National Institute for Health and Care Excellence

Final

Attention deficit hyperactivity disorder (update)

[A] Evidence reviews for risk factors for ADHD

NICE guideline NG87

Prognostic evidence review

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This evidence review was developed by the National Guideline Centre



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1 Risk factors for ADHD

1.1 Review question: Which groups of people are more likely than the general population to have ADHD or are more likely to have missed a diagnosis of ADHD?

1.2 Introduction

Although ADHD is a multifaceted condition that has different types of behavioural symptoms, the popular view of symptoms as mainly related to hyperactivity has led to under- diagnosis in certain populations. This chapter looks at the evidence for increased risk of ADHD in certain populations. Here risk refers to populations in which ADHD occurs at higher rates than in the general population, and where practitioners need to be alert to the diagnosis of ADHD.

There are two main reasons to raise awareness of ADHD in populations at high risk of ADHD. First, the overlap of symptoms with other neurodevelopmental and mental health problems can lead to diagnostic overshadowing and a failure to appropriately diagnosis and treat ADHD. Another problem is failure to identify and treat conditions co-existing with ADHD.

The findings on risk are therefore intended to identify the populations in which practitioners need to pay particular attention to the possibility of ADHD. Here screening for ADHD or how best to diagnose ADHD in the presence of co-existing conditions is not considered, the aim is to raise awareness among practitioners of the circumstances under which there is an increased risk of ADHD.

1.3 PICO table

For full details see the review protocol in appendix A.

Table 1: PICO characteristics of review question

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Population	Children, young people and adults		
Prognostic variables under consideration	 Comorbidities/personal medical history Neurodevelopmental disorders Intellectual disability Autism spectrum disorder (ASD) Mental health disorders Preterm children Social/environmental factors Looked after children Secure estate Children not in mainstream schooling Adults with unstable employment Family history of ADHD Female* 		
Confounding factors	No critical confounding factors were included in this review. The purpose was to identify those at higher risk of ADHD in the general, primary care population and not to prove causality or definitive association. The risk of bias and indirectness ratings have taken into account this impact and the implications discussed by the committee in forming recommendations.		
Outcomes	Diagnosis of ADHD by healthcare professional or trained lay interviewer		

	Missed diagnosis of ADHD				
	*Only missed diagnosis outcome to be extracted for gender risk, as increased prevalence in boys/men compared to girls/women is an accepted aspect of ADHD epidemiology and not priority for this review.				
Study design	 Studies including a general population and assessing prevalence Studies assessing ADHD diagnosis rates in matched cohorts 				

1.4 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. 186 Methods specific to this review question are described in the review protocol in appendix A.

Studies were pooled in this review as default given the lack of importance attached to confounders, however random effects meta-analysis was used to reflect the likely imprecision in effect sizes. Where studies were pooled and substantial heterogeneity was observed, studies were separated and downgraded for inconsistency.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy.

1.5 Clinical evidence

1.5.1 Included studies

Sixteen studies were included in the review; ¹³, ¹⁸, ⁴⁴, ⁵¹, ⁶¹, ⁶⁵, ⁸¹, ⁸⁴, ¹³⁹, ¹⁵⁵, ¹⁷², ¹⁸⁹, ²²⁵, ²²⁹, ²⁶¹, ²⁸⁶ these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 3). See also the study selection flow chart in appendix C, study evidence tables in appendix D, forest plots in appendix E, GRADE tables in appendix F and excluded studies list in appendix I.

Thirteen studies assessed ADHD diagnosis in childhood (aged 5 to 18) and four studies assessed ADHD diagnosis in adulthood (one study provided information on both children and young people 5 years and over and adults). No studies reported on missed ADHD diagnoses.

1.5.2 Excluded studies

See the excluded studies list in appendix I.

1.5.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Population	Prognostic variable(s)	Outcomes	Comments
Children a	nd young people			
Anderson 1987 ¹³	General representative sample of children from Dunedin (New Zealand), n = 782 Age stratum – 5 to 18 (mean age interviewed 11)	Anxiety disorders CD/ODD	ADHD diagnosis Psychiatric interview (DISC-C (DSM-III))	Cross- sectional prevalence Univariable analysis

		Prognostic		
Study	Population	variable(s)	Outcomes	Comments
Bora 2014 ⁴⁴	Preterm group from regional hospital; control group selected from births occurring at same hospital and times as preterm group (New Zealand), n = 815 Age stratum – 5 to 18 (mean age interviewed 9)	Preterm children	ADHD diagnosis Psychiatric interview (DSM-IV)	Retrospective cohort study Univariable analysis
Burnett 2014 ⁵¹	Preterm group from state of Victoria; control group selected to match for mother's country of origin, health insurance and sex of the child (Australia), n = 560 Age stratum – 5 to 18 (mean age interviewed 18)	Preterm children	ADHD diagnosis Psychiatric interview (ChIPS (DSM-IV))	Retrospective cohort study Univariable analysis
Clark 1997 ⁶¹	Substance abuse group from adolescent substance abuse centre; control group recruited via advertisement and systematic community sampling (USA), n = 219 Age stratum – 5 to 18 (mean age interviewed 16)	Substance abuse	ADHD diagnosis Psychiatric interview (K-SADS (DSM-III-R))	Retrospective cohort study Univariable analysis
Costa 2015 ⁶⁵	Epilepsy group consecutive patients treated in secondary care clinic; control group age, gender, SES matched - recruited from nearby primary school (Brazil), n = 73 Age stratum – 5 to 18 (mean age interviewed 11)	Epilepsy	ADHD diagnosis Psychiatric interview (DSM-IV)	Retrospective cohort study Univariable analysis
Elberling 2016 ⁸¹	Random sample of all children born around Copenhagen	ASD CD/ODD Mood disorders	ADHD diagnosis Trained lay interviewer	Cross- sectional prevalence

		Prognostic		
Study	Population	variable(s)	Outcomes	Comments
	in the year 2000, sample enriched with 20% high risk group (Denmark), n = 1585 Age stratum – 5 to 18 (mean age interviewed 6)		(SDQ (ICD-10))	Univariable analysis
Emerson 2003 ⁸⁴	Representative sample of children obtained from ONS (UK), n = 10438 Age stratum – 5 to 18 (interviewed between 5 and 15)	Intellectual disability	ADHD diagnosis Trained lay interviewer (DAWBA (ICD-10))	Cross- sectional prevalence Univariable analysis
Ford 2007 ¹⁰¹	Looked after group composed of random sample of all looked after children in UK, control group randomly sampled from child benefit register, n = 11691 Age stratum – 5 to 18 (interviewed when at least 11)	Looked after children	ADHD diagnosis Trained lay interviewer (DAWBA (ICD-10))	Retrospective cohort study Univariable analysis
Johnson 2010 ¹³⁹	Preterm group composed of all surviving and consenting children born <26 weeks gestation in UK in 1995, control group from index classmates matched for sex, gender, age and ethnicity (UK), n = 321 Age stratum – 5 to 18 (mean age interviewed 11)	Preterm children	ADHD diagnosis Trained lay interviewer (DAWBA (ICD-10))	Retrospective cohort study Univariable analysis
Kurlan 2002 ¹⁵⁵	General representative sample of children aged 9 to 17 (USA), n = 1596 Age stratum – 5 to 18 (interviewed between 9 and 17)	Tic disorders	ADHD diagnosis Psychiatric interview (DISC (DSM-IV))	Cross- sectional prevalence Univariable analysis
Neece 2011 ¹⁸⁹	Samples drawn from Collaborative Family Study in California,	Intellectual disability	ADHD diagnosis	Retrospective cohort study

		Drognostio		
Study	Population	Prognostic variable(s)	Outcomes	Comments
	recruited both those with developmental delays and typical development; ID was defined by IQ <70 (USA), n = 228 Age stratum – 5 to 18 (mean age interviewed 8)		Psychiatric interview (DISC)	Univariable analysis
Roberts 2007 ²²⁵	Sample of households in Houston, oversampling for ethnic minorities (USA), n = 4175 Age stratum – 5 to 18 (interviewed between 11 and 17)	Substance abuse	ADHD diagnosis Trained lay interviewer (DISC-IV (DSM-IV))	Cross- sectional prevalence Univariable analysis
Romano 2005 ²²⁹	Random subsample of children from Quebec whose mothers had completed questionnaires in 1987 (Canada), n = 1201 Age stratum – 5 to 18 (mean age intervious d 15)	Mood disorders Anxiety disorders CD/ODD	ADHD diagnosis Trained lay interviewer (DISC-2.25 (DSM-IV))	Cross- sectional prevalence Univariable analysis
	interviewed 15)			
Adults Arias 2008 ¹⁸	Substance abuse group from larger genetic study and separately recruited control group (USA), n = 2466 Age stratum – over 18 (mean age interviewed 39)	Substance abuse	ADHD diagnosis Interview (SSADDA (DSM-IV))	Retrospective cohort study Univariable analysis
Marwaha 2015 ¹⁷²	General representative sample of adults from English postcode file, stratified by region and socioeconomic characteristics (UK), n = 7403 Age stratum – over 18 (interviewed over age of 16)	Psychotic disorders	ADHD diagnosis Trained lay interviewer (ASRS (DSM-IV))	Cross- sectional prevalence Univariable analysis

		Prognostic		
Study	Population	variable(s)	Outcomes	Comments
Stewart 2006 ²⁶¹	FMH group recruited from Children and Adults with ADD association, clinic referrals, internet advertisements; control participants selected using random dialling procedure, matched on age, gender and area of residence (USA), n = 473 Age stratum – over 18 (mean age at interview approximately 30)	FMH of ADHD	ADHD diagnosis Trained lay interviewer (DSM-IV)	Retrospective cohort study Univariable analysis
Wozniak 1995 ²⁸⁶	Both groups recruited from pre- existing family genetic study (no other information provided) (USA), n = 523 Age stratum – provided information on both adults and children	FMH of ADHD	ADHD diagnosis Trained lay interviewer (DSM-III-R)	Retrospective cohort study Univariable analysis

See appendix D for full evidence tables.

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Table 3: Clinical evidence summary: ADHD diagnosed at age 5 to 18

rable 3: Cliffical evidence Summary: ADHD d	lagilosed at age 5 to 10	1	
Risk factors	No of Participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)
Anxiety disorders	1877 (2 studies)	MODERATE ^a due to risk of bias	RR 3.59 (2.28 to 5.65)
ODD/CD	3502 (3 studies)	MODERATE ^a due to risk of bias	RR 6.96 (4.79 to 10.13)
Preterm birth	897 (3 studies)	MODERATE ^b due to indirectness	RR 2.35 (1.63 to 3.39)
Substance abuse (Clark 1997)	219 (1 study)	VERY LOW ^{a,b,c,d} due to risk of bias, inconsistency, indirectness, imprecision	RR 4.91 (2.01 to 11.99)
Substance abuse (Roberts 2007)	4175 (1 study)	VERY LOW ^{a,b,c,d} due to risk of bias, inconsistency, indirectness, imprecision	OR 1.60 (0.60 to 4.27)
Epilepsy	73 (1 study)	LOW ^{a,d} due to risk of bias, imprecision	RR 6.17 (0.78 to 48.71)
ASD	1585 (1 study)	MODERATE ^a due to risk of bias	RR 39.97 (17.85 to 89.53)
Mood disorders (Elberling 2016)	1585 (1 study)	VERY LOW ^{a,c,d} due to risk of bias, inconsistency, imprecision	RR 12.25 (4.67 to 32.13)
Mood disorders (Romano 2005)	1131 (1 study)	VERY LOW ^{a,c,d} due to risk of bias, inconsistency, imprecision	RR 1.56 (0.63 to 3.86)
Intellectual disability	10666 (2 studies)	LOW ^{a,c} due to risk of bias, inconsistency	RR 6.2 (2.39 to 16.12)
Tic disorder	1596	MODERATE ^a	RR 1.97

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Risk factors	No of Participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)
	(1 study)	due to risk of bias	(1.65 to 2.35)
FMH of ADHD	153 (1 study)	VERY LOW ^{d,e} due to risk of bias, imprecision	RR 2.25 (0.88 to 5.79)
Looked after children	11691 (1 study)	HIGH	RR 7.76 (6.02 to 10.01)

- (a) Downgraded once as majority of evidence at high risk of bias (see evidence tables for more information)
- (b) Downgraded once due to indirectness of population (see evidence tables for more information)
- (c) Downgraded due to inconsistency as I squared ~ 75% when pooled with study of same risk factor
- (d) Downgraded due to imprecision as confidence intervals crossed the line of no effect
- (e) Downgraded twice as majority of evidence at very high risk of bias (see evidence tables)

Table 4: Clinical evidence summary: ADHD diagnosed at age >18

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)
Substance abuse	2466 (1 study)	LOW ^a due to risk of bias	RR 6.14 (2.7 to 13.95)
Psychotic disorders	7325 (1 study)	MODERATE ^b due to risk of bias	RR 22.51 (8.43 to 60.14)
FMH of ADHD	843 (2 studies)	LOW ^a due to risk of bias	RR 2.33 (1.23 to 4.4)

- (a) Downgraded twice as majority of evidence at very high risk of bias (see evidence tables)
- (b) Downgraded once as majority of evidence at high risk of bias (see evidence tables)

See appendix F for full GRADE tables.

1.6 Economic evidence

1.6.1 Included studies

No relevant health economic studies were identified.

1.6.2 Excluded studies

No health economic studies that were relevant to this question were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in appendix G.

1.7 Resource impact

We do not expect recommendations resulting from this review area to have a significant impact on resources.

1.8 Evidence statements

1.8.1 Clinical evidence statements

ADHD diagnosed at age 5 to 18, there was an increased risk of ADHD diagnosis in children and young people with:

- Anxiety disorders, two studies of 1877 people (Moderate quality)
- ODD/CD, three studies of 3502 (Moderate quality)
- Prematurity, three studies of 897 people (Moderate quality)
- Substance abuse disorders, two studies of 4394 people (Very low quality)
- Epilepsy, one study of 73 people(Low quality)
- ASD, one study of 1585 people (Moderate quality)
- Mood disorders, two studies of 2716 people (Very low quality)
- Intellectual disability, two studies of 10666 people (Low quality)
- Tic disorder, one study of 1596 people (Moderate quality)
- Family history of ADHD, one study of 153 people (Very low quality)
- Looked after status, one study of 11691 people (High quality)

ADHD diagnosed at age >18, there was an increased risk of ADHD diagnosis in adults with:

- Substance abuse, one study of 2466 people, (Low quality)
- Psychotic disorders, one study of 7325 people, (Moderate quality)
- Family history of ADHD, two studies of 843 people (Low quality)

1.8.2 Health economic evidence statements

No relevant economic evaluations were identified.

1.9 The committee's discussion of the evidence

1.9.1 Interpreting the evidence

1.9.1.1 The outcomes that matter most

The committee considered increased prevalence rates of ADHD and increased rates of missed diagnoses to be critical outcomes in identifying at risk groups. Identifying groups that have higher rates of ADHD than the general population should raise awareness about people who are likely more likely to have ADHD. Identifying groups with high rates of missed diagnosis will raise awareness about people who are less likely to receive a diagnosis of ADHD, regardless of prevalence. No evidence was identified for the outcome of missed diagnoses.

1.9.1.2 The quality of the evidence

The evidence ranged from moderate to very low quality. The included evidence did not adjust for any confounding factors. This was a deliberate feature of the analysis in the guideline as the aim of the review was not to show causality but to identify risk factors that, in the population seen in primary care, may act as a marker to suggest a higher likelihood of ADHD.

The committee noted that the limitation of this strategy meant that little could be drawn from the magnitudes of association and no statements about causality could be made based on the evidence. The committee also noted that although in some situations no evidence was identified that met the criteria in the protocols to directly answer the research question, there may be existing evidence indirectly supportive of their consensus based recommendations (for example separate studies establishing general prevalence of ADHD and high prevalence of ADHD in specific at risk populations).

The committee agreed that the quality of the evidence was sufficient to make new recommendations to highlight particular groups that may merit increased attention from healthcare professionals to the possibility of exploring an ADHD diagnosis.

1.9.1.3 Benefits and harms

The committee noted that the benefits of identifying groups that are at higher risk of ADHD or having a missed diagnosis of ADHD than the general population would include reducing missed diagnoses and diagnostic overshadowing. This would result in people being offered and receiving treatment appropriate for their ADHD symptoms, reducing impairment and improving their quality of life.

A potential harm of identifying these groups, raising awareness and increasing diagnosis rates is an increase in rates of false diagnoses and some people receiving treatment that is not appropriate.

The committee considered that the benefits outweighed the harms. From the committee's experience, it is clear quite rapidly if medication for ADHD is effective and so if a false diagnosis had occurred this would be quickly identified and ineffective treatment stopped. The risks of treatment in the short term are relatively low compared to the benefits of more people receiving a correct diagnosis and treatment.

1.9.2 Cost effectiveness and resource use

No economic evidence was identified for this question.

The recommendations in relation to this question are intended to raise awareness about particular populations that may be underdiagnosed or misdiagnosed.

The committee noted that these recommendations have little in the way of costs or harms as they do not recommend a specific intervention and are intended to remind healthcare professionals to be vigilant for the possibility of ADHD or a missed diagnosis of ADHD. There may be an impact from these recommendations if better identification leads on to a diagnosis of ADHD and then there is a potential resource use associated with specialist diagnoses and treatments for ADHD being initiated. Identifying misdiagnosis has the potential to be cost neutral, if the treatments that are stopped and the appropriate ones initiated have similar costs and resource use.

1.9.3 Other factors the committee took into account

The committee noted that girls and women are less likely to present with hyperactivity symptoms and co-existing disruptive conditions, as a consequence they are less likely to be

identified and referred for assessment than boys. The committee discussed that the current diagnostic criteria are derived from predominantly male samples and that could be one reason why fewer girls/women are referred, Girls and women with ADHD can have poor social skills with resulting social isolation leading to a negative impact of their self- esteem and well-being. The committee therefore made a separate recommendation for healthcare professionals to be aware of this based on their experience.

Within the recommendations, the committee used the term 'people known to the Youth Justice System or adult Criminal Justice System' whereas the protocols and evidence review used 'people known to the secure estate' .Specific referral to the justice systems was agreed to be a more appropriate term for guidance.

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Appendices

Appendix A: Review protocols

Table 5: Review protocol: Risk factors for ADHD

Field	Content
Review question	Which groups of people are more likely than the general population to have ADHD or are more likely to have missed a diagnosis of ADHD?
Type of review question	Prognostic
Objective of the review	To identify groups of people in whom ADHD is more prevalent than the general population, to encourage clinicians to actively consider whether people in their care may have ADHD
Eligibility criteria – population / disease / condition / issue / domain	Children, young people and adults with ADHD
Eligibility criteria – prognostic factor(s)	 Comorbidities/personal medical history Neurodevelopmental disorders Intellectual disability ASD Mental health disorders Preterm children Social/environmental factors Looked after children Secure estate Children not in mainstream schooling Adults with unstable employment Family history of ADHD Female (only missed diagnoses outcomes) Key confounders: Raw effect sizes only – no confounders to be adjusted. Team and GC to pay particular attention to broader demographics and setting of participants
Outcomes and prioritisation	Formal research diagnoses of ADHD (i.e. diagnoses done as per validated diagnostic criteria on the basis of universally screening the population in question as opposed to incidental diagnoses from health care contacts) Missed diagnoses of ADHD (no diagnosis prior to assessment and new diagnosis after assessment)
Eligibility criteria – study design	Studies in which participants are divided into two groups by the presence/absence of a specified risk factor from the list specified by the GC and all participants are formally assessed for a research diagnosis of ADHD, including both cohort and cross-sectional prevalence studies.
Other inclusion exclusion criteria	Studies in which ADHD diagnosis is based purely on self-report/questionnaire (minimum lay interviewer diagnosis) or ADHD diagnosis is based on previously noted diagnoses and whole population is not formally assessed Cross-sectional prevalence studies including a population that is selected so as not to be generally representative of the primary care population

Proposed sensitivity / subgroup analysis, or meta-regression	All meta-analyses to use random effects on the basis of likely presence of confounders	
	No subgroup analysis was done	
Selection process – duplicate screening / selection / analysis	A sample of at least 10% of the abstract lists were double-sifted by a senior research fellow and discrepancies rectified, with committee input where consensus could not be reached, for more information please see the separate Methods report for this guideline.	
Data management (software)	 Pairwise meta-analyses were performed using Cochrane Review Manager (RevMan5). GRADEpro was used to assess the quality of evidence for each outcome. Endnote for bibliography, citations, sifting and reference management 	
Information sources – databases and dates	Clinical search databases to be used: Medline, Embase, Cochrane Library, PsycINFO Date: From 1978	
	Health economics search databases to be used: Medline, Embase, NHSEED, HTA Date: Medline, Embase from 2014 NHSEED, HTA – from 2008	
	Language: Restrict to English only	
	Supplementary search techniques: backward citation searching	
	Key papers: Not known	
Identify if an update	Not an update	
Author contacts	https://www.nice.org.uk/guidance/cg72	
Highlight if amendment to previous protocol	Not an amendment to previous protocol	
Search strategy – for one database	For details please see appendix B	
Data collection process – forms / duplicate	A standardised evidence table format will be used, and published as appendix D of the evidence report.	
Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or H (health economic evidence tables).	
Methods for assessing bias at outcome / study level	Standard study checklists were used to critically appraise individual studies. For details please see the separate Methods report for this guideline. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group	
	http://www.gradeworkinggroup.org/	
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual.	
	For details please see section 6.4 of Developing NICE guidelines: the	
synthesis Methods for quantitative analysis – combining studies and exploring	For details please see section 6.4 of Developing NICE guidelines: the manual.	

reporting bias	
Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual.
Rationale / context – what is known	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the National Guideline Centre (NGC) and chaired by Gillian Baird in line with section 3 of Developing NICE guidelines: the manual. Staff from NGC undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual.
Sources of funding / support	NGC is funded by NICE and hosted by the Royal College of Physicians.
Name of sponsor	NGC is funded by NICE and hosted by the Royal College of Physicians.
Roles of sponsor	NICE funds NGC to develop guidelines for those working in the NHS, public health and social care in England.
PROSPERO registration number	Not registered

Table 6: Health economic review protocol

Position			
Review question	All questions – health economic evidence		
Objectives	To identify health economic studies relevant to any of the review questions.		
•	·		
Search criteria	Populations, interventions and comparators must be as specified in the clinical review protocols in appendix A above.		
	Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis).		
	Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) Unpublished reports will not be considered unless submitted as part of a call for evidence.		
	Studies must be in English.		
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B. For questions being updated, the search will be run from December 2007, which was the cut-off date for the searches conducted for NICE guideline CG72		
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2001, abstract-only studies and studies from non-OECD countries or the USA will also be excluded.		
	Studies published after 2001 that were included in the previous guideline will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified.		
	Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014). ¹⁸⁶		
	Inclusion and exclusion criteria		

Review question

All questions - health economic evidence

If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile.

If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile.

If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included.

Where there is discretion

The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation as excluded health economic studies in appendix I.

The health economist will be guided by the following hierarchies.

Setting:

UK NHS (most applicable).

OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).

OECD countries with predominantly private health insurance systems (for example, Switzerland).

Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations.

Health economic study type:

Cost–utility analysis (most applicable).

Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis).

Comparative cost analysis.

Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations.

Year of analysis:

The more recent the study, the more applicable it will be.

Studies published in 2001 or later (including any such studies included in the previous guideline) but that depend on unit costs and resource data entirely or predominantly from before 2001 will be rated as 'Not applicable'.

Studies published before 2001 (including any such studies included in the previous guideline) will be excluded before being assessed for applicability and methodological limitations.

Quality and relevance of effectiveness data used in the health economic analysis:

The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Economic evaluations that are based on studies excluded from the clinical review will be excluded.

Appendix B: Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual, Oct 2014, updated 2017 https://www.nice.org.uk/guidance/pmg20/resources/developing-nice-guidelines-the-manual-pdf-72286708700869

For more detailed information, please see the Methodology Review.

B.1 Clinical search literature search strategy

Searches for this review were run in Medline (OVID), Embase (OVID), the Cochrane Library (Wiley). and PsycINFO (ProQuest]. Filters were applied where appropriate.

Table 7: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1978 – 28 April 2017	Exclusions
Embase (OVID)	1978 – 28 April 2017	Exclusions
The Cochrane Library (Wiley)	Cochrane Reviews 1978 to 2017 Issue 4 of 12 CENTRAL 1978 to 2017 Issue 3 of 12 DARE and NHSEED 1978 to 2015 Issue 1 of 4 HTA 1978 to 2017 Issue 1 of 4	None
PsycINFO (ProQuest)	1978 – 28 April 2017	Exclusions

Medline (Ovid) search terms

1.	"attention deficit and disruptive behavior disorders"/ or attention deficit disorder with hyperactivity/
2.	((attenti* or disrupt*) adj3 (adolescent* or adult* or behav* or child* or class or classes or classroom* or condition* or difficult* or disorder* or learn* or people or person* or poor or problem* or process* or youngster*)).ti.
3.	((attenti* or disrupt*) adj3 disorder*).ab.
4.	(adhd or addh or ad hd or ad??hd).ti,ab.
5.	(attenti* adj3 deficit*).ti,ab.
6.	((((hyperkin* or hyper kin*) adj1 (syndrome* or disorder*)) or hkd).ti,ab.
7.	(minimal brain adj2 (dysfunct* or disorder*)).ti,ab.
8.	or/1-7
9.	limit 8 to English language
10.	letter/
11.	editorial/
12.	news/
13.	exp historical article/
14.	Anecdotes as Topic/
15.	comment/
16.	case report/

17.	(letter or comment*).ti.
18.	or/10-17
19.	randomized controlled trial/ or random*.ti,ab.
20.	18 not 19
21.	animals/ not humans/
22.	Animals, Laboratory/
23.	exp animal experiment/
24.	exp animal model/
25.	exp Rodentia/
26.	(rat or rats or mouse or mice).ti.
27.	or/20-26
28.	9 not 27
29.	incidence/ or prevalence/
30.	Epidemiology/
31.	(prevalen* or incidence* or epidemiolog*).ti,ab.
32.	or/29-31
33.	28 and 32

Embase (Ovid) search terms

1.	*attention deficit disorder/
2.	((attenti* or disrupt*) adj3 (adolescent* or adult* or behav* or child* or class or classes or classroom* or condition* or difficult* or disorder* or learn* or people or person* or poor or problem* or process* or youngster*)).ti.
3.	((attenti* or disrupt*) adj3 disorder*).ab.
4.	(adhd or addh or ad hd or ad??hd).ti,ab.
5.	(attenti* adj3 deficit*).ti,ab.
6.	(((hyperkin* or hyper kin*) adj1 (syndrome* or disorder*)) or hkd).ti,ab.
7.	(minimal brain adj2 (dysfunct* or disorder*)).ti,ab.
8.	or/1-7
9.	limit 8 to English language
10.	letter.pt. or letter/
11.	note.pt.
12.	editorial.pt.
13.	case report/ or case study/
14.	(letter or comment*).ti.
15.	or/10-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animal/ not human/
19.	nonhuman/
20.	exp Animal Experiment/
21.	exp Experimental Animal/
22.	animal model/
23.	exp Rodent/
24.	(rat or rats or mouse or mice).ti.

25.	or/17-24
26.	9 not 25
27.	epidemiology/ or incidence/ or prevalence/
28.	(prevalen* or incidence* or epidemiolog*).ti,ab.
29.	27 or 28
30.	26 and 29

Cochrane Library (Wiley) search terms

#1.	[mh ^"attention deficit and disruptive behavior disorders"]
#2.	[mh ^"attention deficit disorder with hyperactivity"]
#3.	((attenti* or disrupt*) near/3 (adolescent* or adult* or behav* or child* or class or classes or classroom* or condition* or difficult* or disorder* or learn* or people or person* or poor or problem* or process* or youngster*)):ti
#4.	((attenti* or disrupt*) near/3 disorder*):ab
#5.	(adhd or addh or ad next hd or ad-hd):ti,ab
#6.	(attenti* near/3 deficit*):ti,ab
#7.	((((hyperkin* or (hyper next kin*)) near/1 (syndrome* or disorder*)) or hkd):ti,ab
#8.	(minimal next brain near/2 (dysfunct* or disorder*)):ti,ab
#9.	(or #1-#8)
#10.	[mh ^incidence]
#11.	[mh ^prevalence]
#12.	[mh ^Epidemiology]
#13.	(prevalen* or incidence* or epidemiolog*):ti,ab
#14.	(or #10-#13)
#15.	#9 and #14
	•

PsycINFO (ProQuest) search terms

<u> </u>	C C C C C C C C C C C C C C C C C C C
1.	SU.EXACT.EXPLODE("Attention Deficit Disorder") OR TI((attenti* OR disrupt*) NEAR/3 (adolescent* OR adult* OR behav* OR child* OR class OR classes OR classroom* OR condition* OR difficult* OR disorder* OR learn* OR people OR person* OR poor OR problem* OR process* OR youngster*)) OR AB((attenti* OR disrupt*) NEAR/3 disorder*) OR TI,AB(adhd OR addh OR ad-hd OR ad??hd) OR TI,AB(attenti* NEAR/3 deficit*) OR TI,AB(((hyperkin* OR (hyper-kin*)) NEAR/1 (syndrome* OR disorder*)) OR hkd) OR TI,AB(minimal NEAR/1 brain NEAR/2 (dysfunct* OR disorder*))
2.	SU.EXACT("Epidemiology") or TI,AB(prevalen* or incidence* or epidemiolog*)
3.	1 AND 2
4.	NOT (Dissertations & Theses AND Books)
5.	English (limit)

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to ADHD population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase.

Table 8: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	2014 – 28 April 2017	Exclusions Health economics
Embase	2014 – 28 April 2017	Exclusions Health economics
Centre for Research and Dissemination (CRD)	HTA - 2008 – 28 April 2017 NHSEED - 2008 to March 2015	None

Medline (Ovid) search terms

1.	"attention deficit and disruptive behavior disorders"/ or attention deficit disorder with hyperactivity/
2.	((attenti* or disrupt*) adj3 (adolescent* or adult* or behav* or child* or class or classes or classroom* or condition* or difficult* or disorder* or learn* or people or person* or poor or problem* or process* or youngster*)).ti.
3.	((attenti* or disrupt*) adj3 disorder*).ab.
4.	(adhd or addh or ad??hd).ti,ab.
5.	(attenti* adj3 deficit*).ti,ab.
6.	((((hyperkin* or hyper kin*) adj1 (syndrome* or disorder*)) or hkd).ti,ab.
7.	(minimal brain adj2 (dysfunct* or disorder*)).ti,ab.
8.	or/1-7
9.	limit 8 to English language
10.	letter/
11.	editorial/
12.	news/
13.	exp historical article/
14.	Anecdotes as Topic/
15.	comment/
16.	case report/
17.	(letter or comment*).ti.
18.	or/10-17
19.	randomized controlled trial/ or random*.ti,ab.
20.	18 not 19
21.	animals/ not humans/
22.	Animals, Laboratory/
23.	exp animal experiment/
24.	exp animal model/
25.	exp Rodentia/
26.	(rat or rats or mouse or mice).ti.
27.	or/20-26
28.	9 not 27
29.	Economics/
30.	Value of life/
31.	exp "Costs and Cost Analysis"/

32.	exp Economics, Hospital/
33.	exp Economics, Medical/
34.	Economics, Nursing/
35.	Economics, Pharmaceutical/
36.	exp "Fees and Charges"/
37.	exp Budgets/
38.	budget*.ti,ab.
39.	cost*.ti.
40.	(economic* or pharmaco?economic*).ti.
41.	(price* or pricing*).ti,ab.
42.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
43.	(financ* or fee or fees).ti,ab.
44.	(value adj2 (money or monetary)).ti,ab.
45.	or/29-44
46.	exp models, economic/
47.	*Models, Theoretical/
48.	*Models, Organizational/
49.	markov chains/
50.	monte carlo method/
51.	exp Decision Theory/
52.	(markov* or monte carlo).ti,ab.
53.	econom* model*.ti,ab.
54.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
55.	or/46-54
56.	28 and (45 or 55)

Embase (Ovid) search terms

1.	attention deficit disorder/
2.	((attenti* or disrupt*) adj3 (adolescent* or adult* or behav* or child* or class or classes or classroom* or condition* or difficult* or disorder* or learn* or people or person* or poor or problem* or process* or youngster*)).ti.
3.	((attenti* or disrupt*) adj3 disorder*).ab.
4.	(adhd or addh or ad hd or ad??hd).ti,ab.
5.	(attenti* adj3 deficit*).ti,ab.
6.	((((hyperkin* or hyper kin*) adj1 (syndrome* or disorder*)) or hkd).ti,ab.
7.	(minimal brain adj2 (dysfunct* or disorder*)).ti,ab.
8.	or/1-7
9.	limit 8 to English language
10.	letter.pt. or letter/
11.	note.pt.
12.	editorial.pt.
13.	case report/ or case study/
14.	(letter or comment*).ti.
15.	or/10-14

16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animal/ not human/
19.	nonhuman/
20.	exp Animal Experiment/
21.	exp Experimental Animal/
22.	animal model/
23.	exp Rodent/
24.	(rat or rats or mouse or mice).ti.
25.	or/17-24
26.	9 not 25
27.	statistical model/
28.	exp economic aspect/
29.	27 and 28
30.	*theoretical model/
31.	*nonbiological model/
32.	stochastic model/
33.	decision theory/
34.	decision tree/
35.	monte carlo method/
36.	(markov* or monte carlo).ti,ab.
37.	econom* model*.ti,ab.
38.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
39.	or/29-38
40.	*health economics/
41.	exp *economic evaluation/
42.	exp *health care cost/
43.	exp *fee/
44.	budget/
45.	funding/
46.	budget*.ti,ab.
47.	cost*.ti.
48.	(economic* or pharmaco?economic*).ti.
49.	(price* or pricing*).ti,ab.
50.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
51.	(financ* or fee or fees).ti,ab.
52.	(value adj2 (money or monetary)).ti,ab.
53.	or/40-52
54.	26 and (39 or 53)

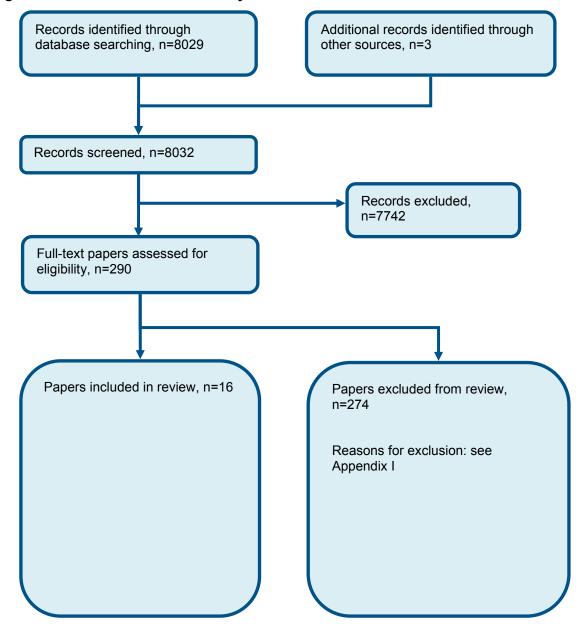
NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Attention Deficit and Disruptive Behavior Disorders
#2.	MeSH DESCRIPTOR Attention Deficit Disorder with Hyperactivity
#3.	(((attenti* or disrupt*) adj3 (adolescent* or adult* or behav* or child* or class or classes or classroom* or condition* or difficult* or disorder* or learn* or people or person* or poor or problem* or process* or youngster*))):TI

#4.	(((attenti* or disrupt*) adj3 disorder*))
#5.	((adhd or addh or ad hd or ad??hd))
#6.	((attenti* adj3 deficit*))
#7.	(((((hyperkin* or hyper kin*) adj1 (syndrome* or disorder*)) or hkd))
#8.	((minimal brain adj2 (dysfunct* or disorder*)))
#9.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#10.	(#9) IN NHSEED, HTA

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of ADHD risk factors



Appendix D: Clinical evidence tables

Reference	Anderson 1987 ^{13,174}
Study type and analysis	Prevalence study using structured psychiatric interview with DISC-C (DSM-III), unadjusted data
Number of participants and characteristics	Total n = 782, representative sample of general population from New Zealand, 925 in original sample, 782 with interview data Children were 11 years old at interview New Zealand
Prognostic variable(s)	Anxiety disorders Oppositional defiant disorder/conduct disorder
Confounders strategy	No confounders adjusted for
Outcomes and effect sizes	Anxiety disorders RR 4.40 (2.54 to 7.62) ODD/CD RR 6.69 (3.94 to 11.37)
Comments	Risk of bias low for anxiety disorders, ODD/CD

Reference	Arias 2008 ¹⁸
Study type and analysis	Cross-sectional cohort study using structured psychiatric interview with SSADDA (DSM-IV), unadjusted data
Number of participants and characteristics	Substance abuse group n = 1761, controls n = 705 Substance abuse group identified from larger genetic study, controls identified from group specifically chosen to provide controls for genetic study Mean age of participants was 39 at interview USA
Prognostic variable(s)	Substance abuse (opioid or cocaine abuse)
Confounders	No confounders adjusted for

strategy	
Outcomes and effect sizes	Substance abuse RR 6.14 (2.70 to 13.95)
Comments	Risk of bias very high for substance abuse due to selection and detection bias

Reference	Bora 2014 ⁴⁴
Study type and analysis	Cross-sectional cohort study using structured psychiatric interview with DSM-IV, unadjusted data
Number of participants and characteristics	Preterm group n = 110, controls n = 705 Preterm group were consecutive preterm births at regional hospital, controls selected from same hospital as infant born second previously or after each index preterm birth Children were interviewed at 9 years old New Zealand
Prognostic variable(s)	Preterm birth (less than or equal to 32 weeks gestation)
Confounders strategy	No confounders adjusted for
Outcomes and effect sizes	Preterm birth RR 2.16 (1.34 to 3.49)
Comments	Risk of bias low

Reference	Burnett 2014 ⁵¹
Study type and analysis	Cross-sectional cohort study using structured psychiatric interview with ChIPS (DSM-IV), unadjusted data
Number of participants and characteristics	Preterm group n = 298, controls n = 262 Preterm group were consecutive extremely premature/extremely low birth weight infants at from Victoria (Australia), controls were normal birthweight and selected from same region and matched for maternal ethnicity, sex of child and health insurance status
	Participants mean age at interview was 18 Australia

Prognostic variable(s)	Preterm birth (<28 weeks gestation or <1000g)
Confounders strategy	No confounders adjusted for
Outcomes and effect sizes	Preterm birth RR 2.05 (1.06 to 3.96)
Comments	Risk of bias low Indirectness due to extremely preterm cut-off

Reference	Clark 1997 ⁶¹
Study type and analysis	Cross-sectional cohort study using structured psychiatric interview with K-SADS (DSM-III-R), unadjusted data
Number of participants and characteristics	Substance abuse group n = 133, controls n = 86 Substance abuse group from adolescent substance abuse centre, control group recruited through advertisements and systematic community sampling Participants mean age at interview was 16 USA
Prognostic variable(s)	Substance abuse (alcohol dependence)
Confounders strategy	No confounders adjusted for
Outcomes and effect sizes	Substance abuse RR 2.05 (1.06 to 3.96)
Comments	Risk of bias high due to selection bias

Reference	Costa 2014 ⁶⁵
Study type and analysis	Cross-sectional cohort study using structured psychiatric interview DSM-IV, unadjusted data
Number of participants	Epilepsy group n = 36, controls n = 37 Epilepsy group from consecutive attendances at outpatient clinic, control group age, gender, SES matched - recruited from nearby

and characteristics	primary school
	Participants mean age at interview was 11 Brazil
Prognostic variable(s)	Epilepsy
Confounders strategy	No confounders adjusted for
Outcomes and effect sizes	Substance abuse RR 6.17 (0.78 to 48.71)
Comments	Risk of bias high due to selection bias

Reference	Elberling 2016 ⁸¹
Study type and analysis	Prevalence study using trained lay person interview with SDQ (ICD-10), unadjusted data
Number of participants and characteristics	Total n = 1585 Random sample of all children born in area around Copenhagen in 2000, 20% of sample selected to enrich group based on positive screening scores
	Interviews conducted at ages 5 to 7 Brazil
Prognostic variable(s)	ASD (pervasive developmental disorders) Mood disorders (emotional disorders) ODD/CD (behavioural disorders)
Confounders strategy	No confounders adjusted for
Outcomes and effect sizes	ASD RR 39.97 (17.85 to 89.53) Mood disorders RR 12.25 (4.67 to 32.13) ODD/CD RR 10.18 (3.17 to 32.71)
Comments	Risk of bias high due to selection bias, detection bias

Reference	Emerson 2003 ⁸⁴
Study type and analysis	Prevalence study using trained lay person interview with DAWBA (ICD-10), unadjusted data, study split into population with and without intellectual disability and risk of being diagnosed with ADHD compared between groups.
Number of participants and characteristics	Total n = 10438 Stratified sample (ONSSSD) of all children aged 5 to 15 in the UK, 83% of target sample interviewed UK
Prognostic variable(s)	Intellectual disability
Confounders strategy	No confounders adjusted for
Outcomes and effect sizes	ID RR 9.63 (6.20 to 14.96)
Comments	Risk of bias low

Reference	Ford 2007 ¹⁰¹
Study type and analysis	Cross-sectional cohort study using structured psychiatric interview with DAWBA (ICD 10), unadjusted data
Number of participants	Total n = 11691, looked after group (n = 1253) composed of random sample of all looked after children in UK, control group (n = 10438) randomly sampled from child benefit register
and	Children were at least 11 years old at interview
characteristics	United Kingdom
Prognostic variable(s)	Looked after children
Confounders strategy	No confounders adjusted for
Outcomes and effect sizes	Looked after children RR 7.76 (6.02 to 10.01)
Comments	Risk of bias low
analysis Number of participants and characteristics Prognostic variable(s) Confounders strategy Outcomes and effect sizes	Total n = 11691, looked after group (n = 1253) composed of random sample of all looked after children in UK, control group (n = 10438) randomly sampled from child benefit register Children were at least 11 years old at interview United Kingdom Looked after children No confounders adjusted for Looked after children RR 7.76 (6.02 to 10.01)

Reference	Johnson 2010 ¹³⁹
Study type and analysis	Cross-sectional cohort study using structured psychiatric interview with DAWBA (DSM-IV), unadjusted data
Number of participants and characteristics	Total n = 321 Premature birth group representing all surviving babies born at <26 weeks gestation in UK in 1995 with parental consent to participate in interview at age 11 (n = 183), control group selected at random from 3 term classmates closest in age and of the same sex and ethnicity (n = 138) not including for those children not in mainstream education UK
Prognostic variable(s)	Preterm birth (<26 weeks gestation)
Confounders strategy	No confounders adjusted for
Outcomes and effect sizes	Pre term birth RR 9.63 (6.20 to 14.96)
Comments	Risk of bias high due to selection bias and detection bias Indirectness due to extremely preterm cut-off

Reference	Kurlan 2002 ¹⁵⁵
Study type and analysis	Prevalence study using structured psychiatric interview with DISC (DSM-IV), unadjusted data
Number of participants and characteristics	Total n = 1596 1596 children aged 9 to 17 in 10 school districts in New York State, little additional information provided on selection of participants. Technician performed psychiatric interviewing for diagnosis of both tic disorders (n = 339) and ADHD. USA
Prognostic variable(s)	Tic disorders
Confounders	No confounders adjusted for

strategy	
Outcomes and effect sizes	Tic disorders RR 1.97 (1.65 to 2.35)
Comments	Risk of bias high due to selection bias and detection bias

Reference	Marwaha 2015 ¹⁷²
Study type and analysis	Prevalence study using face to face interview with ASRS (DSM-IV), unadjusted data
Number of participants and characteristics	Total n = 7403 7403 adults aged over 16 identified from UK postcode file and stratified by socioeconomic data and ethnicity to provide representative sample, ADHD n = 39, psychosis n = 37 UK
Prognostic variable(s)	Psychotic disorders
Confounders strategy	No confounders adjusted for
Outcomes and effect sizes	Psychotic disorders RR 22.51 (8.43 to 60.14)
Comments	Risk of bias high due to selection bias and detection bias

Reference	Neece 2011 ¹⁸⁹
Study type and analysis	Cross-sectional cohort study using structured psychiatric interview with DISC, unadjusted data
Number of participants and characteristics	Total n = 228 Samples drawn from Collaborative Family Study in California, recruited both those with developmental delays and typical development; ID was defined by IQ <70 (n = 63) USA

Prognostic variable(s)	Intellectual disability
Confounders strategy	No confounders adjusted for
Outcomes and effect sizes	Intellectual disability RR 22.51 (8.43 to 60.14)
Comments	Risk of bias very high due to selection bias and detection bias

Reference	Roberts 2007 ²²⁵
Study type and analysis	Prevalence study using face to face interview with DISC-IV (DSM-IV), unadjusted data
Number of participants and characteristics	Total n = 4175 Samples drawn from Houston metropolitan area, children aged 11-17 with oversampling for ethnic minorities. Assessed ORs for substance abuse predicting psychiatric disorder in the previous year. USA
Prognostic variable(s)	Substance abuse (any substance abuse)
Confounders strategy	No confounders adjusted for
Outcomes and effect sizes	Substance abuse OR 1.6 (0.6 to 4.6)
Comments	Risk of bias very high due to selection bias and detection bias

Reference	Romano 2005 ²²⁹
Study type and analysis	Prevalence study using face to face interview with DISC-2.25 (DSM-IV), unadjusted data
Number of participants and	Total n = 1201 Samples drawn from group of children in Canada whose methors had completed questionnairs whilet they were in kindergarten in
anu	Samples drawn from group of children in Canada whose mothers had completed questionnaire whilst they were in kindergarten in

characteristics	1987, children were interviewed once between the ages of 14 to 17 (mean 15). USA
Prognostic variable(s)	Anxiety disorder (any) Mood disorder (depression) ODD/CD
Confounders strategy	No confounders adjusted for
Outcomes and effect sizes	Anxiety disorder RR 2.78 (1.48 to 5.23) Mood disorder RR 1.56 (0.63 to 3.86) ODD/CD RR 7.89 (4.39 to 14.15)
Comments	Risk of bias high due to detection bias and attrition bias

Reference	Stewart 2006 ²⁶¹
Study type and analysis	Cross-sectional cohort study using structured psychiatric interview with DSM-IV criteria, unadjusted data
Number of participants	Total n = 473
and characteristics	FMH group recruited from Children and Adults with ADD association (n = 319), clinic referrals, internet advertisements; control participants (n = 154) selected using random dialling procedure, matched on age, gender and area of residence. USA
Prognostic variable(s)	FMH of ADHD (FMH of ADHD +/- Tourette's disorder)
Confounders strategy	No confounders adjusted for
Outcomes and effect sizes	FMH of ADHD RR 1.74 (0.89 to 3.41)
Comments	Risk of bias high due to selection and detection bias

Reference	Wozniak 1995 ²⁸⁶
Study type and analysis	Cross-sectional cohort study using structured psychiatric interview with DSM-IV criteria, unadjusted data
Number of participants and characteristics	Total n = 523 FMH group (n = 211 (adults) and 92 (children and adolescents)) and control group (n = 159 (adults) and 61 (children)) recruited from pre-existing genetic study, no other information provided
	USA
Prognostic variable(s)	FMH of ADHD
Confounders strategy	No confounders adjusted for
Outcomes and effect sizes	FMH of ADHD (>18) RR 3.34 (1.51 to 7.38) FMH of ADHD (5 to 18) RR 2.25 (0.88 to 5.79)
Comments	Risk of bias very high due to selection and detection bias

Attention deficit hyperactivity disorder (update): FINAL Risk factors for ADHD

Appendix E: Forest plots

E.1 ADHD diagnosis in childhood (aged 5 to 18)

Figure 2: Anxiety disorders

_	Anxiety disc	isorders Control				Risk Ratio	Risk Ratio						
Study or Subgroup	Events	Events	Total	Weight M-H, Random, 95% CI				M-H, Random, 95% CI					
Anderson 1987	14	59	39	723	55.8%	4.40 [2.54, 7.62]							_
Romano 2005	13	152	29	943	44.2%	2.78 [1.48, 5.23]				_		_	
Total (95% CI)		211		1666	100.0%	3.59 [2.28, 5.65]					•	-	
Total events	27		68										
Heterogeneity: Tau ² =		0.1	0.2	0.5	1 2			10					
Test for overall effect:		Fav		ety disorders	Favours	control	Ü	10					

Figure 3: ODD/CD

· ·	ODD/CD		Control			Risk Ratio	Risk Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Rand	om, 95% C	CI	
Anderson 1987	19	72	28	710	50.0%	6.69 [3.94, 11.37]					\rightarrow
Elberling 2016	3	27	17	1558	10.3%	10.18 [3.17, 32.71]				-	→
Romano 2005	14	77	29	1058	39.7%	6.63 [3.66, 12.02]					→
Total (95% CI)		176		3326	100.0%	6.96 [4.79, 10.13]				<	-
Total events	36		74								
Heterogeneity: Tau ² = Test for overall effect:				P = 0.79); I ² = 0%			D.2 0.5 Favours ODD/CD	1 2 Favours c	5 ontrol	10

Figure 4: Premature birth

	Preterm birth		Control			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Bora 2014	40	107	19	110	52.3%	2.16 [1.34, 3.49]	
Burnett 2014	30	205	11	154	35.0%	2.05 [1.06, 3.96]	
Johnson 2010	21	183	4	138	12.7%	3.96 [1.39, 11.27]	
Total (95% CI)		495		402	100.0%	2.35 [1.63, 3.39]	•
Total events	91		34				
Heterogeneity: Chi ² =	1.24, df = 2	(P = 0.5)	54); $I^2 = 0$	%			0.1 0.2 0.5 1 2 5 10
Test for overall effect:	Z = 4.59 (P	< 0.000	001)				Favours preterm birth Favours control

Figure 5: Substance abuse

J	Substance	Control			Risk Ratio	Ris	sk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I M-H, F	ixed, 95% CI
Clark 1997	38	133	5	86	100.0%	4.91 [2.01, 11.99]		
Total (95% CI)		133		86	100.0%	4.91 [2.01, 11.99]		
Total events	38		5					
Heterogeneity: Not ap	plicable						0.1 0.2 0.5	1 2 5 10
Test for overall effect:	Z = 3.50 (P = 6)	0.0005)					Favours substance abuse	

Figure 6: Substance abuse (Roberts 2007)

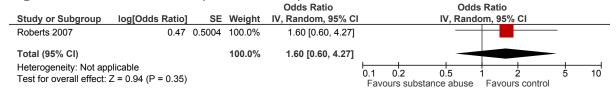


Figure 7: Epilepsy

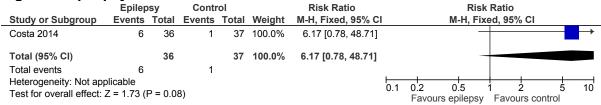


Figure 8: ASD

	ASD		Control		Risk Ratio		Risk Ratio			Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI			M-H, Fixe	ed, 95% CI		
Elberling 2016	8	26	12	1559	100.0%	39.97 [17.85, 89.53]						•
Total (95% CI)		26		1559	100.0%	39.97 [17.85, 89.53]						•
Total events	8		12									
Heterogeneity: Not appropriate the Test for overall effect:	0.2	0.5 Favours ASD	l 2 Favours co	5 ontrol	10							

Figure 9: Mood disorders

	Mood disorders Control			ol		Risk Ratio	R			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Ra	indom, 95% CI		
Elberling 2016	5	42	15	1543	100.0%	12.25 [4.67, 32.13]			_	→
Total (95% CI)		42		1543	100.0%	12.25 [4.67, 32.13]			_	
Total events	5		15							
Heterogeneity: Not applicable Test for overall effect: Z = 5.09 (P < 0.00001)							0.1 0.2 0.5 Favours mood disorder	1 2 s Favours contro	5	10

Figure 10: Mood disorders

	Mood disor	Contr	ol		Risk Ratio		Risk Ratio					
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	l	M-H, Ra	ndom, 95% CI			
Romano 2005	5	88	38	1043	100.0%	1.56 [0.63, 3.86]		_		_		
Total (95% CI)		88		1043	100.0%	1.56 [0.63, 3.86]		-		-		
Total events	5		38									
Heterogeneity: Not applicable Test for overall effect: Z = 0.96 (P = 0.34)							0.1 0 Favour	.2 0.5 rs mood disorders	1 2 Favours contr	ol 5	10	

Figure 11: Intellectual disability

_	ID		Cont	rol		Risk Ratio		Risk	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Rand	om, 95% CI		
Emerson 2003	23	264	92	10174	52.1%	9.63 [6.20, 14.96]				-	-
Neece 2011	22	63	15	165	47.9%	3.84 [2.13, 6.92]					-
Total (95% CI)		327		10339	100.0%	6.20 [2.39, 16.12]			-		
Total events	45		107								
Heterogeneity: Tau ² = Test for overall effect: 2				P = 0.009	9); I² = 85%		0.1 0.2	0.5 1 Favours ID	2 Favours co	5 ntrol	10

Figure 12: Tic disorder

	Tic diso	rder	Contr	rol		Risk Ratio			Risk	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI			M-H, Fix	ed, 95% (CI	
Kurlan 2002	130	339	245	1257	100.0%	1.97 [1.65, 2.35]					•	
Total (95% CI)		339		1257	100.0%	1.97 [1.65, 2.35]				•		
Total events	130		245									
Heterogeneity: Not ap Test for overall effect:		P < 0.00	001)				0.1	0.2 Favours	0.5 tic disorder	1 2 Favours	5 control	10

Figure 13: FMH of ADHD

	FMH of A	ADHD	Contr	ol		Risk Ratio			Risl	(Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI			M-H, Fix	ced, 95%	CI		
Wozniak 1995	17	92	5	61	100.0%	2.25 [0.88, 5.79]						_	
Total (95% CI)		92		61	100.0%	2.25 [0.88, 5.79]						_	
Total events	17		5										
Heterogeneity: Not ap Test for overall effect:	•	= 0.09)					0.1 Fa	0.2 avours FN	0.5 //H of ADHE	1 2 1 2) Favours	s control	5	10

Figure 14: Looked after children

	LAC	;	Cont	rol		Risk Ratio			Ris	k Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI			M-H, Fi	xed, 95% C	:1	
Ford 2007	109	1253	117	10438	100.0%	7.76 [6.02, 10.01]						-
Total (95% CI)		1253		10438	100.0%	7.76 [6.02, 10.01]						•
Total events	109		117									
Heterogeneity: Not approximately Test for overall effect:		(P < 0.	00001)				0.1	0.2 F	0.5 avours LAC	1 2 Favours	5 control	10

E.2 ADHD diagnosis in adulthood (aged >18)

Figure 15: Substance abuse

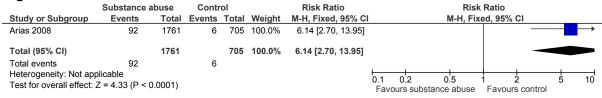


Figure 16: Psychotic disorders

	Psychotic disc	orders	Contr	ol 💮		Risk Ratio		Risk	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixe	ed, 95% CI		
Marwaha 2015	4	37	35	7288	100.0%	22.51 [8.43, 60.14]					\rightarrow
Total (95% CI)		37		7288	100.0%	22.51 [8.43, 60.14]					-
Total events	4		35								
Heterogeneity: Not app Test for overall effect:		0001)					0.1 0.2 Favours p	0.5 sychotic Sx	1 2 Favours co	5 ontrol	10

Figure 17: FMH of ADHD

_	FMH of	ADHD	Contr	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	I M-H, Random, 95% CI
Stewart 2006	36	319	10	154	55.4%	1.74 [0.89, 3.41]	
Wozniak 1995	31	211	7	159	44.6%	3.34 [1.51, 7.38]	
Total (95% CI)		530		313	100.0%	2.33 [1.23, 4.40]	
Total events	67		17				
Heterogeneity: Tau ² = Test for overall effect:			•	0.22);	I ² = 34%		0.1 0.2 0.5 1 2 5 10 Favours FMH of ADHD Favours control

Appendix F: GRADE tables

Table 9: Clinical evidence profile: Children aged 5 to 18

Table	. Cillica	ii evidenc	e prome: Cn	nuren ageu	3 10 10							
			Quality ass	essment				ients with HD		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Risk factor	Control	Relative (95% CI)	Absolute		
Anxiety d	isorders	_		_								
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	27/211 (12.8%)	68/1666 (4.1%)	RR 3.59 (2.28 to 5.65)	106 more per 1000 (from 52 more to 190 more)	⊕⊕⊕O MODERATE	CRITICAL
ODD/CD		_		_								
3	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	36/176 (20.5%)	74/3326 (2.2%)	RR 6.96 (4.79 to 10.13)	133 more per 1000 (from 84 more to 203 more)	⊕⊕⊕O MODERATE	CRITICAL
Preterm b	oirth											
3	randomised trials		no serious inconsistency	serious ²	no serious imprecision	none	91/495 (18.4%)	34/402 (8.5%)	RR 2.35 (1.63 to 3.39)	114 more per 1000 (from 53 more to 202 more)	⊕⊕⊕O MODERATE	CRITICAL
Substanc	e abuse (Cla	rk 1997)		•	•				•		•	
1	randomised trials	serious ¹	serious ³	serious ²	serious ⁴	none	38/133 (28.6%)	5/86 (0.6%)	RR 4.91 (2.01 to 11.99)	227 more per 1000 (from 59 more to 639 more)	⊕000 VERY LOW	CRITICAL
Substanc	e abuse (Rob	perts 2007)										_
1	randomised trials	serious ¹	serious ³	serious ²	serious ⁴	none	-	-	OR 1.60 (0.60 to 4.27)	-	⊕000 VERY LOW	CRITICAL

Epilepsy			T	T	<u> </u>		1	T .	T	T	T	
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁴	none	6/36 (16.7%)	1/37 (2.7%)	RR 6.17 (0.78 to 48.71)	140 more per 1000 (from 6 fewer to 1000 more)	⊕⊕OO LOW	CRITICAL
ASD			<u>, </u>						,			
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	8/26 (30.8%)	12/1559 (0.77%)	RR 39.97 (17.85 to 89.53)	300 more per 1000 (from 130 more to 681 more)	⊕⊕⊕O MODERATE	CRITICAL
Mood dis	orders (Elber	ling 2016)										
1	randomised trials	serious ¹	serious ³	no serious indirectness	serious ⁴	none	5/42 (11.9%)	15/1543 (0.97%)	RR 12.25 (4.67 to 32.13)	109 more per 1000 (from 36 more to 303 more)	⊕000 VERY LOW	CRITICAL
Mood dis	orders (Roma	ano 2005)										
1	randomised trials	serious ¹	serious ³	no serious indirectness	serious ⁴	none	5/88 (5.7%)	38/1043 (3.6%)	RR 1.56 (0.63 to 3.86)	20 more per 1000 (from 13 fewer to 104 more)	⊕000 VERY LOW	CRITICAL
Intellectu	ıal disability	'	-		<u>'</u>							
2	randomised trials	serious ¹	serious ³	no serious indirectness	no serious imprecision	none	45/327 (13.8%)	107/10339 (1%)	RR 6.2 (2.39 to 16.12)	54 more per 1000 (from 14 more to 156 more)	⊕⊕OO LOW	CRITICAL
Tic disor	der	'	-		<u>'</u>							
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	130/339 (38.3%)	245/1257 (19.5%)	RR 1.97 (1.65 to 2.35)	189 more per 1000 (from 127 more to 263 more)	⊕⊕⊕O MODERATE	CRITICAL
FMH of A	ADHD											
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ⁴	none	17/92 (18.5%)	5/61 (8.2%)	RR 2.25 (0.88 to 5.79)	102 more per 1000 (from 10 fewer to 393 more)	⊕000 VERY LOW	CRITICAL
Looked a	after children											

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Downgraded once as majority of evidence at high risk of bias or twice as majority of evidence at very high risk of bias (see evidence tables for more information)

Table 10: Clinical evidence profile: Adults over 18

			Quality as	sessment			No of pation			Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Risk factor	Control	Relative (95% CI)	Absolute		
Substanc	e abuse											
1	randomised trials	- , .	no serious inconsistency	no serious indirectness	no serious imprecision	none	92/1761 (5.2%)	6/705 (0.85%)	RR 6.14 (2.7 to 13.95)	44 more per 1000 (from 14 more to 110 more)	⊕⊕OO LOW	
Psychotic	disorders											
1	randomised trials		no serious inconsistency	no serious indirectness	no serious imprecision	none	4/37 (10.8%)	35/7288 (0.48%)	RR 22.51 (8.43 to 60.14)	103 more per 1000 (from 36 more to 284 more)	⊕⊕⊕O MODERATE	
FMH of A	DHD											
2	randomised trials	1 1 1	no serious inconsistency	no serious indirectness	no serious imprecision	none	67/530 (12.6%)	17/313 (5.4%)	RR 2.33 (1.23 to 4.4)	72 more per 1000 (from 12 more to 185 more)	⊕⊕OO LOW	

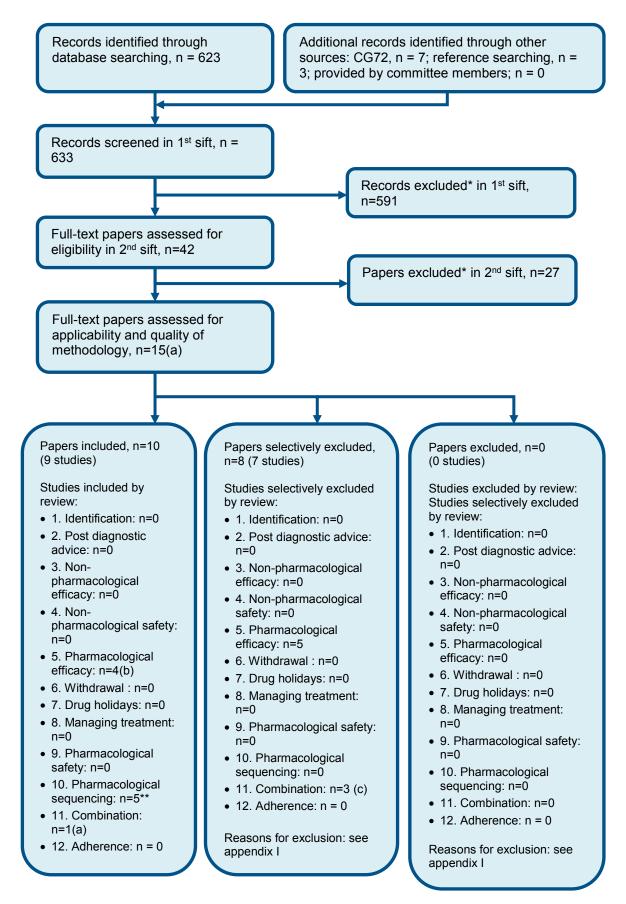
¹ Downgraded once as majority of evidence at high risk of bias or twice as majority of evidence at very high risk of bias (see evidence tables for more information)

² Downgraded once due to indirectness of population (see evidence tables for more information)

³ Downgraded due to inconsistency as I squared ~ 75%

⁴ Downgraded due to imprecision as confidence intervals crossed the line of no effect

Appendix G: Health economic evidence selection



^{*} Non-relevant population, intervention, comparison, design or setting; non-English language (a) note that there were 2 original models from the previous guideline (either included or excluded) which is why the numbers add to more than 15.

⁽b) Two articles identified were applicable to Q5 and Q10, for the purposes of this diagram it has been included

under Q5 only.

(c) One of these is a model from the previous guideline that was exclude. Two articles identified were applicable to both Q5 and Q11 and have only been included here under Q11. One paper here was selectively excluded in Q11 but included in Q5 and so is double counted in this flowchart.

Appendix H: Health economic evidence tables

None.

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Appendix I: Excluded studies

I.1 Excluded clinical studies

Table 11: Studies excluded from the clinical review

Reference	Reason for exclusion
Aarons 2008 ¹	No usable outcomes
Abiodun 2011 ²	No usable outcomes
Al Hamed 2008 ⁴	No usable outcomes
Alfonsson 2013 ⁵	No usable outcomes
Alizadeh 2015 ⁶	No usable outcomes
Al-Mamari 2015 ³	No usable outcomes
Almeida Montes 2007 ⁷	Inappropriate population
Almqvist 19998	No usable outcomes
Alpaslan 2015 ⁹	No usable outcomes
Alyanak 2011 ²⁰³	Not in English
Ambuabunos 2011 ¹⁰	No usable outcomes
Amiri 2014 ¹²	No usable outcomes
Amiri 2010 ¹¹	No usable outcomes
Andreassen 2016 ¹⁴	No usable outcomes
Andres 1999 ¹⁵	No usable outcomes
Antshel 2016 ¹⁶	No usable outcomes
Antshel 2008 ¹⁷	No usable outcomes
Arnold 2005 ¹⁹	Inappropriate population
Arruda 2015 ²⁰	No usable outcomes
August 1992 ²¹	Inappropriate population
August 1996 ²²	Inappropriate population
Ayoub 2009 ⁷¹	No usable outcomes
Baker 2010 ²³	No usable outcomes
Ballon 2015 ²⁴	Inappropriate population
Bansal 2011 ²⁵	No usable outcomes
Barbaresi 2004 ²⁶	No usable outcomes
Barbaresi 2002 ²⁷	No usable outcomes
Bellelli 2015 ²⁸	No usable outcomes
Bener 2014 ²⁹	Inadequate ADHD diagnosis
Bertelsen 2016 ³⁰	Unable to access
Bhatia 1991 ³¹	Inappropriate population
Biederman 2012 ³³	No usable outcomes
Biederman 2013 ³²	No usable outcomes
Bijlenga 2013 ³⁴	No usable outcomes
Bird 1994 ³⁵	Inappropriate population
Birmaher 2010 ³⁶	No usable outcomes
Birmaher 2009 ³⁷	No usable outcomes

Reference	Reason for exclusion
	No usable outcomes
Bishry 2014 ³⁸ Bitter 2010 ³⁹	
	No usable outcomes
Bittner 2007 ⁴⁰	Inappropriate population
Black 2013 ⁴¹	No usable outcomes
Bleck 2013 ⁴²	No usable outcomes
Bleck 2015 ⁴³	Inadequate ADHD diagnosis
Boulet 2011 ⁴⁵	Inadequate ADHD diagnosis
Boyle 1991 ⁴⁶	No usable outcomes
Breslau 2000 ⁴⁷	No usable outcomes
Brewerton 2016 ⁴⁸	Inappropriate population
Brogan 2014 ⁴⁹	No usable outcomes
Brook 1998 ⁵⁰	No usable outcomes
Byrd 2013 ⁵²	No usable outcomes
Canals 2016 ⁵³	Inappropriate population
Cantwell 1991 ⁵⁴	Systematic review not matching PICO
Capusan 2016 ⁵⁵	Inadequate ADHD diagnosis
Chen 2007 ⁵⁶	Inadequate ADHD diagnosis
Chen 2015 ⁵⁸	No usable outcomes
Chou 2013 ⁵⁹	Inadequate ADHD diagnosis
Chudal 2015 ⁶⁰	No usable outcomes
Copeland 2013 ⁶²	No usable outcomes
Cortese 2016 ⁶⁴	No usable outcomes
Cortese 2013 ⁶³	No usable outcomes
Costello 2003 ⁶⁶	Inappropriate population
Cuffe 2001 ⁶⁷	Inappropriate population
Cuffe 2015 ⁶⁸	No usable outcomes
De Alwis 2014 ⁶⁹	No usable outcomes
de Zwaan 2012 ⁷⁰	Inadequate ADHD diagnosis
Disney 1999 ⁷²	Inappropriate population
Dopfner 2008 ⁷⁴	No usable outcomes
Dougherty 2014 ⁷⁵	No usable outcomes
Dowson 2008 ⁷⁶	No usable outcomes
DuPaul 2014 ⁷⁷	No usable outcomes
Egan 2000 ⁷⁸	No usable outcomes
El Marroun 2012 ⁷⁹	Inadequate ADHD diagnosis
Elberling 2010 ⁸⁰	No usable outcomes
Elgen 2013 ⁸²	No usable outcomes
Elumour 2014 ⁸³	No usable outcomes
Ercan 2016 ⁸⁵	No usable outcomes
Ersan 2004 ⁸⁶	No usable outcomes
Esser 1990 ⁸⁷	No usable outcomes
Estevez 2014 ⁸⁸	No usable outcomes
Eyestone 1994 ⁸⁹	No usable outcomes
Ezpeleta 2014 ⁹⁰	Inappropriate population
Famularo 1992 ⁹¹	Inappropriate population
I diffidiate 1002	mappi opriate population

Reference	Reason for exclusion
Farahat 201492	No usable outcomes
Faraone 2000 ⁹³	Inappropriate population
Faravelli 2009 ⁹⁴	No usable outcomes
Farbstein 2014 ⁹⁵	No usable outcomes
Fayyad 2016 ⁹⁷	No usable outcomes
Fayyad 2007 ⁹⁶	Inadequate ADHD diagnosis
Fevang 2016 ⁹⁸	Inadequate ADHD diagnosis
Field 2014 ⁹⁹	No usable outcomes
Fombonne 1994 ¹⁰⁰	No usable outcomes
Fornaro 2013 ¹⁰²	No usable outcomes
Fortes 2016 ¹⁰³	No usable outcomes
Frank-Briggs 2010 ¹⁰⁴	No usable outcomes
Freeman 2016 ¹⁰⁵	Inappropriate population
Fullana 2013 ¹⁰⁶	No usable outcomes
Gada 1987 ¹⁰⁷	No usable outcomes
Gadow 2002 ¹⁰⁸	Inadequate ADHD diagnosis
Gadow 2001 ¹⁰⁹	No usable outcomes
George 2006 ¹¹⁰	No usable outcomes
Ghanizadeh 2008 ¹¹¹	No usable outcomes
Ghossoub 2017 ¹¹²	No usable outcomes
Giacobini 2014 ¹¹³	Inadequate ADHD diagnosis
Gomez 2016 ¹¹⁴	No usable outcomes
Gonzalez-Heydrich 2012 ¹¹⁵	No usable outcomes
Gordon 2005 ¹¹⁶	Inappropriate population
Gordon 2014 ¹¹⁷	Inappropriate population
Gorlin 2016 ¹¹⁸	No usable outcomes
Gross-Tsur 1991 ¹¹⁹	No usable outcomes
Gudjonsson 2014 ¹²⁰	No usable outcomes
Gudmundsson 2013 ¹²¹	No usable outcomes
Hack 2009 ¹²²	Inadequate ADHD diagnosis
Halldner 2014 ¹²³	No usable outcomes
Halmoy 2012 ¹²⁴	No usable outcomes
Hanc 2015 ¹²⁵	No usable outcomes
	No usable outcomes
Hanprathet 2015 ¹²⁶ Harris 2013 ¹²⁷	Inadequate ADHD diagnosis
Hastings 2005 ¹²⁸	No usable outcomes
Hauck 2017 ¹²⁹	
	Inadequate ADHD diagnosis
Heiervang 2007 ¹³⁰	Inappropriate population
Heneghan 2013 ¹³¹	No usable outcomes
Hernandez Vega 2015 ²⁷⁶ Hirschtritt 2015 ¹³²	Inappropriate population
	Inappropriate population
Hirshfeld-Becker 2006 ¹³³	No usable outcomes
Hunna 2016 ¹³⁴	Inadequate ADHD diagnosis
Huang 2016 ¹³⁴	Inadequate ADHD diagnosis
Huss 2008 ¹³⁵	No usable outcomes

Hysing 2016 ¹³⁸ No usable outcomes	Reference	Reason for exclusion
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McGee 1990 ¹⁷⁴ Outcomes reported elsewhere McLeer 1994 ¹⁷⁵ Inappropriate population Meyer 1998 ¹⁷⁶ No usable outcomes Milin 1991 ¹⁷⁷ Inappropriate population Modestino 2013 ¹⁷⁸ No usable outcomes Molina 2002 ¹⁷⁹ No usable outcomes Morgan 2014 ¹⁸⁰ Inadequate ADHD diagnosis Musser 2014 ¹⁸¹ Inadequate ADHD diagnosis	Martin 2006 ¹⁷¹	Inappropriate population
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Morgan 2014 ¹⁸⁰ Inadequate ADHD diagnosis Musser 2014 ¹⁸¹ Inadequate ADHD diagnosis	Modestino 2013 ¹⁷⁸	
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Musser 2014 ¹⁸¹ Inadequate ADHD diagnosis	Morgan 2014 ¹⁸⁰	Inadequate ADHD diagnosis
Myers 1993 ¹⁸² Inappropriate population		Inadequate ADHD diagnosis
	Myers 1993 ¹⁸²	Inappropriate population

Reference	Reason for exclusion
Nafi 2011 ¹⁸⁴	No usable outcomes
Namdari 2012 ¹⁸⁵ Nazar 2014 ¹⁸⁷	No usable outcomes
	No usable outcomes
Ndukuba 2014 ¹⁸⁸	No usable outcomes
Neuman 2005 ¹⁹⁰	No usable outcomes
N'Goran 2015 ¹⁸³	No usable outcomes
Niemczyk 2015 ¹⁹¹	Inadequate ADHD diagnosis
Nierenberg 2005 ¹⁹²	Inappropriate population
Nolan 2001 ¹⁹³	No usable outcomes
Norwich 2002 ¹⁹⁴	No usable outcomes
Nylander 2015 ¹⁹⁵	Inadequate ADHD diagnosis
O'Callaghan 1996 ¹⁹⁶	Inadequate ADHD diagnosis
Odlaug 2013 ¹⁹⁸	No usable outcomes
Oerlemans 2016 ¹⁹⁹	Inappropriate population
Ofovwe 2006 ²⁰⁰	No usable outcomes
O'Shea 2013 ¹⁹⁷	Review
Osman 2015 ²⁰¹	No usable outcomes
Ottman 2011 ²⁰²	Inadequate ADHD diagnosis
Panevska 2014 ²⁰⁴	No usable outcomes
Pastor 2002 ²⁰⁶	Inadequate ADHD diagnosis
Pastor 2008 ²⁰⁷	Inadequate ADHD diagnosis
Pastor 2015 ²⁰⁵	Inadequate ADHD diagnosis
Peterson 2001 ²⁰⁸	No usable outcomes
Petresco 2014 ²⁰⁹	No usable outcomes
Pheula 2011 ²¹⁰	No usable outcomes
Phillips 2014 ²¹¹	Inadequate ADHD diagnosis
Pierrehumbert 2006 ²¹²	No usable outcomes
Pineda 2003 ²¹⁴	Inappropriate population
Pineda 1999 ²¹³	No usable outcomes
Pinto 2016 ²¹⁵	Inadequate ADHD diagnosis
Ponde 2007 ²¹⁶	No usable outcomes
Rastam 2013 ²¹⁷	Inappropriate population
Ray 2009 ²¹⁸	No usable outcomes
Reich 1993 ²¹⁹	No usable outcomes
Rey 1994 ²²⁰	Inappropriate population
Reyes 2013 ²²¹	No usable outcomes
Richa 2014 ²²²	No usable outcomes
Ristovska 2013 ²²³	No usable outcomes
Roberts 2009 ²²⁴	No usable outcomes
Roberts 2007 ²²⁶	No usable outcomes
Rodgers 2015 ²²⁷	Inadequate ADHD diagnosis
Rojo-Moreno 2015 ²²⁸	No usable outcomes
Rosler 2004 ²³⁰	Inappropriate population
Rowland 2001 ²³²	No usable outcomes
Rowland 2015 ²³¹	No usable outcomes

Reference	Reason for exclusion
Ruhl 2009 ²³³	No usable outcomes
Runfola 2014 ²³⁴	No usable outcomes
Russ 2012 ²³⁵	Inadequate ADHD diagnosis
Russell 2014 ²³⁶	No usable outcomes
Safavi 2016 ²³⁷	No usable outcomes
Sagiv 2013 ²³⁸	Inadequate ADHD diagnosis
Salazar 2015 ²³⁹	No usable outcomes
Sanchez 2011 ²⁴²	No usable outcomes
Sanchez 2014 ²⁴¹	No usable outcomes
Sanchez-Gistau 2015 ²⁴⁰	No usable outcomes
Sarkhel 2006 ²⁴³	No usable outcomes
Sawyer 2007 ²⁴⁴	No usable outcomes
Schneider 2006 ²⁴⁵	Inadequate ADHD diagnosis
Sciberras 2014 ²⁴⁶	No usable outcomes
Segenreich 2015 ²⁴⁷	No usable outcomes
Seitz 2013 ²⁴⁸	No usable outcomes
Singh 2013 ²⁴⁹	Inadequate ADHD diagnosis
Sivertsen 2015 ²⁵⁰	No usable outcomes
Smalley 2007 ²⁵¹	No usable outcomes
Smidts 2007 ²⁵²	No usable outcomes
Snowling 2006 ²⁵³	No usable outcomes
Soma 2009 ²⁵⁴	Inadequate ADHD diagnosis
Sonneville 2015 ²⁵⁵	No usable outcomes
Spencer 1998 ²⁵⁶	No usable outcomes
Sprich 2000 ²⁵⁷	No usable outcomes
Stampoltzis 2012 ²⁵⁸	No usable outcomes
Steinsbekk 2015 ²⁵⁹	No usable outcomes
Stevens 2016 ²⁶⁰	Inadequate ADHD diagnosis
Strang-Karlsson 2008 ²⁶²	No usable outcomes
Subchartanan 2015 ²⁶³	No usable outcomes
Suren 2012 ²⁶⁴	Inadequate ADHD diagnosis
Takahashi 2016 ²⁶⁵	Inadequate ADHD diagnosis
Tashakori 2011 ²⁶⁶	No usable outcomes
Termine 2006 ²⁶⁷	No usable outcomes
Thabet 2010 ²⁶⁸	No usable outcomes
Thompson 1996 ²⁶⁹	No usable outcomes
Tibu 2016 ²⁷⁰	No usable outcomes
Tsao 2017 ²⁷¹	No usable outcomes
Turkyilmaz 2012 ²⁷²	No usable outcomes
Turner 2002 ²⁷³	No usable outcomes
Umar 2015 ²⁷⁴	No usable outcomes
Van Damme 2015 ²⁷⁵	No usable outcomes
Velez-Galarraga 2016 ²⁷⁷	No usable outcomes
Venkata 2013 ²⁷⁸	No usable outcomes
Verhulst 1997 ²⁷⁹	No usable outcomes

Reference	Reason for exclusion
Vingilis 2015 ²⁸⁰	No usable outcomes
Vitola 2016 ²⁸¹	No usable outcomes
Voigt 2006 ²⁸²	Inadequate ADHD diagnosis
Wang 2016 ²⁸⁴	Inadequate ADHD diagnosis
Wang 2017 ²⁸³	No usable outcomes
Wong 1992 ²⁸⁵	No usable outcomes
Wu 2013 ²⁸⁷	Inappropriate population
Yahia 2014 ²⁸⁸	Inappropriate population
Yau 2013 ²⁸⁹	No usable outcomes
Zorlu 2015 ²⁹⁰	No usable outcomes
Zucker 2015 ²⁹¹	No usable outcomes
Zwirs 2007 ²⁹²	No usable outcomes

I.2 Excluded health economic studies

None.