Web Appendix 1

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6-7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Registered at POSPERO - CRD42017055827 https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017055827
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7

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Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	See E-figure-1 – Trial Flow Diagram 7-8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	See E-figure-1 – Trial Flow Diagram 7-8 Available upon request
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7-8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	See Table 1. 7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8,10
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8-9

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Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	We were unable to calculate publication bias since we only had 7 studies
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9-10 Sensitivity and meta-regression
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	See E-figure-1 – Trial Flow Diagram
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	See Table 1.
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	See Table 1. Further bias for each study is available upon request
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	See Figures 1,2

			E-figures 2,3,4,5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	11-12
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	We were unable to calculate publication bias since we only had 7 studies
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	11-13
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13-18
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	18-19
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	20
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1 None

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Prenatal Exposure to Acetaminophen and Risk for Attention Deficit Hyperactivity Disorder, and Autism: A Systematic Review, Meta-Analysis and Meta-Regression Analysis of Cohort Studies

Criteria		**Brief description of how the criteria were handled in the meta-analysis**
Reporting of background should include		
√	Problem definition	Acetaminophen is the most commonly used analgesic and antipyretic medication in pregnancy. ADHD is the most common neurobehavioral in children. Recent data suggest neuro-disruptive properties of acetaminophen in the developing fetus exposed prenatally to acetaminophen.
√	Hypothesis statement	Prenatal exposure to acetaminophen increases the risk for ADHD and autism in early childhood.
√	Description of study outcomes	ADHD, ASD, hyperactivity symptoms and conduct disorder.
√	Type of exposure or intervention used	Acetaminophen
√	Type of study designs used	We included RCTs, cohorts and case-control studies.
√	Study population	Women exposed to acetaminophen during pregnancy.
Reporting of search strategy should include		
√	Qualifications of searchers	The credentials of the two investigators RM and EG are indicated in the manuscripts and author contributions.
√	Search strategy, including time period included in the synthesis and keywords	PubMed from 1965 – January 2017 EMBASE from 1974 – January 2017 Cochrane library- up to January 2017 Clintrials.gov- up to January 2017 See Trial flow and results in the manuscript.
√	Databases and registries searched	PubMed, EMBASE, Cochrane and Clintrials.gov
√	Search software used, name and version, including special features	We did not employ a software for the search. Mendeley was used to import and retrieve citations
√	Use of hand searching	We hand-searched bibliographies of retrieved papers for additional references.
√	List of citations located and	Details of the literature search process are outlined in the

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	those excluded, including justifications	trial flow. The citation list is available upon request.
√	Method of addressing articles published in languages other than English	We placed no restrictions on language in our search strategy.
√	Method of handling abstracts and unpublished studies	We had contacted a few authors for unpublished studies and missing data, when needed.
√	Description of any contact with authors	We contacted authors who had conducted multivariate analysis with diabetes as a covariate, but had not reported relative risk for diabetes.
Reporting of methods should include		
√	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Detailed inclusion and exclusion criteria are described in the methods section in the manuscript.
√	Rationale for the selection and coding of data	Data extracted from each of the studies were relevant to the exposure (acetaminophen), outcome, and possible effect of modifiers on the association.
√	Assessment of confounding	Conducted meta-regression to assess the contribution of relevant covariates to the observed effect. Conducted sensitivity analyses by eliminating the only study that was not conducted in recent years (1987).
√	Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	Study quality was assessed using the Newcastle-Ottawa Scale (NOS). Quality of study was included as a covariate in meta-regression.
√	Assessment of heterogeneity	Heterogeneity of the studies was explored by using the I^2 statistic that provides the relative amount of variance of the summary effect due to the between-study heterogeneity.
√	Description of statistical methods in sufficient detail to be replicated	Description of methods of meta-analysis, sensitivity analysis, meta-regression are detailed in the methods.
√	Provision of appropriate tables and graphics	We included the terms used for database search in the methods section in the manuscript, Trial flow for the search strategy, Table 1 for study characteristics, Table 2 for meta regression and forest plots for all outcomes.
Reporting of results should include		
√	Graph summarizing individual study estimates and overall	Figures 1 and 2

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	estimate	
√	Table giving descriptive information for each study included	Table 1
√	Results of sensitivity testing	Manuscript: Results section – ADHD and ASD outcomes
√	Indication of statistical uncertainty of findings	95% confidence intervals were presented with all summary estimates, I^2 values and results of sensitivity analysis
Reporting of discussion should include		
√	Quantitative assessment of bias	Quality of studies was included in meta-regression.
√	Justification for exclusion	We excluded studies that had not adjusted for maternal characteristics. Sub-cohorts from the same author were excluded. Different outcomes for the same author and cohort were only included once in the analysis.
√	Assessment of quality of included studies	Study quality was assessed using the Newcastle-Ottawa Scale (NOS). Quality of study was included as a covariate in meta-regression.
Reporting of conclusions should include		
√	Consideration of alternative explanations for observed results	We discussed that potential unmeasured confounders such as paternal age and maternal thyroid disorders, other parental chronic and behavioral diseases may have caused residual confounding. Also we discussed confounding by indication; mothers with background diseases will use more acetaminophen during pregnancy and will more likely to expose the fetus to stress and therefore increase the risk for ADHD and ASD. In addition, the medium-high heterogeneity may be attributes to different tools used in the studies to diagnose ADHD and ASD. We noted that the variations in the strengths of association may be due childs' age at diagnosis, duration of exposure to acetaminophen and maternal age at birth.
√	Generalization of the conclusions	We noted that all the studies were undertaken in western countries- West Europe and USA, where healthcare services are widely available and therefore the results cannot be extrapolated for the entire population.
√	Guidelines for future research	We recommend future studies to assess the dose-response effect of acetaminophen on neurodevelopmental disorders and also to find a uniform validated tool to assess exposure to acetaminophen. In addition uniform tools should be used to assess ADHD and ASD in epidemiological studies.
√	Disclosure of funding source	No external funding was used for the review

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√	PROSEPERO registry	CRD42017055827

Web Table 1. Characteristics of Cohort Studies Included in Meta-Analysis

Author(s), year, Country	Population (exposure range)	Prevalence of Acetaminophen ever users in cohort	Main Outcome Measurement(s)	Child age at Follow-up, years (range)	Trimester Exposure and Weeks of Exposure Exposure Assessment	Total Range of Duration of Exposure and Mean Duration of Exposure	Quality (NOS) - stars
A.P Streissguth, 1987, Washington DC (USA),(29)	Total-1529 Exposed- 183 Not-Exposed-238 (1 per month [18.3%], daily [1.4%])	41%	Attention score Child IQ score	4 (4-4.3)	Trimester(S)-1+2 Gestational weeks- ≤ week 20 assessment-Interview during the fifth month of pregnancy	Total Range of Duration - NA Exposure Mean duration- 7 days	6
Brandilstuen, 2013, Norway,(28)	Total-48631 Exposed- 20587 Not-Exposed-26213 (1-27 days, median: 2, >28 days, median: 37)	43%	Behaviour problems Psychomotor problems Temperament problems	3 (NA*)	Trimester(S)-All Exposure Gestational weeks- NA assessment-Two prenatal and one postnatal questionnaire	Total Range of Duration >28 days Mean duration- 7 days	5
Liew Z, 2014, Denmark,(14)	Total-64322 Exposed- 36187 Not-Exposed-28135 (ever users	56%	ADHD like behaviors (SDQ score) HKD hospital diagnosis	10.7 (8.2-13.4)	Trimester(S)-All Exposure Gestational weeks- All	Total Range of Duration - ≤ 28 days Mean duration- 7	7

	versus never users)		ADHD medication redemption		assessment- telephone interviews	days	
Thompson, 2014, New Zealand,(16)	Total-1714 Exposed- 435 Not-Exposed- 434 (ever users versus never users)	50%	SDQ score CRS:R questionnaire (DSM-IV)	11 (3.5-11)	Trimester(S)- All Gestational weeks- ≤ NA assessment- telephone interviews soon after birth	Total Range of Duration- NA Mean duration- NA	6
Liew Z, 2015, Denmark, (18)	Total-64322 Exposed- 36187 Not-Exposed- 28135 (ever users versus never users)	56%	Hospital diagnosis of ASD	12.7 (10.4-15.6)	Trimester(S)- All Exposure Gestational weeks- All assessment- telephone interviews	Total Range of Duration ≤ 28 days Mean duration- 7 days	7
Avella, 2016, Spain,(15)	Total-2001 Exposed- 828 Not-Exposed- 1173 (ever users versus never users)	41%	Measure of neuro-developmental outcomes: BSID MCSA CAST ADHD-DSM-IV K-CPT	4.8 (1.2-5)	Trimester(S)- All Exposure Gestational weeks- ≤ week 32 assessment- prospective interviews at weeks 12 and 32	Total Range of Duration - NA Mean duration- NA	6

Stergiakouli, 2016, Engalnd,(17)	Total-14541 Exposed- 3381 Not-Exposed-11160 (ever users versus never users)	42-53%	SDQ	7 (4-16)	Trimester(S)-All Exposure Gestational weeks- ≤ week 32 assessment-interviews at weeks 18 and 32	Total Range of Duration - NA Mean duration-NA	7

Web Table 2. Supplemental to figures 2-5

	Log RR	SE	Exposed-Total	Non-Exposed-Total	Weight%
Figure 2.					
A.P. Streissguth, 1987 (29)	0.293	0.186	183	238	6.1%
Brandilstuen, 2013 (28)	0.182	0.026	20587	26213	30.8%
Liew Z, 2014 (14)	0.255	0.057	36187	28135	23.9%
Thompson, 2014 (16)	0.489	0.124	435	434	11.9%
Avella, 2016 (15)	0.223	0.152	828	1173	11.4%
Stergiakouli, 2016 (17)	0.335	0.103	3381	11160	15.9%
Figure 3.					
A.P. Streissguth, 1987 (29)	0.293	0.186	183	283	2.7%
Brandilstuen, 2013 (28)	0.148	0.026	20587	26213	60.0%
Liew Z, 2015 (18)	0.174	0.067	36187	28135	21.0%
Avella, 2016 (15)	0.293	0.095	828	1173	6.1%
Stergiakouli, 2016 (17)	0.215	0.090	3381	11160	10.1%
Figure 4.					
Brandilstuen, 2013 (28)	-0.041	0.021	20587	26213	23.2%
Liew Z, 2014 (14)	0.046	0.002	36187	28135	22.4%
Thompson, 2014 (16)	0.365	0.123	435	434	17.5%
Avella, 2016 (15)	0.344	0.172	828	1173	15.3%
Stergiakouli, 2016 (17)	0.293	0.069	3381	11160	21.6%
Figure 5.					
Brandilstuen, 2013 (28)	0.000	0.026	20587	26213	23.4%
Liew Z, 2014 (14)	0.140	0.044	36187	28135	22.1%
Thompson, 2014 (16)	0.365	0.123	435	434	17.4%
Stergiakouli, 2016 (17)	0.336	0.069	3381	11160	19.6%