24,29,33,41,44}, depressive disorders (hereafter depression)^{23–26,28,29,33,35,37,40–42,44}, all-cause dementia^{20–22,27,30–32,34,36,38,46} and schizophrenia spectrum and other psychotic disorders (hereafter psychotic disorders)^{43,45}. Table 1 summarizes the available cohort evidence on the associations between CRF and mental disorders in the general population.

Methodological quality and certainty of evidence

Among the included studies, 57.1% were rated as good quality and 42.9% were rated as fair quality (Supplementary Table 4). Cohort studies with fair quality were deficient in three key criteria: (1) a detailed definition of exposure measures; (2) multiple exposure measurements; and (3) an acceptable overall follow-up rate (>80%). A Grading of Recommendations, Assessment, Development and Evaluation (GRADE) assessment indicated moderate certainty of evidence for all-cause dementia and a very low certainty of evidence for anxiety, depression and psychotic disorders when comparing high versus low CRF. The GRADE assessment for a 1-MET increase in CRF indicated very low certainty of evidence for both depression and all-cause dementia. The very low certainty of evidence was primarily driven by risk of bias,

inconsistency, imprecision and the inability to assess publication bias (Supplementary Tables 5 and 6).

Summary of outcomes not meta-analyzed

The prospective associations between CRF levels and some mental disorders were only analyzed in one study and were not included in the meta-analyses (Supplementary Table 3). In the general adult population, higher levels of CRF were significantly associated with a lower risk of bipolar and related disorders⁴², dissociative, obsessive-compulsive, somatic symptom and stressor-related disorders⁴³, and sleep apnea³⁹. Furthermore, higher levels of CRF were significantly associated with a reduced risk of anxiety and attention-deficit/hyperactivity disorder in children (boys and girls), whereas the association with depression was significant only in girls⁴⁴.

Summary of outcomes meta-analyzed

A total of 22 cohort studies^{20–23,25–33,35–38,40,42–45} were included in the meta-analyses. Given that the general adult population was mostly aged 18–64 years at baseline, the pooled hazard ratios (HRs) comparing the associations between the highest (versus lowest) category of CRF and the risk of mental and neurocognitive disorders (Fig. 2) were (1) 0.90 (95% CI: 0.75–1.09; *I*-squared (I^2) = 56.9%; n = 2 (refs. 29,33)) for anxiety (n = 36,687; incident cases, 1,009; mild to severe symptoms; follow-up, 7–11 years); (2) 0.64 (95% CI: 0.56–0.74; I^2 = 67.9%; predication interval (PI), 0.43–0.97; n = 9 (refs. 23,25,26,28,29,33,35,40,42)) for depression (n = 1,504,915; incident cases, 18,958; medical registry-based or mild to severe symptoms; follow-up, 4–17 years); (3) 0.61 (95% CI: 0.55–0.68; I^2 = 0%; PI, 0.47–0.79; n = 7 (refs. 22,27,30–32,36,38)) for all-cause dementia (n = 1,287,561; incident cases, 4,170; medical registry-based; follow-up, 8–29 years); and (4) 0.71 (95% CI: 0.65–0.77; I^2 = 0%; n = 2, male-only cohorts^{43,45}) for psychotic disorders (n = 1,112,007; incident cases, 10,420; medical registry-based; follow-up, 23–25 years). One of the included studies did not report the number of incident cases for anxiety and depression³³. In the meta-analysis of CRF as a continuous variable (Fig. 3), an increase of 1 MET (3.5 ml kg^{−1} min^{−1}) was associated with a lower incidence of depression (HR = 0.95; 95% CI: 0.92–0.98; I^2 = 17.0%; PI,

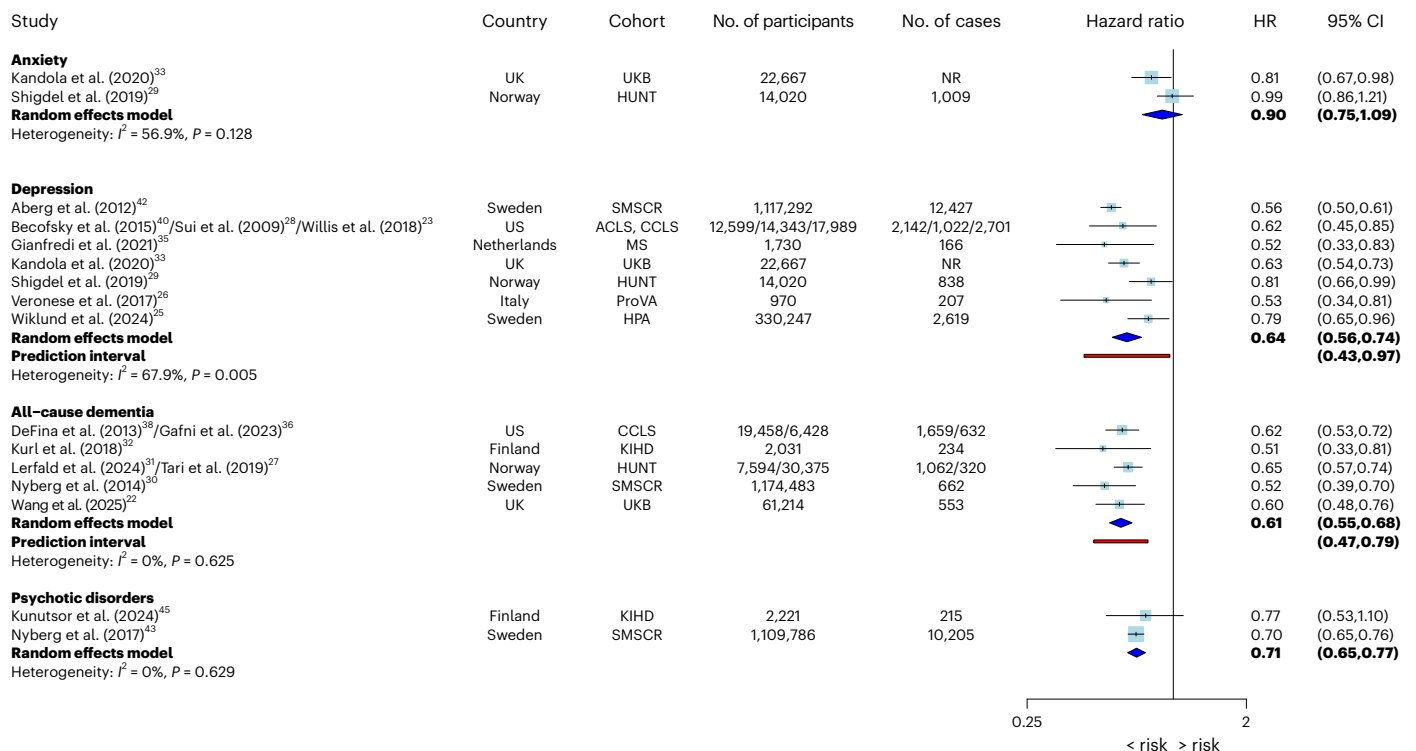


Fig. 2 | Pooled HRs between high versus low levels of CRF and the risk of mental and neurocognitive disorders. Results from two-sided random-effects meta-analyses of prospective cohort studies are shown categorized by disorder: anxiety^{29,33}, depression^{23–26,28,29,33,35,40,42}, all-cause dementia^{22,27,30–32,36,38} and psychotic disorders^{43,45}. Individual squares represent study-specific HRs, with horizontal lines indicating 95% CIs. Diamond symbols denote pooled HRs from random-effects models, and red horizontal bars indicate 95% prediction intervals where available (that is, when more than two studies are included).

Point estimates represent HRs. HR values < 1 indicate a lower risk associated with higher CRF. Statistical inference is two-sided and based on 95% CIs, with no adjustments for multiple comparisons. ACLS, Aerobics Center Longitudinal Study; CCLS, Cooper Center Longitudinal Study; HPA, Health Profile Assessment; HUNT, Trøndelag Health Study; KIHD, Kuopio Ischemic Heart Disease study; MS, Maastricht Study; NR, not reported; ProVA, Progetto Veneto Anziani study; SMSCR, Swedish Military Service Conscript Register; UK, United Kingdom; UKB, UK Biobank; US, United States of America.

0.72–1.25; $n = 5$ (refs. [23,25,28,29,37](#)); $n = 362,256$; incident cases, 6,158; medical registry-based or mild to severe symptoms; follow-up, 5–12 years) and all-cause dementia (HR = 0.81; 95% CI: 0.67–0.98; $I^2 = 97.3\%$; PI, 0.07–9.12; $n = 5$ (refs. [20,21,27,36,38](#)); $n = 123,229$; incident cases, 2,971; medical registry-based; follow-up, 8–24 years).

Subgroup and sensitivity analysis

Subgroup analyses are presented in Supplementary Table 7. High (versus low) CRF was significantly associated with a lower risk of depression and all-cause dementia in participants younger than 50 years (HR = 0.64, 95% CI: 0.52–0.79 and HR = 0.62, 95% CI: 0.54–0.70, respectively) and those aged older than 50 years (HR = 0.65, 95% CI: 0.52–0.80 and HR = 0.60, 95% CI: 0.47–0.72, respectively). Similar associations were observed in both female (HR = 0.51; 95% CI: 0.39–0.66) and male (HR = 0.55; 95% CI: 0.51–0.60) participants for depression. In turn, the pooled HR remained statistically significant in studies of good and fair methodological quality, as well as in those assessing CRF using indirect maximal or submaximal tests and depression defined either by clinical diagnosis or by mild to severe self-reported symptoms. No significant differences were observed across subgroup comparisons ($P > 0.05$). Furthermore, the findings of sensitivity analyses were consistent with the primary results. The pooled effect sizes comparing the associations between the highest (versus lowest) category of CRF and the risk of depression and all-cause dementia were not modified when applying separate analyses by the type of risk estimate (Supplementary Table 8) and removing each study one by one (Supplementary Figs. 1 and 2). Finally, when a standardized effect size correction (Hedges' g) was applied to mitigate potential biases, the results remained consistent (Supplementary Figs. 3 and 4).

Discussion

This systematic review and meta-analysis synthesizes the available evidence on the associations between CRF and the risk of mental and neurocognitive disorders in the general population across all age groups. Overall, high (versus low) CRF was associated with a reduced risk of depression (very low certainty), all-cause dementia (moderate certainty) and psychotic disorders (very low certainty, male-only evidence) in adults. No significant associations were found for anxiety (very low certainty). Furthermore, an increase of 1 MET ($3.5 \text{ ml kg}^{-1} \text{ min}^{-1}$) in CRF was associated with a lower risk of depression and all-cause dementia (very low certainty). These findings suggest a potential role for CRF in mental and neurocognitive health, but given the very low certainty for most outcomes, the results should be interpreted with caution. Additional cohort studies are needed to confirm these findings, particularly for underrepresented populations (that is, individuals under 18 years and over 65 years), and to investigate mental disorders that are currently understudied or have not yet been examined.

The results align with previous systematic reviews and meta-analyses^{18,19} suggesting an inverse association of CRF with depression and all-cause dementia but extend the evidence base by incorporating a broader range of outcomes and a more comprehensive synthesis of available cohort studies. Specifically, this meta-analysis updates previous evidence in adults regarding anxiety, depression and all-cause dementia in adults^{18,19}. Additionally, it integrates evidence on other mental disorders, including bipolar and related disorders, psychotic disorders, stressor-related disorders and sleep–wake disorders in adults, and anxiety, attention-deficit/hyperactivity disorder and depression in children. However, the limited number of studies restricts the ability to draw firm conclusions. Furthermore, no studies

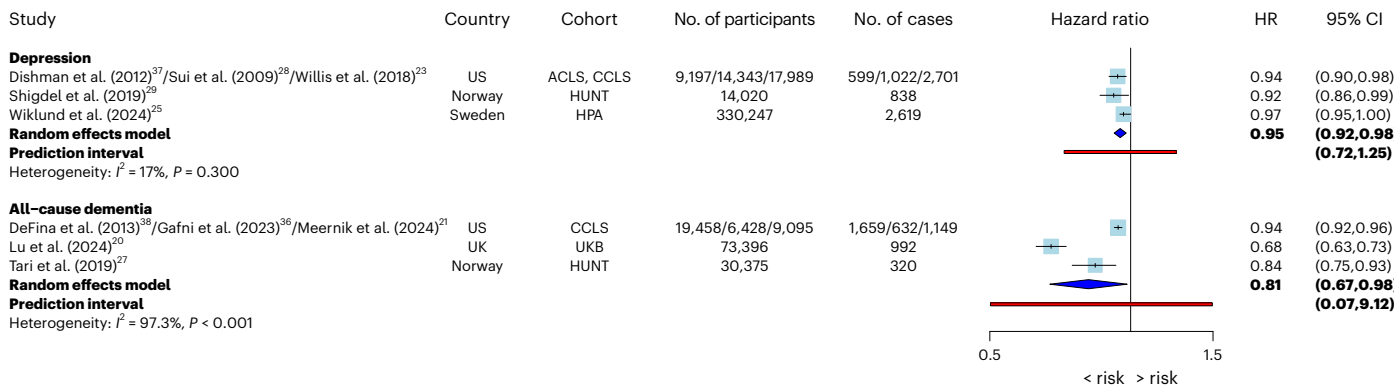


Fig. 3 | Pooled HRs between 1-MET increase in CRF and the risk of mental and neurocognitive disorders. Results from two-sided random-effects meta-analyses of prospective cohort studies are shown categorized into depression^{23–25,28,29,37} and all-cause dementia^{20,21,27,36,38}. Individual squares represent study-specific HRs, with horizontal lines indicating 95% CIs. Diamond

symbols denote pooled HRs from random-effects models, and red horizontal bars indicate 95% prediction intervals. Point estimates represent HRs. HR values < 1 indicate a lower risk associated with higher CRF. Statistical inference is two-sided and based on 95% CIs, with no adjustments for multiple comparisons. Abbreviations as in Fig. 2.

were found on certain mental disorders, such as autism spectrum disorders, disruption, impulse-control and conduct disorders, and feeding and eating disorders.

Several potential mechanisms may explain the observed protective associations of CRF on mental and neurocognitive disorders. From a physiological perspective, exercise and CRF improvements induce structural, cellular and molecular adaptations in the brain that enhance neuroplasticity and support cognitive and emotional regulation^{17,47,48}. One key pathway involves the reduction of systemic inflammation and oxidative stress, both of which are implicated in the pathophysiology of mental and neurocognitive disorders^{17,49}. Improvements in cardiovascular health may further mediate this relationship, as higher CRF is linked to better vascular function and cerebral perfusion, which help reduce inflammation and support brain integrity¹⁷. Chronic inflammation and oxidative damage have been associated with neurodegeneration, impaired synaptic function and disruptions in neurotransmitter systems, which may contribute to the onset and progression of conditions such as depression⁴⁹ and dementia¹⁷. Additionally, exercise and higher CRF has been shown to promote hippocampal volumetric retention, a key neuroprotective adaptation given the hippocampus' role in emotion regulation, memory and cognitive resilience¹⁷. Atrophy in this region has been consistently linked to mental^{50,51} and neurocognitive⁵² disorders. Moreover, higher CRF has been associated with increased global white-matter volume and local integrity⁵³, which are essential for maintaining efficient neural connectivity and information processing. Deficits in white-matter microstructure have been observed in individuals with mental and neurocognitive disorders^{54–57}, suggesting that CRF-related improvements may contribute to better cognitive and emotional stability. Furthermore, regular physical activity⁵⁸, a major determinant of CRF⁵⁹, has been shown to regulate the hypothalamic–pituitary–adrenal axis by reducing cortisol levels and blunting excessive stress responses⁶⁰. Dysregulation of this axis is a well-established mechanism in the development of certain mental and neurocognitive disorders^{61,62}, highlighting the potential role of CRF in modulating neuroendocrine function and improving stress resilience.

Despite biological plausibility, reverse causation remains a major challenge in disentangling the relationship between CRF and mental or neurocognitive health. Prodromal disorders and subthreshold symptoms may precede the observed associations and contribute to higher risk of mental and neurocognitive disorder^{63,64} and to lower CRF levels^{65–67}, for instance through reduced motivation or engagement in physical activity^{49,68}. Such temporal bias could lead to overestimation of the protective effects attributed to CRF. Although all studies included in this meta-analysis excluded participants with clinically diagnosed

mental or neurocognitive disorders at baseline, there remains a possibility that early, undetected symptoms could have influenced CRF trajectories. However, bidirectional Mendelian randomization studies suggest a causal effect of physical activity on depression, with no evidence for the reverse direction⁶⁹. So far, one genetically informed analysis examining CRF and Alzheimer's disease has reported no statistically significant findings²⁰, underscoring the need for further studies applying this approach. Addressing this challenge will require longitudinal cohorts with repeated CRF and mental and neurocognitive health assessments, the use of time-varying exposure models and, where feasible, multistate approaches to capture dynamic transitions between health states. Beyond observational evidence, randomized controlled trials are needed to establish whether specifically improving CRF can prevent the onset or progression of mental and neurocognitive disorders. Although numerous trials show robust antidepressant effects of exercise across baseline depression severity⁷⁰, as well as promising cognitive benefits¹⁷, few have formally examined whether gains in CRF mediate these outcomes. Future trials should therefore incorporate neurobiological markers of neuroplasticity and behavioral indices of self-regulation to stratify participants, identify responders and optimize design⁴⁸. Embedding such precision approaches into trial methodology will maximize CRF improvements, strengthen causal inference, and clarify the contribution of CRF to mental and neurocognitive health trajectories.

Genetic factors also warrant consideration when interpreting the link between CRF and mental or neurocognitive outcomes. In adults, responses to physical training vary considerably, with some individuals showing large improvements in CRF, and others only minimal gains^{71,72}. Approximately half of this interindividual variability appears to be heritable⁷, suggesting that genetic factors may contribute to the observed findings. It is therefore plausible that part of the associations between CRF and mental or neurocognitive disorders reflects genetic pleiotropy, whereby individuals genetically predisposed to higher CRF also have a lower genetic liability for these disorders. However, evidence supporting this hypothesis remains limited. For instance, a large genome-wide association study found no single-nucleotide polymorphisms reaching statistical significance for exercise-induced changes in VO_{2max} ⁷², although recent evidence has identified candidate loci and polygenic predictors explaining a proportion of its variance⁷³. The biological mechanisms through which these genetic variants influence CRF remain largely unclear^{71,74}. Notably, CRF-associated genetic variants are involved in the regulation of gene expression in key cardio-metabolic tissues⁷⁵, and exercise may induce epigenetic modifications such as DNA methylation and microRNA activity⁷⁶ that could mediate its

long-term neuroprotective effects¹⁷. In addition, evidence on racial and ethnic differences in CRF remains inconsistent and often attenuates after adjustment for metabolic, lifestyle and socioeconomic factors⁷⁷, suggesting that observed disparities are largely explained by modifiable environmental influences rather than fixed biological differences.

Importantly, CRF is a highly modifiable trait, and physical activity and exercise interventions can substantially improve it while simultaneously activating converging molecular and systemic pathways that support neuroplasticity, neurovascular health, immune regulation and metabolic resilience, including the upregulation of brain-derived neurotrophic factor and other neurotrophins, enhanced angiogenesis, modulation of gut microbiota, improved mitochondrial function, and reduced neuroinflammation and oxidative stress^{17,78}. They also confer psychosocial benefits such as enhanced social support, self-esteem, self-efficacy and body image^{79,80}. Overall, these considerations underscore the need for future research integrating genomic data and family-based designs to disentangle causality and to clarify the relative contributions of genetic, sociocultural and behavioral components of CRF to mental and neurocognitive health outcomes.

Despite the robust methodology employed in this meta-analysis, several limitations should be acknowledged. First, the limited number of available studies restricted the ability to explore or complete subgroup analyses (for example, by geographic region or CRF assessment method) and was insufficient ($n < 10$) to allow additional statistical assessments such as meta-regression or publication bias analyses^{81,82}. As a result, the potential influence of sources of heterogeneity, residual confounding, and unpublished or selectively reported findings cannot be excluded. Second, some pooled estimates were accompanied by moderate to substantial between-study heterogeneity. Part of this heterogeneity may reflect methodological differences, such as variation in CRF assessments, outcome definitions and covariate adjustment strategies, which could introduce bias. Third, residual confounding due to mostly unmeasured factors—such as genetic predispositions, chronic pain, multimorbidity, social support and lifestyle behaviors (for example, physical activity, diet, smoking status)—cannot be ruled out. Fourth, subgroup analyses by age were based on aggregated study-level data rather than individual participant data, limiting the ability to draw definitive conclusions about age-specific associations. Fifth, because most cohorts consisted predominantly of white participants (either of European ancestry or non-Hispanic in US cohorts), generalizability to racially and ethnically diverse populations may be limited. Similarly, evidence for psychotic disorders was derived exclusively from two male conscript cohorts, limiting generalizability to female participants. Lastly, future studies should explore within-person variability in CRF over time and develop standardized CRF categories with defined cutoff values to enable dose–response analyses and inform thresholds for mental and neurocognitive risk reduction.

The findings have important implications for public health, clinical practice and future research. Given the inverse associations observed with depression, psychotic disorders (male-only evidence) and particularly all-cause dementia (moderate-certainty evidence for high versus low CRF), incorporating CRF into population-based evaluations could be considered. Measuring CRF may help identify individuals at increased risk of mental and neurocognitive disorders and inform interventions such as structured exercise programs and physical activity promotion aimed at improving CRF. This study underscores key limitations in the current body of evidence and offers specific recommendations to enhance the methodological quality and comparability of future research on the study associations (Supplementary Table 9). Briefly, it is recommended that future studies concentrate on identifying optimal CRF thresholds for mental and neurocognitive health benefits and explore potential sex- and age-specific associations. Accordingly, normalizing CRF to fat-free mass in future studies would improve the precision and comparability of measurements⁸³. Additionally, subsequent studies should track co-existing long-term health

conditions as part of the clinical complexity of general adult populations and examine how specific patterns (for example, accumulation, clusters, trajectories) may influence the associations under investigation. Genetically informed designs, such as Mendelian randomization studies using genetic variants associated with CRF, could help clarify the causal direction of these associations and disentangle genetic from behavioral or environmental pathways. Considering that physical activity and CRF are related but distinct phenotypes, future studies employing this approach should examine their independent and combined associations with mental and neurocognitive disorders. In addition, methods such as linkage disequilibrium score regression could be applied to quantify genetic correlations, providing complementary evidence on shared genetic architecture even in the absence of genome-wide significant variants. Finally, given the potential influence of population health profiles, healthcare systems, socioeconomic conditions, lifestyle factors and disease burden across different contexts, the results of this study underscore the need for future research to include underrepresented populations—both racially and ethnically diverse groups and those from regions such as Africa, Asia, Latin America and the Caribbean, and Oceania—to enhance the generalizability and applicability of evidence related to CRF and mental and neurocognitive disorders.

Conclusion

This systematic review and meta-analysis provides a comprehensive synthesis of the evidence on the associations between CRF and the incidence of mental and neurocognitive disorders in the general population across all age groups. The findings suggest that higher CRF is associated with lower risks of depression, dementia and psychotic disorders (male-only evidence) in adults. CRF may be considered a candidate marker for risk stratification. However, additional cohort studies are needed to clarify its preventive potential, particularly for anxiety, depression and psychotic disorders, where evidence remains of very low certainty. Other mental disorders have only been examined in single studies, limiting the ability to draw firm conclusions. Evidence across specific age groups, including children, adolescents and older adults, should be examined for all mental disorders to ensure comprehensive coverage across the lifespan.

Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 (ref. 84) and the Meta-analysis of Observational Studies in Epidemiology (MOOSE)⁸⁵ statements. The study protocol was registered with PROSPERO (CRD42024547081). Two researchers (V.D.-G. and B.B.-P.) independently conducted the literature search, screening, study selection, data extraction, methodological quality, and certainty of evidence assessments. Any disagreements were resolved by consensus after consultation with a third investigator (V.M.-V.). The following sections provide a concise overview of the methods employed. Additional methodological details are available in Supplementary Methods.

Data sources and search strategy

The search process was conducted in accordance with the PRISMA-S guidelines⁸⁶. Systematic searches were conducted in the following electronic databases from inception to 20 January 2025: PsycINFO, PubMed, Scopus, SPORTDiscus and Web of Science. Additional search methods were performed on online resources (Google Scholar) and citation searching (references of included studies and relevant systematic reviews). A comprehensive account of the search strategies employed is provided in Supplementary Table 10.

Eligibility criteria

To be included, studies retrieved from the scientific literature must report the following: (1) participants (general populations without

mental or neurocognitive disorders at baseline assessments, encompassing all age groups); (2) exposure (CRF levels estimated via three methods¹⁶: (i) maximal cardiopulmonary exercise tests with gas analysis (that is, direct measures of $\text{VO}_{2\text{max}}$), (ii) maximal or submaximal exercise tests (laboratory or field-based) without gas analysis (that is, indirect measures using exercise prediction equations or exercise performance data) or (iii) non-exercise prediction equations); (3) comparison (low levels of CRF); (4) outcome (mental and neurocognitive disorders, categorized according to the DSM-5-TR (*Diagnostic and Statistical Manual of Mental Disorders*, 5th edition—text revision) classification of the American Psychiatric Association⁸⁷, were considered either as clinical diagnoses or as measures of symptom severity); and (5) study design (prospective or retrospective cohort studies published in peer-reviewed journals). No language or publication date restrictions were applied. The eligibility criteria are detailed in Supplementary Methods.

Study selection

All identified studies were uploaded to the Rayyan review system online⁸⁸ and underwent deduplication. Subsequently, a two-step process was used. First, studies that did not address the study associations in the general population, as indicated by their title and abstract, were excluded. Second, the remaining studies were analyzed in full to ascertain whether they met the eligibility criteria.

Data extraction

The following data were extracted from the included studies: (1) authors and year of publication; (2) country where the data were collected; (3) main cohort or register; (4) data collection period and years of follow-up; (5) characteristics of the study population, including sample size, age, percentage of female participants, and body mass index; (6) characteristics related to CRF, including type of measure, assessment test, metric applied, mean value and data analysis (comparison across CRF categories and/or higher CRF as a continuous variable); (7) mental and neurocognitive health outcomes and assessment tools; and (8) prospective study associations, including effect size estimates and covariate adjustments. Data extraction was performed using Microsoft Excel (version 2510; Microsoft Corporation) between March and May 2025.

Methodological quality and certainty of evidence

The methodological quality of the cohort studies was evaluated using the National Institutes of Health (NIH) Quality Assessment Tool for Observational Cohort Studies⁸⁹. The GRADE methodology was employed to determine the certainty of the evidence⁹⁰. A summary of the details pertaining to the quality assessment tools for grading cohort studies is provided in Supplementary Methods.

Effect sizes

The studies mostly used HRs and odds ratios (ORs) as effect size estimators. Given the analysis of general populations (that is, excluding individuals with mental and neurocognitive disorders at baseline) and the low incidence of events across most included studies during follow-up periods (<12%), ORs and HRs were assumed to be equivalent and were thus combined as HRs^{82,91,92}. Accordingly, the HRs and 95% CIs were considered the effect size for the meta-analyses and subjected to log transformations before being analyzed⁸². An HR value of less than 1 indicates a lower risk of mental and neurocognitive disorders in favor of higher levels of CRF. A complete list of effect sizes and the primary results from the studies included are provided in Supplementary Table 3.

Data synthesis

Meta-analyses were performed when at least two studies addressed the same outcome⁹³. To facilitate the interpretation and comparison between studies, separate analyses were performed depending on whether CRF was reported as categorical (highest versus lowest

levels as the reference category) or continuous (1-MET increase, that is, $3.5 \text{ ml kg}^{-1} \text{ min}^{-1}$) variables. Meta-analyses were conducted using a random effect model with the Sidik–Jonkman method⁹⁴. Heterogeneity was estimated using the I^2 statistic and classified as not important (0–40%), moderate (30–60%), substantial (50–90%) or considerable (75–100%)⁸². For I^2 values falling within overlapping ranges, the corresponding P values were incorporated to enhance interpretation⁸³. PIs were also reported to quantify the expected between-study dispersion of true effects⁸². Forest plots were used to display the pooled HRs for the associations between CRF (that is, highest versus lowest levels or 1-MET increase) and the risk of mental and neurocognitive disorders. Subgroup analyses were performed according to participant characteristics (age and sex), CRF assessment method, outcome measure and methodological quality of the included studies. Given the limited availability of stratified results by age groups within individual studies, subgroup analyses were performed based on the mean age of the study participants at baseline. Sensitivity analyses were performed to assess the robustness of the summary estimates using the leave-one-out method⁸² and performing separate analyses by the type of risk estimate applied in the included studies (HR and OR). Additionally, a sensitivity analysis was performed to calculate the standardized effect size, expressed as Hedges' g , to account for potential biases arising from unequal sample sizes and variability in the outcome assessment tools⁸². Other methodological considerations pertaining to data collection and analysis are provided in Supplementary Methods.

Statistics and reproducibility

This study was a systematic review and meta-analysis of previously published data (observational cohort evidence). No statistical method was used to predetermine sample size, as sample sizes were defined by the included studies. No data were excluded from the analyses other than those not meeting the predefined eligibility criteria. Randomization and blinding were not applicable. All analyses were conducted following established Cochrane methodological guidelines to ensure transparency and reproducibility⁸². Statistical significance was set at a two-sided $P < 0.05$. All analyses were conducted using R software version 4.4.0 (R Foundation for Statistical Computing) with the meta⁹⁵ and metafor⁹⁶ packages.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

This systematic review and meta-analysis does not include original data. All data were extracted from published studies and are publicly available. The unprocessed data correspond to the original effect size estimates and related values reported in the included studies. The meta-analytic database generated and analyzed in this study, including study identifiers, effect sizes, confidence intervals and data used for visualization, is available via the Open Science Framework repository⁹⁷.

Code availability

Analyses were performed using standard functions in R software with the meta and metafor packages. The R code used to conduct the meta-analysis is available via the Open Science Framework repository⁹⁷.

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Author contributions

V.D.-G. and B.B.-P. conceived and designed the study. V.D.-G., V.M.-V. and B.B.-P. performed the screening and study selection. V.D.-G., V.M.-V. and B.B.-P. conducted the quality and certainty of evidence assessments. E.R.-G., M.E.V.-A., E.J.-L. and I.S.-D. contributed to data collection. V.D.-G., V.M.-V. and B.B.-P. performed the statistical analysis. J.F.L.-G., E.R.-G., M.E.V.-A., E.J.-L., I.S.-D., F.B.O., J.C.-P., A.E.M. and M.S.-L. contributed to data interpretation. V.D.-G., J.F.L.-G. and B.B.-P. drafted the paper, with input from E.R.-G., M.E.V.-A., E.J.-L., I.S.-D., F.B.O., J.C.-P., A.E.M., M.S.-L., V.M.-V. and B.B.-P. supervised the work. All authors have read and approved the final version of the paper.

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Competing interests

The authors declare no competing interests.

Additional information

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Reporting Summary

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Please do not complete any field with "not applicable" or n/a. Refer to the help text for what text to use if an item is not relevant to your study. For final submission: please carefully check your responses for accuracy; you will not be able to make changes later.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed
☐	☒ The exact sample size (<i>n</i>) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒ The statistical test(s) used AND whether they are one- or two-sided <i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i>
☐	☒ A description of all covariates tested
☐	☒ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒ For null hypothesis testing, the test statistic (e.g. <i>F</i> , <i>t</i> , <i>r</i>) with confidence intervals, effect sizes, degrees of freedom and <i>P</i> value noted <i>Give P values as exact values whenever suitable.</i>
☒	☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☐	☒ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒ Estimates of effect sizes (e.g. Cohen's <i>d</i> , Pearson's <i>r</i>), indicating how they were calculated

Our web collection on [statistics for biologists](#) contains articles on many of the points above.

Software and code

Policy information about [availability of computer code](#)

Data collection	Study selection: Rayyan review system online. Data extraction: Microsoft Excel (version 2510; Microsoft Corporation).
Data analysis	All analyses were conducted using R software version 4.4.0 (R Foundation for Statistical Computing) with the meta and metafor packages.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio [guidelines for submitting code & software](#) for further information.

Data

Policy information about [availability of data](#)

All manuscripts must include a [data availability statement](#). This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our [policy](#)

Dataset available at: <https://doi.org/10.17605/OSF.IO/BJSJN>. The complete statements for both data availability and code availability are detailed in the manuscript.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender

Reporting on race, ethnicity, or other socially relevant groupings

Population characteristics

Recruitment

Ethics oversight

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☐ Life sciences

☒ Behavioural & social sciences

☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see [nature.com/documents/nr-reporting-summary-flat.pdf](https://www.nature.com/documents/nr-reporting-summary-flat.pdf)

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size

Data exclusions

Replication

Randomization

Blinding

Behavioural & social sciences study design

All studies must disclose on these points even when the disclosure is negative.

Study description

Systematic review and meta-analysis of prospective cohort studies (quantitative data).

Research sample

The included studies comprised both population-representative and non-representative cohort samples from the general population across all age groups, free of mental disorders/dementia at baseline. In total, 4,007,638 participants (30.5% women) from Finland, Italy, the Netherlands, Norway, Sweden, Taiwan, the UK, and the USA were included.

Sampling strategy

Not applicable. This study is a meta-analysis of observational cohort studies; sampling strategies were defined within the original studies and are described in the respective publications.

Data collection

Data extraction was conducted between March and May 2026 and included study characteristics, participant characteristics, CRF tests, outcomes with their assessment tools, and prospective associations.

Timing

Systematic searches were conducted from inception to 20 January 2025.

Data exclusions

Clinical populations; self-reported CRF; disorders related to pregnancy; conference abstracts.

Non-participation

Not applicable. This study is a meta-analysis of observational cohort studies; information on non-participation was reported, where available, in the original studies.

Randomization

Not applicable. This study is a meta-analysis of observational cohort studies; no participant allocation was performed by the investigators.

Ecological, evolutionary & environmental sciences study design

All studies must disclose on these points even when the disclosure is negative.

Study description	
Research sample	
Sampling strategy	
Data collection	
Timing and spatial scale	
Data exclusions	
Reproducibility	
Randomization	
Blinding	

Did the study involve field work? ☐ Yes ☐ No

Field work, collection and transport

Field conditions	
Location	
Access & import/export	
Disturbance	

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☒	☐ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used	
Validation	

Eukaryotic cell lines

Policy information about [cell lines and Sex and Gender in Research](#)

Cell line source(s)

Authentication

Mycoplasma contamination

Commonly misidentified lines
(See [ICLAC](#) register)

Palaeontology and Archaeology

Specimen provenance

Specimen deposition

Dating methods

☐ Tick this box to confirm that the raw and calibrated dates are available in the paper or in Supplementary Information.

Ethics oversight

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Animals and other research organisms

Policy information about [studies involving animals](#); [ARRIVE guidelines](#) recommended for reporting animal research, and [Sex and Gender in Research](#)

Laboratory animals

Wild animals

Reporting on sex

Field-collected samples

Ethics oversight

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Clinical data

Policy information about [clinical studies](#)

All manuscripts should comply with the ICMJE [guidelines for publication of clinical research](#) and a completed [CONSORT checklist](#) must be included with all submissions.

Clinical trial registration

Study protocol

Data collection

Outcomes

Dual use research of concern

Policy information about [dual use research of concern](#)

Hazards

Could the accidental, deliberate or reckless misuse of agents or technologies generated in the work, or the application of information presented in the manuscript, pose a threat to:

No	Yes
☐	☐ Public health
☐	☐ National security
☐	☐ Crops and/or livestock
☐	☐ Ecosystems
☐	☐ Any other significant area

Experiments of concern

Does the work involve any of these experiments of concern:

No	Yes
☐	☐ Demonstrate how to render a vaccine ineffective
☐	☐ Confer resistance to therapeutically useful antibiotics or antiviral agents
☐	☐ Enhance the virulence of a pathogen or render a nonpathogen virulent
☐	☐ Increase transmissibility of a pathogen
☐	☐ Alter the host range of a pathogen
☐	☐ Enable evasion of diagnostic/detection modalities
☐	☐ Enable the weaponization of a biological agent or toxin
☐	☐ Any other potentially harmful combination of experiments and agents

Plants

Seed stocks	
Novel plant genotypes	
Authentication	

ChIP-seq

Data deposition

- ☐ Confirm that both raw and final processed data have been deposited in a public database such as [GEO](#).
- ☐ Confirm that you have deposited or provided access to graph files (e.g. BED files) for the called peaks.

Data access links <i>May remain private before publication.</i>	
Files in database submission	
Genome browser session (e.g. UCSC)	

Methodology

Replicates	
Sequencing depth	
Antibodies	
Peak calling parameters	
Data quality	

Software

Flow Cytometry

Plots

Confirm that:

- ☐ The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).
- ☐ The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).
- ☐ All plots are contour plots with outliers or pseudocolor plots.
- ☐ A numerical value for number of cells or percentage (with statistics) is provided.

Methodology

Sample preparation

Instrument

Software

Cell population abundance

Gating strategy

- ☐ Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.

Magnetic resonance imaging

Experimental design

Design type

Design specifications

Behavioral performance measures

Imaging type(s)

Field strength

Sequence & imaging parameters

Area of acquisition

Diffusion MRI

☐ Used☐ Not used

Preprocessing

Preprocessing software

Normalization

Normalization template

Noise and artifact removal

Volume censoring

Statistical modeling & inference

Model type and settings

Effect(s) tested

Specify type of analysis: ☐ Whole brain ☐ ROI-based ☐ Both

Statistic type for inference

(See [Eklund et al. 2016](#))

Correction

Models & analysis

n/a | Involved in the study

☐ ☐ Functional and/or effective connectivity☐ ☐ Graph analysis☐ ☐ Multivariate modeling or predictive analysis

Functional and/or effective connectivity

Graph analysis

Multivariate modeling and predictive analysis

