Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Covariate Adjustment and Interpretation of Mortality Estimates in ADHD: A Systematic Review and Meta-analysis

Yu Chang
Chung Shan Medical University Hospital
Ming-Hong Hsieh
Chung Shan Medical University Hospital
Yi-Chun Liu
purpplewhale@yahoo.com.tw

Kaohsiung Show Chwan Memorial Hospital

Research Article

Keywords: attention-deficit/hyperactivity disorder, mortality, certainty, covariate adjustment, systematic review, meta-analysis

Posted Date: October 14th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10794763/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License

Additional Declarations: No competing interests reported.

Abstract

Although attention-deficit/hyperactivity disorder (ADHD) has been associated with elevated mortality, the certainty of this association and the implications of differing adjustment strategies remain unclear. We searched PubMed, Embase, and Web of Science through August 2026. Covariates were classified by domain and assessed for potential causal roles. For each study, we selected the model most closely addressing the overall association, avoiding additional adjustment for potentially post-exposure or causally ambiguous variables when possible. Random-effects meta-analyses used restricted maximum likelihood estimation with Hartung-Knapp intervals. Fifteen studies included 489,666 individuals with ADHD. Adjustment strategies varied substantially, and only three studies reported sequential models. Eleven studies comprising 452,393 individuals contributed to the primary all-cause synthesis (risk ratio [RR], 2.02; 95% confidence interval [CI], 1.59–2.58; I^2 = 95.8%; 95% prediction interval, 0.94–4.35). External-cause mortality was elevated but highly heterogeneous (RR, 2.76; 95% CI, 1.99–3.81; I^2 = 90.5%; 95% prediction interval, 0.98–7.72), whereas natural-cause mortality was imprecisely estimated (RR, 1.63; 95% CI, 0.61–4.33; I^2 = 87.6%). In one sequential comparison, adjustment for psychiatric comorbidity shifted the external-cause OR from 2.37 to 0.88, crossing the null. Prediction intervals for all-cause and external-cause mortality also crossed the null. All studies were rated at high risk of bias using ROBINS-E, and certainty of evidence was very low. These findings caution against interpreting pooled estimates as precise measures of mortality risk across settings and highlight the importance of study-specific adjustment strategies and contrasts.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by difficulties with attention, impulsivity, and executive functioning [1]. In addition to impaired quality of life [2], ADHD has been associated with premature mortality from external and natural causes [3–6]. Quantifying this association is relevant to public mental health and assessment of disease burden [7–11].

Existing syntheses of ADHD and mortality have generally reported a single pooled point estimate, often framed as a two- to threefold increase in risk [12]. However, interpretation of such estimates also depends on between-study heterogeneity and the certainty of the underlying evidence, which have received less systematic attention, including through prediction intervals and GRADE-based certainty assessments. A further issue is variation in the underlying study-specific contrast, including differences in population, time horizon, and covariate adjustment [13–16]. In observational studies, adjustment for variables with uncertain temporal or causal roles may change the interpretation of the resulting estimate, particularly when ADHD symptoms precede formal diagnosis or database entry. These differences may limit the comparability of adjusted estimates across studies.

To address these gaps, we conducted a systematic review and meta-analysis of observational studies of ADHD and mortality, focusing on evidence certainty and how differing covariate adjustment strategies affect the interpretation of mortality estimates.

Methods

Protocol and Registration

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [17]. The PRISMA checklist is provided in Method S1. The protocol was prospectively registered on the Open Science Framework (OSF; https://osf.io/8np5a). Method S2 details protocol amendments.

Data Sources and Search Strategy

We conducted the initial search on October 26, 2025, updated it on November 20, 2025, and reran the searches on August 18, 2026. Sources included PubMed, Embase, and the Web of Science Core Collection. To improve completeness, we conducted forward citation searching from the most recent systematic review [12]. Searches combined terms for ADHD with terms for mortality, death, fatality, survival, all-cause mortality, cause-specific mortality, and standardized mortality ratio. Full searching strategies are reported in Method S3.

Eligibility Criteria and Estimand Framework

We included cohort and case-control studies of individuals with a recorded formal clinical ADHD diagnosis. Eligible exposure definitions included ICD-9, ICD-10, ICD-11, or DSM-III through DSM-5 criteria and diagnostic coding systems mapped to clinical ADHD diagnoses. Eligible studies included a comparison group without ADHD and reported a ratio measure, such as a hazard ratio (HR), risk ratio (RR), odds ratio (OR), standardized mortality ratio (SMR), incidence rate ratio (IRR) or mortality ratio, with a 95% confidence interval (CI).

We characterized the study-specific mortality contrasts according to their population, comparator, outcome, adjustment strategy, and temporal and analytic features. For each study, the population of interest comprised eligible individuals in the source population, classified according to the presence or absence of a recorded clinical ADHD diagnosis. The exposure group comprised individuals with a recorded ADHD diagnosis, and the comparator comprised individuals without such a diagnosis in the same source population. The primary outcome was all-cause mortality, with external- and natural-cause mortality as secondary outcomes. Time zero, follow-up duration, comparator definition, and effect measure were determined by each study's design and were not harmonized across studies. Because these design and analytic features varied across studies, the review does not identify a single fully harmonized estimand.

Covariates were classified into seven domains: demographic, socioeconomic or educational, parental or familial, birth-related, psychiatric, physical health, and health behavior or healthcare use. Demographic, socioeconomic, parental, and birth-related variables were considered candidate antecedent confounders when they plausibly preceded ADHD. Psychiatric and physical comorbidities, health behaviors, and healthcare use were treated as potentially post-exposure or causally ambiguous. Reviewers considered whether each covariate could act as a common cause, mediator, collider, or marker of severity or ascertainment, with causal interpretation informed by timing and study context. Variables recorded before diagnosis were not considered antecedent solely on the basis of recording time.

For the primary quantitative synthesis, we aimed to summarize the overall association between recorded ADHD diagnosis and subsequent mortality in each study population. We selected the model that most closely addressed this association, favoring adjustment for plausible antecedent confounders and avoiding additional adjustment for potentially post-exposure or causally ambiguous variables when alternative models were available. Unadjusted estimates were retained when no adjusted estimate was available.

When a study reported sequential models, we also extracted the most extensively adjusted estimate and recorded the added covariate domains. Studies reporting life expectancy loss without ratio measures or insufficient mortality data were excluded. No restrictions were applied by year or language.

Study Selection and Data Extraction

We removed duplicate records before screening and managed the screening process in Rayyan. When multiple reports used the same cohort, we prioritized the report that most directly addressed the review question and provided the most complete data. Two board-certified psychiatrists (YC and MHH) independently screened titles and abstracts and then assessed full texts. Rayyan's machine learning ratings were used only as a screening aid after manual review of successive batches of 100 records. Reviewers made all final eligibility decisions.

Two same reviewers (YC and MHH) independently extracted study design, setting, geographic region, coverage period, follow-up duration, sample size, participant characteristics, number of deaths, exposure and outcome definitions, effect measures, model-specific estimates, reported covariates, and availability of sequential models. These data informed the characterization of study-specific mortality contrasts described above. Disagreements were resolved by discussion or consultation with a third senior reviewer (YCL).

Quality Assessment and Certainty of Evidence

Reviewers independently assessed risk of bias. We used the Newcastle-Ottawa Scale (NOS) to maintain comparability with previous literature and the Risk of Bias in Non-randomized Studies of Exposures (ROBINS-E) tool [18], a structured framework covering seven bias domains. Certainty of evidence was evaluated using GRADE. Funnel plots and Egger's test were treated as exploratory because of the small number and marked heterogeneity of studies.

Evidence Mapping and Statistical Synthesis

The primary methodological outcomes were the distribution of covariate domains and availability of sequential models. The primary clinical outcome was all-cause mortality; external- and natural-cause mortality were secondary outcomes. Quantitative synthesis was performed for outcomes reported by at least three studies. Because absolute mortality risks were low, ORs and SMRs were treated as approximations of RRs under rare outcome assumptions [19, 20], and HRs were pooled on the same ratio scale. The primary all-cause synthesis used estimates for populations including both sexes. When only mutually exclusive male and female estimates were available, we derived a combined estimate by fixed-effect inverse-variance pooling on the log-ratio scale. We synthesized the selected estimates using random-effects models in the R package meta [21], with between-study variance estimated by restricted maximum likelihood and Hartung-Knapp confidence intervals. For syntheses with at least five contributing studies, we also reported 95% prediction intervals to characterize the expected range of the true effect across settings.

For studies with sequential models, we compared estimates within studies and calculated the ratio of the more extensively adjusted estimate to the selected estimate. Ratios below 1 indicate attenuation of the reported association. Leave-one-out analyses, prespecified subgroup analyses by risk-of-bias category and geographic region, and sensitivity analyses excluding studies reporting OR or SMR estimates directly were performed as supporting analyses.

Results

Study Selection and Characteristics

The updated search and eligibility reassessment identified 15 eligible studies. The August 18, 2026 update identified no additional eligible peer-reviewed study. Compared with the previous meta-analysis [12], four additional eligible reports were identified [6, 22–24], and one earlier report was replaced by a longer follow-up of the same cohort [6, 25]. Study selection and reasons for exclusion are presented in Fig. 1 and Result S1.

The 15 studies included 489,666 individuals with ADHD and varied in design, setting, age, ADHD definition, comparator, follow-up, and effect measure (Result S2). The covariate domain map showed marked heterogeneity in adjustment strategies (Table 1). Five studies reported unadjusted estimates, and only a minority reported sequential models suitable for within-study comparison.

Table 1
Covariate domains of included studies

Study	Candidate antecedent confounder domains				Potentially post-exposure or causally ambiguous domains			Model-reporting feature
	Demographic	Socioeconomic or educational	Parental or familial	Birth-related	Psychiatric comorbidity	Physical-health conditions	Health behavior or healthcare use	Sequential models reported
Kuperman [28]	●							No
Barkley [29]								No
Klein [30]								No
Barbaresi [31]	●							No
Dalsgaard [3]	●	●	●					No
Hechtman [32]	●							No
London [33]	●							No
Chen [5]	●	●		△	△		●	Yes
Sun [4]	●	●	●	●				No
Yeh [34]	●	●			△			Yes
Fitzgerald [35]	●							No
Schiavone [6]	●							No
Kim [22] – all-cause outcome	●	●			●	△	△	Yes
Kim [22] – external-cause outcome	●	●			△	△	△	Yes
Bowden [23]	●	●						No
O'Nions [24]	●							No

● indicates a domain included in the selected (primary) model, or in the single reported model for studies without sequential models. △ indicates a domain added only in the more extensively adjusted model, for the three studies with sequential models.

Primary Mortality Synthesis and Cause-Specific Mortality

Eleven studies comprising 452,393 individuals with ADHD contributed to the primary synthesis of all-cause mortality. ADHD was associated with higher mortality (pooled RR, 2.02; 95% CI, 1.59–2.58), but heterogeneity was substantial ($I^2 = 95.8\%$; $p < 0.001$; Fig. 2). Given this heterogeneity, the 95% prediction interval for the true effect in a new study population was wide (0.94–4.35).

External-cause mortality was elevated and highly heterogeneous (RR, 2.76; 95% CI, 1.99–3.81; I^2 = 90.5%; 95% prediction interval, 0.98–7.72; k = 11; Result S3). Natural-cause mortality was imprecisely estimated (RR, 1.63; 95% CI, 0.61–4.33; I^2 = 87.6%; k = 3; Result S4), and a reliable prediction interval could not be estimated for this outcome given the small number of contributing studies. In sex-specific all-cause analyses, the male analysis included six studies (RR, 2.15; 95% CI, 1.34–3.47; I^2 = 98.1%) and the female analysis included five studies (RR, 2.64; 95% CI, 1.43–4.86; I^2 = 95.7%; Results S5-S6). Sex-specific external-cause mortality was also elevated in both sexes (female: RR, 3.15; 95% CI, 1.49–6.64; I^2 = 90.6%; male: RR, 2.50; 95% CI, 1.38–4.53; I^2 = 97.5%; Results S7-S8). Table 2 summarizes the selected estimates for all-cause, external-cause, and natural-cause mortality, with full study-level detail in Result S9.

Table 2
Pooled estimates for all-cause and cause-specific mortality associated with ADHD

Outcome	No. of studies	ADHD participants	Pooled Ratio (95% CI)	95% Prediction Interval	I^2
All-cause mortality, both sexes	11	452,393	2.02 (1.59–2.58)	0.94–4.35	95.8
External-cause mortality, both sexes	11	433,080	2.76 (1.99–3.81)	0.98–7.72	90.5
Natural-cause mortality, both sexes	3	394,711	1.63 (0.61–4.33)	Not estimable	87.6

Estimates were selected to most closely address the overall association, with preference for adjustment for plausible antecedent confounders and without additional adjustment for potentially post-exposure variables when alternative models were available. A reliable prediction interval could not be estimated for natural-cause mortality (k = 3). ADHD, attention-deficit/hyperactivity disorder; CI, confidence interval; I^2, proportion of total variation due to between-study heterogeneity.

Influence of Individual Studies

In leave-one-out analyses, pooled all-cause mortality RRs ranged from 1.80 to 2.19 (Result S10). Excluding Sun et al. reduced I^2 from 95.8% to 82.7% and lowered the pooled RR to 1.80, indicating that substantial heterogeneity persisted after removal of the most influential study. Subgroup analyses by risk-of-bias category and geographic region did not resolve this heterogeneity either (pooled RR range, 1.77–2.06 across Newcastle-Ottawa Scale categories and 1.63–2.71 across regions; Results S11-S12). Excluding the two studies reporting SMR or OR estimates yielded a similar result (k = 9; 451,372 individuals with ADHD; RR, 2.06; 95% CI, 1.52–2.78; I^2 = 96.6%; Result S13).

Within-Study Changes Across Adjustment Strategies

Sequential all-cause mortality models were available in only three studies (Table 3). Further adjustment attenuated the HR in Chen et al. from 1.32 to 1.07 (ratio of estimates, 0.81) and the HR in Kim et al. from 1.67 to 1.39 (ratio of estimates, 0.83). In Chen et al., the additional model included congenital anomalies and psychiatric comorbidities. For external-cause mortality, additional adjustment produced varying degrees of attenuation, with ratios of estimates of 0.93 in Chen et al., 0.37 in Yeh et al., and 0.54 in Kim et al. The corresponding ratio of estimates for natural-cause mortality in Chen et al. was 0.80.

Table 3
Within-study changes after additional covariate adjustment

Outcome and study	Selected ratio estimate (95% CI)	More extensively adjusted ratio estimate (95% CI)	Ratio of more extensively adjusted to selected estimate	Added covariate domains
All-cause: Chen et al. [5]	**1.32 (1.22–1.43)**	1.07 (1.00-1.17)	0.81	Birth-related factor (congenital anomalies) and psychiatric comorbidity
All-cause: Kim et al. [22]	**1.67 (1.13–2.46)**	1.39 (0.94–2.05)	0.83	Physical comorbidity and health behaviors
External cause: Chen et al. [5]	**1.63 (1.43–1.86)**	**1.51 (1.32–1.72)**	0.93	Birth-related factor (congenital anomalies) and psychiatric comorbidity
External cause: Yeh et al. [34]	**2.37 (1.79–3.15)**	0.88 (0.66–1.18)	0.37	Psychiatric comorbidity
External cause: Kim et al. [22]	1.79 (0.25–12.73)	0.97 (0.14–6.88)	0.54	Physical and psychiatric comorbidity and health behaviors
Natural cause: Chen et al. [5]	**1.14 (1.02–1.27)**	0.91 (0.80–1.15)	0.80	Birth-related factor (congenital anomalies) and psychiatric comorbidity

CI, confidence interval.

Risk of Bias and Certainty

Ten studies were rated as low risk and five as moderate risk using the Newcastle-Ottawa Scale (Result S14), but all were rated at high risk of bias using ROBINS-E (Result S15). Residual confounding and uncertainty about the temporal and causal roles of adjusted variables were the main concerns. Egger's test did not indicate funnel plot asymmetry (intercept = 0.90; p = 0.707; Result S16). GRADE certainty was very low for all-cause, external-cause, and natural-cause mortality because of the observational design, inconsistency, and indirectness arising from heterogeneous effect measures and adjustment strategies, with an additional imprecision downgrade for natural-cause mortality (Result S17).

Discussion

This review found a general pattern of elevated mortality among people diagnosed with ADHD, although the certainty of the evidence was very low and the magnitude of the association varied substantially across studies. All-cause mortality was approximately twofold higher overall. For both outcomes with estimable prediction intervals, the intervals crossed the null: 0.94–4.35 for all-cause mortality and 0.98–7.72 for external-cause mortality. These findings indicate considerable uncertainty in the magnitude of the association expected across settings. Previous syntheses have largely emphasized a single pooled estimate, while our findings highlight the importance of between-study heterogeneity and study-specific adjustment strategies when interpreting ADHD-associated mortality.

The substantial heterogeneity may reflect multiple differences across studies, including diagnostic era, ascertainment, age, comparator population, follow-up, effect measure, and adjustment strategy. Time zero is particularly relevant: birth cohorts can observe factors before symptom development, whereas registry studies beginning at diagnosis capture only the documented prediagnosis period. These differences limit the extent to which apparently similar estimates can be interpreted as representing comparable population contrasts or confounding structures. The available subgroup and sensitivity analyses did not identify a single study characteristic that accounted for the observed heterogeneity.

Covariate adjustment is one important source of this interpretive heterogeneity. Adjustment may improve confounding control while also changing the conditional contrast being estimated. Congenital anomalies are more readily interpreted as antecedent factors, whereas psychiatric comorbidity, physical illness, health behaviors, and healthcare use may reflect shared liability, downstream consequences of ADHD, or diagnostic ascertainment. Their causal roles may differ according to timing and study

context. Consequently, the same variable may reduce confounding in one setting while blocking a pathway of interest in another [13, 14]. The within-study comparisons provide empirical support for this interpretive uncertainty. Additional adjustment produced attenuation in the all-cause estimates and larger, more variable changes in external-cause estimates.

These findings have practical implications for clinical communication and public mental health. Clinically, the approximately twofold pooled estimate for all-cause mortality should not be presented as a precise individual-level prognosis, given the substantial between-study heterogeneity, wide prediction interval, and very low certainty of evidence. The particularly elevated, although heterogeneous, estimates for external-cause mortality also highlight the importance of assessing psychiatric comorbidity and other potentially modifiable factors relevant to external-cause mortality. Importantly, attenuation after adjustment for psychiatric comorbidity should not be interpreted as showing that excess mortality is simply explained away, because such adjustment may control confounding, block pathways associated with ADHD, or change the conditional contrast being estimated. At the population level, estimates that adjust for plausible antecedent confounders without conditioning on potentially downstream factors may be more informative for characterizing the overall mortality burden associated with diagnosed ADHD.

Future studies should define the estimand according to the research question and explicitly specify the target population, comparator, outcome, time horizon, and relevant temporal anchor. In ADHD research, distinguishing symptom onset, clinical diagnosis, and database entry is particularly important because recorded diagnosis reflects healthcare access and clinical recognition as well as underlying ADHD. Estimands intended to characterize overall mortality burden may differ from those designed to investigate mechanisms or treatment effects, including questions of medication class and dose [26]. Stronger control of antecedent confounding may be achieved through linkage to parental, socioeconomic, and early-life data, while sibling comparisons [27], negative controls, and other quasi-experimental approaches may help evaluate shared familial confounding under different assumptions. Systematic reviews should preserve these distinctions when synthesizing estimates across study designs.

Limitations

This review has several limitations. First, the causal roles of covariates were inferred retrospectively from published descriptions and plausible timing because individual-level temporal information was unavailable. We reduced this uncertainty by systematically classifying covariates by domain and considering their potential causal roles, although some misclassification remains possible. Second, sequential models were available for only a small number of studies. We treated within-study changes descriptively and did not pool attenuation ratios. Third, the meta-analysis combined different effect measures and comparator structures. A sensitivity analysis excluding studies reporting SMR or OR estimates yielded similar results, although residual differences in interpretation and comparability remain. Fourth, substantial clinical and methodological heterogeneity limited the precision and generalizability of the pooled estimates. We addressed this through random-effects models, prediction intervals, and supporting sensitivity and subgroup analyses, but these approaches could not fully account for the observed heterogeneity. Finally, we did not obtain unpublished models or additional data from study authors.

Conclusion

ADHD was associated with higher mortality, but the certainty of this evidence was very low and the magnitude varied substantially across studies. Variation in adjustment strategies may have resulted in estimates corresponding to different underlying contrasts, limiting their comparability across studies. These findings caution against treating pooled estimates as precise measures of mortality risk across settings. Future studies should specify target estimands and temporal anchors, strengthen control of antecedent confounding, and report sequential adjustment models to clarify the magnitude and interpretation of the association.

Declarations

Competing interests

The authors declare that they have no competing interests.

Ethics approval

This systematic review used data from published studies and did not involve new research with human participants; ethics approval was not required.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Funding

The authors received no funding for this work.

Author Contribution

YC and YCL conceived and designed the study. YC and MHH conducted the literature search, study selection, and data extraction. YC and YCL performed the risk-of-bias assessment and statistical analysis. YC drafted the manuscript. MHH and YCL critically revised the manuscript. All authors read and approved the final manuscript.

Data and code availability

All data used in the review are reported in the article and its supplementary material. Analytic code is available from the corresponding author on reasonable request.

References

1. Faraone SV, Banaschewski T, Coghill D, Zheng Y, Biederman J, Bellgrove MA, Newcorn JH, Gignac M, Al Saud NM, Manor I, Rohde LA, Yang L, Cortese S, Almagor D, Stein MA, Albatti TH, Aljoudi HF, Alqahtani MMJ, Asherson P, Atwoli L, Bölte S, Buitelaar JK, Crunelle CL, Daley D, Dalsgaard S, Döpfner M, Espinet S, Fitzgerald M, Franke B, Gerlach M, Haavik J, Hartman CA, Hartung CM, Hinshaw SP, Hoekstra PJ, Hollis C, Kollins SH, Sandra Kooij JJ, Kuntsi J, Larsson H, Li T, Liu J, Merzon E, Mattingly G, Mattos P, McCarthy S, Mikami AY, Molina BSG, Nigg JT, Purper-Ouakil D, Omigbodun OO, Polanczyk GV, Pollak Y, Poulton AS, Rajkumar RP, Reding A, Reif A, Rubia K, Rucklidge J, Romanos M, Ramos-Quiroga JA, Schellekens A, Scheres A, Schoeman R, Schweitzer JB, Shah H, Solanto MV, Sonuga-Barke E, Soutullo C, Steinhausen H-C, Swanson JM, Thapar A, Tripp G, van de Glind G, van den Brink W, Van der Oord S, Venter A, Vitiello B, Walitza S, Wang Y (2021) The World Federation of ADHD International Consensus Statement: 208 Evidence-based conclusions about the disorder. Neurosci Biobehav Rev 128:789–818. https://doi.org/10.1016/j.neubiorev.2021.01.022
2. Coghill DR, Banaschewski T, Soutullo C, Cottingham MG, Zuddas A (2017) Systematic review of quality of life and functional outcomes in randomized placebo-controlled studies of medications for attention-deficit/hyperactivity disorder. Eur Child Adolesc Psychiatry 26:1283–1307. https://doi.org/10.1007/s00787-017-0986-y
3. Dalsgaard S, Østergaard SD, Leckman JF, Mortensen PB, Pedersen MG (2015) Mortality in children, adolescents, and adults with attention deficit hyperactivity disorder: a nationwide cohort study. Lancet 385:2190–2196. https://doi.org/10.1016/S0140-6736(14)61684-6
4. Sun S, Kuja-Halkola R, Faraone SV, D'Onofrio BM, Dalsgaard S, Chang Z, Larsson H (2019) Association of Psychiatric Comorbidity With the Risk of Premature Death Among Children and Adults With Attention-Deficit/Hyperactivity Disorder. JAMA Psychiatry 76:1141–1149. https://doi.org/10.1001/jamapsychiatry.2019.1944

5. Chen VC-H, Chan H-L, Wu S-I, Lee M, Lu M-L, Liang H-Y, Dewey ME, Stewart R, Lee CT-C (2019) Attention-Deficit/Hyperactivity Disorder and Mortality Risk in Taiwan. JAMA Netw Open 2:e198714. https://doi.org/10.1001/jamanetworkopen.2019.8714
6. Schiavone N, Virta M, Leppämäki S, Launes J, Vanninen R, Tuulio-Henriksson A, Järvinen I, Lehto E, Michelsson K, Hokkanen L (2022) Mortality in individuals with childhood ADHD or subthreshold symptoms - a prospective perinatal risk cohort study over 40 years. BMC Psychiatry 22:325. https://doi.org/10.1186/s12888-022-03967-3
7. GBD 2019 Diseases and Injuries Collaborators (2020) Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet 396:1204–1222. https://doi.org/10.1016/S0140-6736(20)30925-9
8. Li N, Zhao J, Zhou F (2025) The burden of attention deficit hyperactivity disorder and incidence rate forecast in China from 1990 to 2021. Front Psychiatry 16:1532156. https://doi.org/10.3389/fpsyt.2025.1532156
9. Fan Y, Fan A, Yang Z, Fan D (2025) Global burden of mental disorders in 204 countries and territories, 1990–2021: results from the global burden of disease study 2021. BMC Psychiatry 25:486. https://doi.org/10.1186/s12888-025-06932-y
10. Wang Z, Dou Y, Yang X, Guo X, Ma X, Zhou B, Zhang W (2025) Global, regional, and national burden of mental disorders among adolescents and young adults, 1990–2021: a systematic analysis for the Global Burden of Disease Study 2021. Transl Psychiatry 15:397. https://doi.org/10.1038/s41398-025-03623-w
11. Cortese S, Song M, Farhat LC, Yon DK, Lee SW, Kim MS, Park S, Oh JW, Lee S, Cheon K-A, Smith L, Gosling CJ, Polanczyk GV, Larsson H, Rohde LA, Faraone SV, Koyanagi A, Dragioti E, Radua J, Carvalho AF, Il Shin J, Solmi M (2023) Incidence, prevalence, and global burden of ADHD from 1990 to 2019 across 204 countries: data, with critical re-analysis, from the Global Burden of Disease study. Mol Psychiatry 28:4823–4830. https://doi.org/10.1038/s41380-023-02228-3
12. Catalá-López F, Hutton B, Page MJ, Driver JA, Ridao M, Alonso-Arroyo A, Valencia A, Macías Saint-Gerons D, Tabarés-Seisdedos R (2022) Mortality in Persons With Autism Spectrum Disorder or Attention-Deficit/Hyperactivity Disorder: A Systematic Review and Meta-analysis. JAMA Pediatr 176:e216401. https://doi.org/10.1001/jamapediatrics.2021.6401
13. Schisterman EF, Cole SR, Platt RW (2009) Overadjustment Bias and Unnecessary Adjustment in Epidemiologic Studies. Epidemiology 20:488–495. https://doi.org/10.1097/EDE.0b013e3181a819a1
14. van Zwieten A, Blyth FM, Wong G, Khalatbari-Soltani S (2024) Consideration of overadjustment bias in guidelines and tools for systematic reviews and meta-analyses of observational studies is long overdue. Int J Epidemiol 53:dyad174. https://doi.org/10.1093/ije/dyad174
15. Shi Y, Hunter Guevara LR, Dykhoff HJ, Sangaralingham LR, Phelan S, Zaccariello MJ, Warner DO (2021) Racial Disparities in Diagnosis of Attention-Deficit/Hyperactivity Disorder in a US National Birth Cohort. JAMA Netw Open 4:e210321. https://doi.org/10.1001/jamanetworkopen.2021.0321
16. Mowlem FD, Rosenqvist MA, Martin J, Lichtenstein P, Asherson P, Larsson H (2019) Sex differences in predicting ADHD clinical diagnosis and pharmacological treatment. Eur Child Adolesc Psychiatry 28:481–489. https://doi.org/10.1007/s00787-018-1211-3
17. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D (2021) The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 372:n71. https://doi.org/10.1136/bmj.n71
18. Higgins JPT, Morgan RL, Rooney AA, Taylor KW, Thayer KA, Silva RA, Lemeris C, Akl EA, Bateson TF, Berkman ND, Glenn BS, Hróbjartsson A, LaKind JS, McAleenan A, Meerpohl JJ, Nachman RM, Obbagy JE, O'Connor A, Radke EG, Savović J, Schünemann HJ, Shea B, Tilling K, Verbeek J, Viswanathan M, Sterne JAC (2024) A tool to assess risk of bias in non-randomized follow-up studies of exposure effects (ROBINS-E). Environ Int 186:108602. https://doi.org/10.1016/j.envint.2024.108602
19. Greenland S, Thomas DC (1982) On the need for the rare disease assumption in case-control studies. Am J Epidemiol 116:547–553. https://doi.org/10.1093/oxfordjournals.aje.a113439
20. Symons MJ, Taulbee JD (1981) Practical considerations for approximating relative risk by the standardized mortality ratio. J Occup Med 23:413–416. https://doi.org/10.1097/00043764-198106000-00013

21. Balduzzi S, Rücker G, Schwarzer G (2019) How to perform a meta-analysis with R: a practical tutorial. Evid Based Ment Health 22:153–160. https://doi.org/10.1136/ebmental-2019-300117
22. Kim H, Jung JH, Han K, Jeon HJ (2025) Risk of suicide and all-cause death in patients with mental disorders: a nationwide cohort study. Mol Psychiatry 30:2831–2839. https://doi.org/10.1038/s41380-025-02887-4
23. Bowden N, Schluter PJ, Asaka U, Dacombe J, Hii J, Lee J, Mirfin-Veitch B, Muir C, Nazari Orakani S, Schmidt L, Szymanska K, Cruice E, Vu H, Lawrence Lodge R (2025) Mortality Risk of Youth With Neurodevelopmental Conditions: An Aotearoa New Zealand Nationwide Birth Cohort Study. https://doi.org/10.1001/jamapediatrics.2025.4335. JAMA Pediatr e254335
24. O'Nions E, El Baou C, John A, Lewer D, Mandy W, McKechnie DGJ, Petersen I, Stott J (2025) Life expectancy and years of life lost for adults with diagnosed ADHD in the UK: matched cohort study. Br J Psychiatry 226:261–268. https://doi.org/10.1192/bjp.2024.199
25. Koisaari T, Michelsson K, Holopainen JM, Maksimainen R, Päivänsalo J, Rantala K, Tervo T (2015) Traffic and Criminal Behavior of Adults with Attention Deficit-Hyperactivity with a Prospective Follow-Up from Birth to the Age of 40 Years. Traffic Inj Prev 16:824–830. https://doi.org/10.1080/15389588.2015.1029068
26. Chang Y, Ju P-C, Hsieh M-H, Liu Y-C, Chang C-C (2026) Dose-response, net clinical benefit and optimal dose ranges of stimulants in children and adolescents with ADHD: a network meta-analysis. Eur Child Adolesc Psychiatry. https://doi.org/10.1007/s00787-026-03025-3
27. Frisell T (2020) Invited Commentary: Sibling-Comparison Designs, Are They Worth the Effort? Am J Epidemiol 190:738–741. https://doi.org/10.1093/aje/kwaa183
28. Kuperman S, Black DW, Burns TL (1988) Excess Mortality Among Formerly Hospitalized Child Psychiatric Patients. Arch Gen Psychiatry 45:277–282. https://doi.org/10.1001/archpsyc.1988.01800270095011
29. Barkley RA, Fischer M, Edelbrock CS, Smallish L (1990) The adolescent outcome of hyperactive children diagnosed by research criteria: I. An 8-year prospective follow-up study. J Am Acad Child Adolesc Psychiatry 29:546–557. https://doi.org/10.1097/00004583-199007000-00007
30. Klein RG, Mannuzza S, Olazagasti MAR, Roizen E, Hutchison JA, Lashua EC, Castellanos FX (2012) Clinical and functional outcome of childhood attention-deficit/hyperactivity disorder 33 years later. Arch Gen Psychiatry 69:1295–1303. https://doi.org/10.1001/archgenpsychiatry.2012.271
31. Barbaresi WJ, Colligan RC, Weaver AL, Voigt RG, Killian JM, Katusic SK (2013) Mortality, ADHD, and psychosocial adversity in adults with childhood ADHD: a prospective study. Pediatrics 131:637–644. https://doi.org/10.1542/peds.2012-2354
32. Hechtman L, Swanson JM, Sibley MH, Stehli A, Owens EB, Mitchell JT, Arnold LE, Molina BSG, Hinshaw SP, Jensen PS, Abikoff HB, Perez Algorta G, Howard AL, Hoza B, Etcovitch J, Houssais S, Lakes KD, Nichols JQ, MTA Cooperative Group (2016) Functional Adult Outcomes 16 Years After Childhood Diagnosis of Attention-Deficit/Hyperactivity Disorder: MTA Results. J Am Acad Child Adolesc Psychiatry 55:945–952e2. https://doi.org/10.1016/j.jaac.2016.07.774
33. London AS, Landes SD (2016) Attention Deficit Hyperactivity Disorder and adult mortality. Prev Med 90:8–10. https://doi.org/10.1016/j.ypmed.2016.06.021
34. Yeh H-H, Westphal J, Hu Y, Peterson EL, Williams LK, Prabhakar D, Frank C, Autio K, Elsiss F, Simon GE, Beck A, Lynch FL, Rossom RC, Lu CY, Owen-Smith AA, Waitzfelder BE, Ahmedani BK (2019) Diagnosed Mental Health Conditions and Risk of Suicide Mortality. Psychiatr Serv 70:750–757. https://doi.org/10.1176/appi.ps.201800346
35. Fitzgerald C, Dalsgaard S, Nordentoft M, Erlangsen A (2019) Suicidal behaviour among persons with attention-deficit hyperactivity disorder. Br J Psychiatry 1–6. https://doi.org/10.1192/bjp.2019.128

Figures

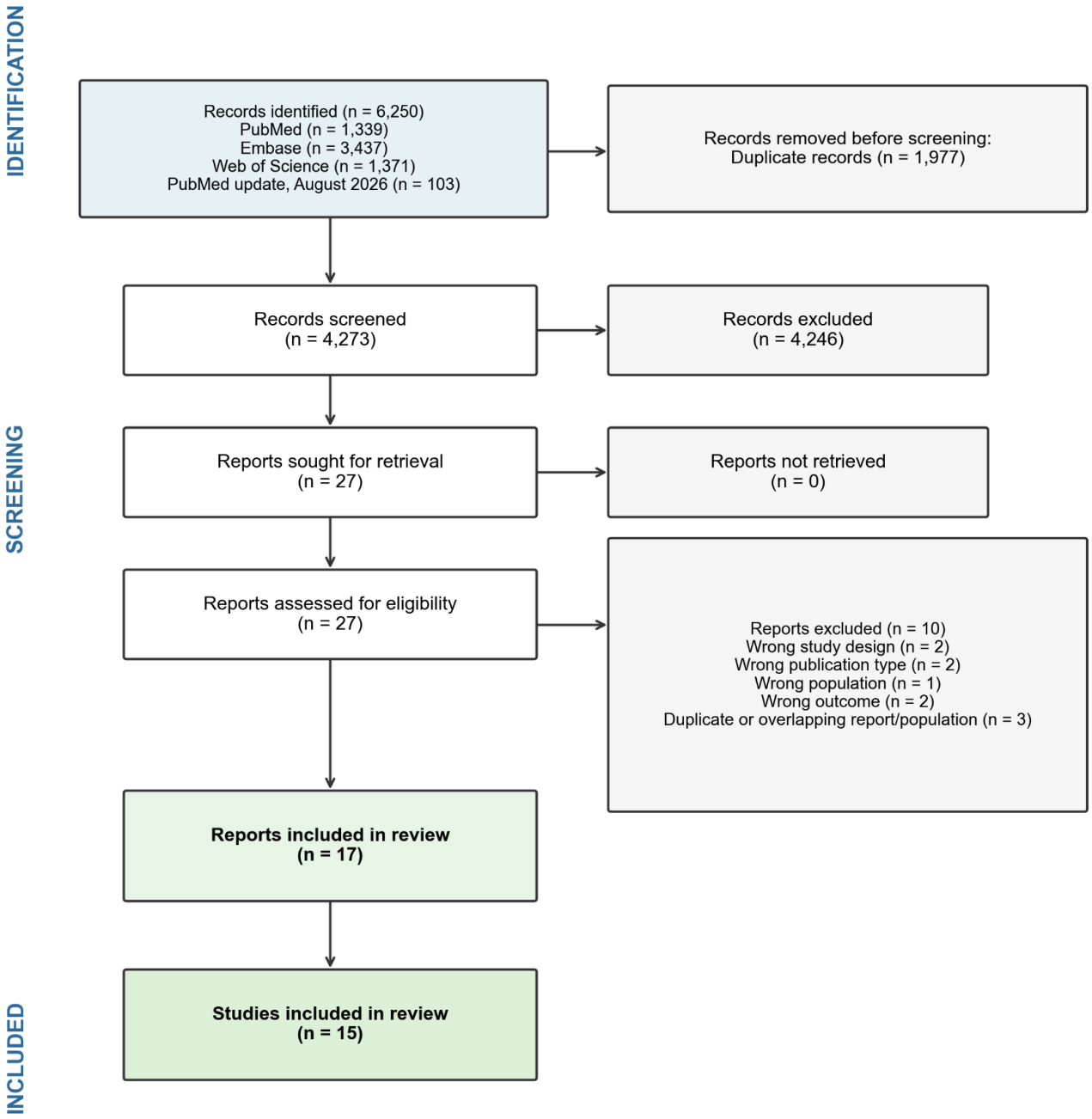

Figure 1

PRISMA 2020 flow diagram for study selection

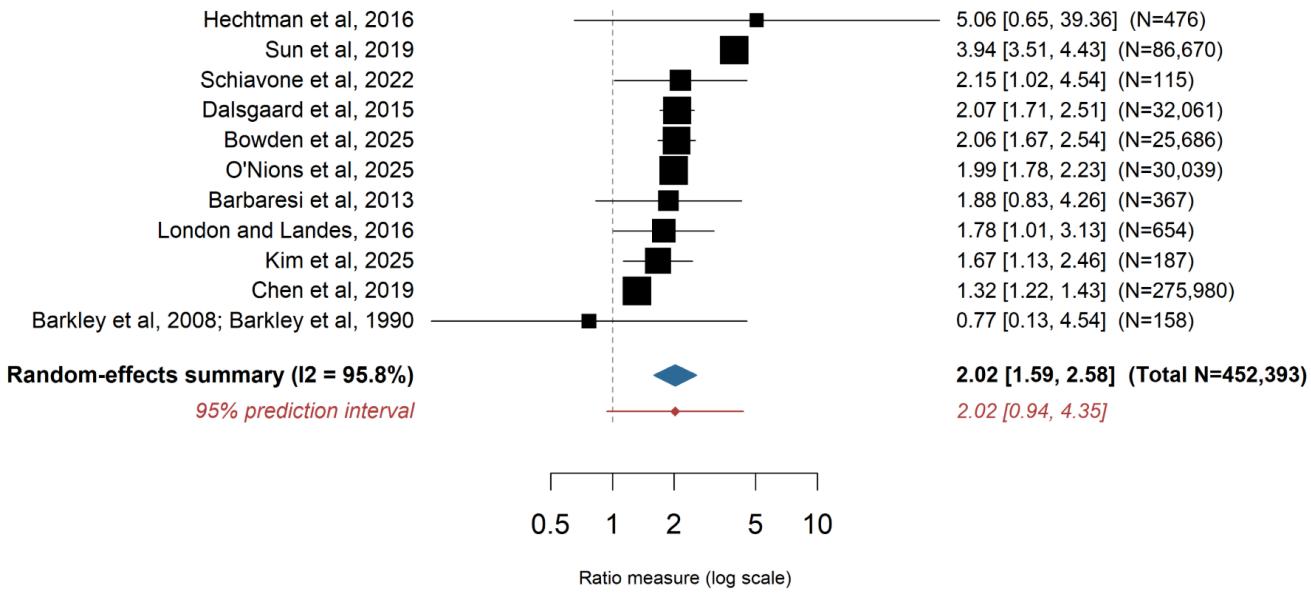

Figure 2

Forest plot of the estimates for the association between ADHD and all-cause mortality. Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CI, confidence interval; PI, prediction interval; I^2, proportion of total variation due to between-study heterogeneity.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementary.docx