Hormones and Behavior 101 (2018) 125–147

Contents lists available at ScienceDirect

Hormones and Behavior

journal homepage: www.elsevier.com/locate/yhbeh

Review article

Prenatal paracetamol exposure and child neurodevelopment: A review

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ARTICLE INFO

Keywords:
Paracetamol
Acetaminophen
APAP
Neurodevelopment
Autism
Autism spectrum disorder
ASD
Attention deficit hyperactivity disorder
ADHD
Hyperactivity
Behavior

ABSTRACT

Background: The non-prescription medication paracetamol (acetaminophen, APAP) is currently recommended as a safe pain and fever treatment during pregnancy. However, recent studies suggest a possible association between APAP use in pregnancy and offspring neurodevelopment.
Objectives: To conduct a review of publications reporting associations between prenatal APAP use and offspring neurodevelopmental outcomes.
Methods: Relevant sources were identified through a key word search of multiple databases (Medline, CINAHL, OVID and TOXNET) in September 2016. All English language observational studies of pregnancy APAP and three classes of neurodevelopmental outcomes (autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), and intelligence quotient (IQ)) were included. One reviewer (AZB) independently screened all titles and abstracts, extracted and analyzed the data.
Results: 64 studies were retrieved and 55 were ineligible. Nine prospective cohort studies fulfilled all inclusion criteria. Data pooling was not appropriate due to heterogeneity in outcomes. All included studies suggested an association between prenatal APAP exposure and the neurodevelopmental outcomes; ADHD, ASD, or lower IQ. Longer duration of APAP use was associated with increased risk. Associations were strongest for hyperactivity and attention-related outcomes. Little modification of associations by indication for use was reported.
Conclusions: Together, these nine studies suggest an increased risk of adverse neurodevelopmental outcomes following prenatal APAP exposure. Further studies are urgently needed with; precise indication of use and exposure assessment of use both in utero and in early life. Given the current findings, pregnant women should be cautioned against indiscriminate use of APAP. These results have substantial public health implications.

1. Introduction

The number of women taking medications during pregnancy has more than doubled over the past 30 years, and now nine out of ten women take at least one medication while pregnant (Mosley II et al., 2015). Pregnant women are generally excluded from clinical trials so the vast majority of maternal medications have not been adequately studied in human pregnancy and the risks to the fetus are often poorly understood (Adam et al., 2011). Emerging research suggests that medication use during pregnancy may increase the risk of long-term adverse neurodevelopmental outcomes including autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) (Landrigan, 2010; El Marroun et al., 2014).

Paracetamol (APAP, Acetaminophen), an analgesic and antipyretic generally available without prescription, is the most commonly used medication in pregnancy (Werler et al., 2005). APAP has been estimated to be used by up to 65% of US, and > 50% of European women during their pregnancies (Brandlistuen et al., 2013; Servey and Chang, 2014). Although APAP has a narrow therapeutic index and is the leading cause of acute liver injury (Guggenheimer and Moore, 2011), it is considered among the safest options during pregnancy (Thiele et al., 2013). This is in part because there has been no strong evidence associating APAP with structural birth defects (Servey and Chang, 2014). However, a growing body of research suggests APAP may alter fetal development in a number of ways. Research has shown APAP may have endocrine disruptive properties capable of altering reproductive function (Kristensen et al., 2016; Holm et al., 2015; Kristensen et al., 2011; Snijder et al., 2012; Fisher et al., 2016). APAP use during pregnancy has been associated with an increased risk of asthma (Lourido-Cebreiro et al., 2016), immune alterations (Prymula et al., 2009; Thiele et al.,

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https://doi.org/10.1016/j.yhbeh.2018.01.003
Received 11 October 2017; Received in revised form 9 December 2017; Accepted 3 January 2018
Available online 03 February 2018
0018-506X/

Table 1
Cohort studies summary characteristics - pregnancy APAP and offspring neurodevelopmental outcomes.

Study author date	Population	Prevalence of APAP use	Exposure assessment	Outcome and assessment tools	Main Outcomes	Effect estimates (95% CI) - ever exposed	Effect estimates (95% CI) -prolonged exposure
Brandlistuen et al. (2013)	**Norwegian Mother and Child Cohort Study (MoBA)** 2919 3 year old sibling control pairs discordant on exposure within cohort of 48,631 born 1999–2008	46%	**APAP -Maternal report** -gestation weeks 17 and 30 & 6 months postpartum questionnaires w/ 10 exposure windows to name med, days of use & indication. Exposure divided into short-term (1–27 days use) and long term (28 days or more)	**Adverse Neurodevelopment at 3 yrs** Maternal report using: 1) Psychomotor Development - Norwegian Ages and Stages 2) Externalizing and Internaling behaviors - Child Behavior Checklist (CBCL/11/2–5/LDS) 3) Temperament - Emotionality, Activity and Shyness Temperament Questionnaire (EAS)	**Measures in Sibling control analysis:** 1) Gross motor 2) Communication 3) Externalizing behaviors 4) Internalizing behaviors 5) Hyperactivity 6) Motor/walking delay	**Less than 28 days:** 1) β = 0.10 (0.02–0.19) 6) β = 0.10 (0.02–0.18)	**More than 28 days:** 1) β = 0.24 (0.12–0.51) RR~1.67 2) β = 0.20 (0.01–0.39) RR ~ 1.57 3) β = 0.28 (0.15–0.42) RR ~ 1.69 4) β = 0.14 (0.01–0.28) RR ~ 1.40 5) β = 0.24 (0.11–0.38) RR ~ 1.67 6) β = 0.26 (0.06–0.45)
Vlenterie et al. (2016)	**Norwegian Mother and Child Cohort Study (MoBA)** 51,200 mother & child pairs from MOBA version 6 born 1999–2008	41%	**APAP -Maternal report** -gestation weeks 17 and 30 & 6 months postpartum questionnaires w/ 10 exposure windows to name med, days of use & indication. Exposure divided into short-term (1–27 days use) and long term (28 days or more)	**Adverse neurodevelopment at 1.5 yrs** Maternal report using; 1) Psychomotor Development - Norwegian Ages and Stages Questionnaire (ASQ) 2) Externalizing and Internaling behaviors - Child Behavior Checklist (CBCL/11/2–5/LDS) 3) Temperament - Emotionality, Activity and Shyness Temperament Questionnaire (EAS)	**Measures in propensity score matched cohort:** 1) Communication problems 2) Motor/walking delay		**More than 28 days:** 1) OR = 1.38 (0.98–1.95) 2) OR = 1.35 (1.07–1.70)
Liew et al. (2014)	**Danish National Birth Cohort (DNBC)** 64,322 children & mothers enrolled 1996–2002	56%	**APAP-Maternal report** -Telephone interview gestation weeks 12, 30, 6 months after birth. Provided w/ list of 44 med, asked gestation weeks of use on week by week basis.	**ADHD/hyperkinetic disorder at 7 yrs** using: 1) Hospital records-hyperkinetic disorder (HKD) 2) ADHD medications −2+ prescriptions 3) Parent report ADHD like behavior- Strengths and Difficulties Questionnaire (SDQ)	**3 measures:** 1) HKD diagnosis 2) Use of ADHD med 3) SDQ total difficulties	1) HR 1.37 (1.19–1.59) 2) HR 1.29 (1.15–1.44) 3) HR 1.13 (1.01–1.27)	> **20 weeks:** 1) HR 1.84 (1.39–2.45) 2) HR 1.53 (1.21–1.94) 3) HR 1.46 (1.16–1.85)

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Table 1 (*continued*)

Study author date	Population	Prevalence of APAP use	Exposure assessment	Outcome and assessment tools	Main Outcomes	Effect estimates (95% CI) - ever exposed	Effect estimates (95% CI) -prolonged exposure
Liew et al. (2016c)	**Danish National Birth Cohort (DNBC)** 64,322 children & mothers enrolled 1996–2002	56%	**APAP-Maternal report** -Telephone interview gestation weeks 12, 30, 6 months after birth. Provided w/ list of 44 med, asked gestation weeks of use on week by week basis	**Autism Spectrum Disorders (ASD)- avg. followup 12.7 yrs** using: Danish hospital and psychiatric registries records identifying autism and Hyperkinetic Disorder (HKD) International Classification of Disease 10th addition (ICD-10) codes	**ICD-10 codes**: 1) ASD w/ HKD symptoms (31% of those w/ ASD) 2) Infantile Autism w/ HKD symptoms (26% of those w/ infantile autism) 3) Autism without HKD	 1) HR 1.51 (1.19–1.92) 2) HR 1.55 (0.98–2.45) 3) HR 1.07 (0.92–1.24)	**3 trimesters exposed**: 1) HR 1.77 (1.24–2.53) 2) HR 2.45 (1.32–4.53) 3) HR 1.25 (0.98–1.60)
Liew et al. (2016a)	**Danish National Birth Cohort (DNBC)** 1491 mothers and children w/ IQ assessment from DNBC 1996–2002 cohort of 101,041	56%	**APAP-Maternal report** -Telephone interview gestation weeks 12, 30, 6 months after birth. Provided w/ list of 44 med, asked gestation weeks of use on week by week basis	**IQ-Performance & verbal at age 5 using**: Wechler Primary and Preschool Scales of Intelligence- Revised (WPPSI-R) administered by psychologists-short version including 3 verbal & 3 performance subtests	**IQ (WPPSI-R)**: 1) APAP w/o fever, Performance IQ: 2) Fever w/o APAP, Verbal IQ: 3) Fever w/o APAP, Performance IQ:	Mean difference: 1) 3.4 pts. lower (0.30–6.6) 2) 2.7 pts. lower (−0.19–5.6) 3) 4.3 pts. lower (0.30–8.3)	**> 1 trimester**: 1) 3.8 pts. lower (0.49–7.1)
Liew et al. (2016b)	**Danish National Birth Cohort (DNBC)** 1491 mothers and children in DNBC 1996–2002	56%	**APAP-Maternal report** -Telephone interview gestation weeks 12, 30, 6 months after birth. Provided w/ list of 44 med, asked gestation weeks of use on week by week basis	**Attention & executive function at 5 yrs using**: 1) Psychologists assessed attention function- Test Everyday Attention Children @ Five (TEACh-5). Subnormal = 1 SD below mean 2)Teachers & parents assessed executive function- Behavior Rating Inventory Executive Function (BRIEF) Subnormal = 1 SD above mean	**Neuropsychological measures**: 1) Subnormal overall attention 2) Overall attention (TEACh-5) cont. 4) Selective attention (TEACh-5) 3) Exec function (metacognition index) (BRIEF)	 1) OR = 1.5 (1.0–2.5) 4) OR = 1.5 (1.0–2.4) 3) OR = 1.5 (0.9–2.3)	**(a) Prolonged use, (b) 1st Trimester**: 1) mean dif = −0.34 (−0.63–0.05) (b) 2) OR = 2.8 (1.5–5.5) (b) 3) OR = 2.4 (1.0–4.4) (a)
Thompson et al. (2014)	**Auckland Birthweight Collaborative Cohort** 871 mothers & children born 1995–1997	50%	**APAP Maternal Report** (and aspirin, antacids, antibiotics). Questionnaire soon after birth yes/no used med, no dose or weeks of use info	**ADHD symptoms at 7 & 11 yrs using**: 1) Strengths and Difficulties Questionnaire (SDQ) 2) Conners' Behavioral rating scale: revised-Long Format (CRS:R-L)	**ADHD measures**: 1) Parent report at 7 yrs (SDQ) 2) Parent report at 11 yrs (SDQ) 3) Child report at 11 yrs (SDQ) 4) Parent report 7 yrs (CRS:R-L) 5) Parent report at 11 yrs (CRS:R-L)	 1) SDQ Total difficulty @ -7 2) SDQ Total Difficulty-child@11 3) CRS:R-L parent @ 7 4) SDQ Hyperactivity-Child@11 5)CRS:R-L hyperactivity	 1) mean dif = 1.1 (0.2–2.0) 2) mean dif = 1.1 (0.2–2.0) 3) mean dif = 1.6 (0.3–2.9) unadj. 4) mean dif = 0.4 (0.0–0.8) 5) dif = 2.0 (0.3–3.6)

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Table 1 (*continued*)

Study author date	Population	Prevalence of APAP use	Exposure assessment	Outcome and assessment tools	Main Outcomes	Effect estimates (95% CI) - ever exposed	Effect estimates (95% CI) -prolonged exposure
Avella-Garcia et al. (2016)	**Spanish Infancia y Medio Ambiente (INMA project)** 2644 mother child pairs born 2004–2008	41–43%	**APAP Maternal Report** - Data collected at regular clinical visits and by questionnaire gestation weeks 12 & 32. APAP use after 32 wks not evaluated. APAP single & combo meds identified	**Autism Spectrum (ASD) & Attention function symptoms at 1 & 5 yrs**: 1) ADHD-DSM-IV form list (age 5) 2) The Childhood Autism Spectrum Test (CAST) (TP) (age 5) 3) & 3a) Conner's Kiddie Continuous Performance Test (K-CPT) (age 5)	**ASD and attention function measures**: 1) Hyperactivity ADHD-DSM-V 2) CAST scores males (ASD) 3) K-CPT commission errors 3a) K-CPT low detectability/reaction time	**Sporadic use (1 or 2 trimesters)**: 1) IRR 1.41 (1.01–1.98) 2) β = 0.56 (0.001–1.11) Males 3)IRR 1.14 (1.03–1.26) Females 3a) β = −0.10 (−0.18 to −0.02)Females	**Persistent Use (3 trimesters)**: 1) IRR 2.01 (0.95–4.24) 2) β = 1.91 (0.44–3.38) Males 3) IRR 1.32 (1.05–1.66) Females 3a) β = −0.18 (−0.36–0.00)Females
Stergiakouli et al. (2016)	**Avon Longitudinal Study of Parents & Children (ALSPAC)** 7796 mothers & children born 1991–1992	53% @ 18 wks 42% @ 32 wks	**APAP Maternal report** - 2 pregnancy interviews 18 weeks & 32 weeks. APAP use not evaluated after 32 wks in pregnancy, mother and partner APAP use when child 61 months	**ADHD symptoms at age 7 using**: Maternal report of behavior problems at 7 years using the Strengths and Difficulties Questionnaire (SDQ)	ADHD Behaviors (SDQ) 1) Total difficulties 2) Conduct problems 3) Hyperactivity	**Exposure at 18 weeks**: 3) RR 1.18 (1.01–1.38)	**Exposure at 32 weeks**: 1) RR 1.37 (1.07–1.75) 2) RR 1.35 (1.13–1.60) 3) RR 1.22 (1.04–1.43)

Study author date	Authors' conclusions	Dose-response?	Trimester effects?	Specificity?	Quality assessment	Strengths	Limitations
Brandlistuen et al. (2013)	Children exposed to long-term use of APAP during pregnancy had substantially adverse developmental outcomes at 3 years of age	Yes, stronger effects for long-term exposure vs. short -term use.	Yes, trends of 3rd trimester effects observed, but power to detect limited	Yes, No association found to Ibuprofen in adjusted models. Power may have been limited to detect association	**7** **NEWCASTLE- OTTAWA OTTAWA scale (out of 9)**	Prospective design allowing collection of exposure data at 3 time points before diagnosis, large established cohort, sibling controls design, extensive and validated measures of neurodevelopmental outcomes and additional confounder control. Information on indication specifically for APAP use.	Parent report of exposure and outcome may be subject to misclassification, no specific dose info, maternal report of "soft" outcomes, possible selection bias due to low participation in MoBa, differential characteristics of participants vs. non-participants & loss to follow up, possible residual confounding
Vlenterie et al. (2016)	Long-term exposure to APAP in utero was associated w/ modestly increased risk of motor milestones delay & impaired communication skills among children at 18 months.	Yes, no increased risk observed from short-term exposure, only long-term	N/A did not investigate	Not identified, but controlled for other meds including NSAIDS, antiepileptics, antidepressants, opioids, triptans & benzodiazepines	**7**	Prospective design, exposure data at 3 time points, large established cohort, info on many confounders including maternal depression, indication & use of other meds. Used propensity score matching that mimics unbiased effect estimation from randomization,extensive and validated measures of neurodevelopmental outcomes.	In addition to those discussed above, women excluded from PS-matched analyses were more likely to suffer from headache or migraine & use addt'l med. Possibility of residual confounding, from unknown sources including the severity of infections or headaches. A large number of outcomes, chance finding are a possibility.

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Table 1 (*continued*)

Study author date	Authors' conclusions	Dose-response?	Trimester effects?	Specificity?	Quality assessment	Strengths	Limitations
Liew et al. (2014)	Maternal APAP use during pregnancy is associated w/ higher risk of HKDs and ADHD-like behaviors in children.	Yes, higher risk for all 3 trimester exposure. p-value for trend by weeks of use- all 3 outcomes $p < .001$.	Yes, estimates consistently higher for use in 2nd or 3rd trimester	Controlled for ibuprofen and aspirin in analysis, not enough power to do separate analyses	**9**	Prospective design allowing collection of exposure data at 3 time points before diagnosis, large established cohort, 3 outcomes w/ consistent association, Rx & hospital diagnosis not subject to recall bias, important confounder control	Possible selection bias, 30% moms missed 1 or more interviews (ADHD heritability may influence), Self -report of exposure possible recall bias, no specific dose info, indications were not reported in relation to use of APAP, possible residual confounding
Liew et al. (2016c)	Maternal use of APAP in pregnancy was associated with ASD with hyperkinetic symptoms only, suggesting APAP exposure early in fetal life may specifically impact the hyperactive behavioral phenotype.	Yes, higher risk from all 3 trimester exposure. Dose–response by weeks of use (p-trend = 0.006 and 0.052 for ASD & infantile autism, respectively)	Likely, greatest ASD risk 2nd trimester, infantile autism 3rd, but power to detect limited	Controlled for ibuprofen and aspirin in analysis, not enough power to do separate analyses	**9**	Prospective design allowing collection of exposure data at 3 time points before diagnosis, large established cohort, long follow-up, identified sub-population risk, observed dose–response, outcome from hospital records and controlled for important confounders	Self-report exposure, no specific dose info so unable to determine trimester effects, potential recall bias, indications were not reported in relation to use of APAP, possible residual confounding
Liew et al. (2016a)	Maternal APAP use during pregnancy was associated w/ lower performance IQ in 5 year olds. However, APAP treatment of maternal fever in pregnancy showed a compensatory association with IQ scores.	No exposure -response patterns were observed with cumulative weeks of use.	Yes, stronger effects 1st and 2nd trimester	Yes, found no association to aspirin and ibuprofen. However, power to detect association limited	**8**	Prospective design, exposure data at 3 time points, subset of large established cohort, trained psychologists administered IQ tests, methods used to minimize effects of selection bias, power for interaction analysis, important confounder control	Exposure misclassification possible no dose and refined frequency obtained, uncertainty about the exact timing of fever occurrence and APAP use. NSAIDS controlled for but not other meds. Possible uncontrolled genetic, lifestyle or residual confounding by indication.
Liew et al. (2016b)	Some evidence that maternal paracetamol use during pregnancy was associated with poorer attention and executive function in 5 yr olds.	Yes, the risk for subnormal overall attention or executive function were higher for longer duration of APAP use	Yes, Stronger association in 1st trimester	Yes, Results did not change after controlling for aspirin and ibuprofen	**9**	Prospective design, collection of exposure data at 3 time points before diagnosis, subset of large established cohort, trained psychologists administered tests of functional measures, methods used to minimize effects of selection bias, enough power for interaction analysis, important confounder control	Possible selection bias, Self -report of exposure possible recall of APAP timing, no specific dose info,indications were not reported in relation to use of APAP, possible residual confounding
Thompson et al. (2014)	These findings strengthen the contention that APAP exposure in pregnancy increases risk of ADHD-like behaviors	Not investigated	Not investigated	Yes, no significant differences associated with any other drug.	**5**	Prospective design, outcome assessed at two time points,by both parent and child report using two validated instruments. Good confounder control	Follow up rate of 59–70% of original population. Specialized cohort disproportionally sampled for small for gestational age. Small study, marginally significant results

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Table 1 (*continued*)

Study author date	Authors' conclusions	Dose-response?	Trimester effects?	Specificity?	Quality assessment	Strengths	Limitations
Avella-Garcia et al. (2016)	Prenatal APAP exposure was associated w/ a greater # of ASD symptoms in males & showed adverse effects on attention-related outcomes for both genders	Yes, "associations seemed dependent on frequency of exposure".	N/A No trimester effect investigation & exposure last assessed at 32 wks	No change in effect estimates after adjustment for other pregnancy medications	**9**	Prospective design allowing collection of exposure data at 2 time points before diagnosis, established cohort, 3 levels of exposure, identified dose–response gradient, multiple outcomes evaluated, some on continuous scale allowing examination of milder conditions. Important confounders controlled, sensitivity analyses on various indications with no change in results	Exposure only measured through wk. 32 of pregnancy, self-reported exposure, no specific dose, potential residual confounding, potential unmeasured genetic confounding, some associations may be due to chance given multiple comparisons
Stergiakouli et al. (2016)	Children exposed to APAP prenatally are at increased risk of multiple behavioral difficulties, association does not appear to be explained by unmeasured behavioral or social factors	N/A Dose-response not assessed.	Yes, stronger 3rd trimester effects than 2nd but exposure last assessed at 32 weeks	N/A did not control for other meds	**5**	Prospective design allowing collection of exposure data at 2 time points, established cohort, important confounders controlled including polygenic risk factors and comparison to parental postnatal APAP use.	Identified potential confounding from partner's APAP use. Exposure only measured through wk. 32 of pregnancy, self-reported exposure, no specific dose, potential residual confounding, No maternally reported indication for use but adjusted for common use reasons reported separately

2015), and, most recently, functional changes in behavior and cognition (Andrade, 2016).

Long-term neurodevelopmental consequences of APAP were first hypothesized fourteen years ago by Dr. Anthony Torres who noted that ASD was associated with infection during pregnancy (Torres, 2003). He proposed that antipyretics might interfere with normal immunological development in the brain leading to neurodevelopmental disorders, such as ASD, in those genetically and immunologically predisposed. This hypothesis was followed by two supportive ecological analyses (Becker and Schultz, 2010; Bauer and Kriebel, 2013), but this question has only recently been investigated in well-conducted studies.

The purpose of this review is to summarize and assess the findings of observational studies evaluating the association between prenatal exposure to APAP and offspring adverse neurodevelopmental outcomes and to provide an overview of plausible biological mechanisms for such a relationship.

2. Methods

2.1. Search strategy

Relevant studies were identified by searching several online databases: the database of the National Library of Medicine (MEDLINE/PubMed); the Cumulative Index to Nursing and Allied Health Literature (CINAHL); University of Massachusetts Lowell collection of 66 health related journals (OVID UML Journals@OVID); and the National Institute of Health Toxicology Network (TOXNET) September 28–29, 2016. The search was limited to English language studies. For the MEDLINE and CINAHL Boolean searches were conducted as follows: (paracetamol or acetaminophen or APAP) AND ("attention function" or "neurodevelopmental problems" or behavior or neurodevelopment or "neurological development" or hyperactivity or autism or "autism spectrum disorder" or attention or IQ or "attention deficit hyperactivity disorder" or ADHD or hyperkinetic or ASD) AND (Prenatal or Pregnancy). For OVID a Boolean search was done as follows: (paracetamol or acetaminophen or APAP) AND (pregnancy or prenatal) with limits to original articles in journals related to clinical medicine, health professions, life & biomedical sciences, life sciences, nursing, pharmacology or public health with key words in the abstracts. For an advanced search on TOXNET terms were "paracetamol, pregnancy, cohort" utilizing the limits of all word variants, records with all words and searching all fields. We searched manually through the reference lists of previously published reviews and the studies included in this review for additional eligible studies.

Daily searches of the new studies in PubMed under the search term "paracetamol" were conducted after the original databases search on September 29, 2016 until February 27, 2017 to identify any newly published eligible studies.

2.2. Inclusion criteria, quality assessment and outcome measures

Observational studies investigating maternal APAP use during pregnancy and its association with neurodevelopmental outcomes in offspring children, including autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD) and Hyperkinetic Disorder (HKD) symptoms, as well as intelligence quotient (IQ) were included in this review. A study was considered eligible if it met the following criteria: 1) the report contained original data from human observational studies; 2) exposure to APAP during pregnancy was reported in the main analysis; 3) there was an unexposed comparison group; 4) risk ratios (RR) or hazard ratios (HR) were reported; and 5) the study was unique and the outcome did not overlap with another included study on the same population. If studies overlapped, the study with the earliest publication date was included. Citations that did not meet these criteria were excluded. One author (AZB) screened all retrieved citations based on titles and abstracts. Study eligibility was assessed by reading the full text.

Data extraction was completed by one author (AZB) and is presented in Table 1. The study characteristics extracted from full text included: year of publication, country, study design, population size, dates of study, exposure assessment methodology, outcome assessment methodology, main outcome, outcome for short and long term exposure, evidence of dose-response, evidence of trimester effects, evidence of specificity, overall quality assessment rating, strengths and limitations of each study. Potential confounders that were included in multivariable analyses are also reported (Appendix A). The Newcastle-Ottawa scale was used for quality and bias assessment rating of study methodologies (Stang, 2010) (Appendix B).

3. Results

Sixty four records were initially identified. Overlapping studies were compared and only the study with the earliest publication date was selected for full text review, the additional studies were excluded. After exclusion of non-relevant articles, twelve full text articles were screened and nine eligible studies in five populations were identified. The search flowchart is presented in Fig. 1.

Due to the large variation in outcomes and outcome measurement methods we could not combine the results using meta-analysis. We therefore followed qualitative review methodology guidelines whereby we evaluated key characteristics of each study, applying consistent evaluation criteria (Moher et al., 2010). Studies were of high quality with an average Newcastle-Ottawa score of 7.7 (Appendix B). The results of this review are presented in a summary table (Table 1) and are described below. Each of the nine studies is briefly summarized and its strengths and weaknesses discussed below.

3.1. Norwegian Mother and Child Birth Cohort (MoBa) - 2 studies

Two studies utilized the prospective Norwegian Mother and Child Birth Cohort (MoBa) to investigate the relationship between neurodevelopmental outcomes and the use of APAP in pregnancy (Brandlistuen et al., 2013; Vlenterie et al., 2016). For both studies participants were recruited at their routine ultrasound examination at gestational week 17 between 1999 and 2008. Women reported information about illness (headache, fever, cold and back pain) and medications used for these illnesses by questionnaires administered at weeks 17 and 30 of gestation and six months after birth. Both studies examined timing and duration of exposure, and confounding variables including indication for use. The studies assessed neurodevelopmental outcomes by parent report utilizing the validated instruments of the Ages and Stages Questionnaire (ASQ), Child Behavior Checklist (CBCL/11/2-5LDS) and Emotionality, Activity and Shyness Temperament Questionnaire (EAS).

Brandlistuen et al. (2013) examined **long term neurodevelopment outcomes** at age 3. This analysis included 48,631 children whose mothers returned the 3-year follow-up MoBa questionnaire (Brandlistuen et al., 2013). Within this cohort they identified 2919 same-sex sibling pairs that were utilized for sibling control analyses. A sibling control design allows the separation of the effects of familial and genetic confounding from effects of medication because siblings share a familial environment and 50% of genetic factors but may differ on medication exposure during pregnancy. The authors also adjusted in their analyses for indication for use (Appendix C) and concomitant use of other medications.

In the sibling-control analysis, children exposed to prenatal APAP for > 28 days had poorer gross motor development, communication skills, externalizing behavior and internalizing behaviors, and exhibited more hyperactivity and delay in the walking milestone. Shorter term use was associated with poorer gross motor outcomes. There were trends of stronger effects when exposure occurred in the third trimester. Associations were specific to APAP, as no associations were found for another common analgesic, ibuprofen. Effect estimates were unchanged

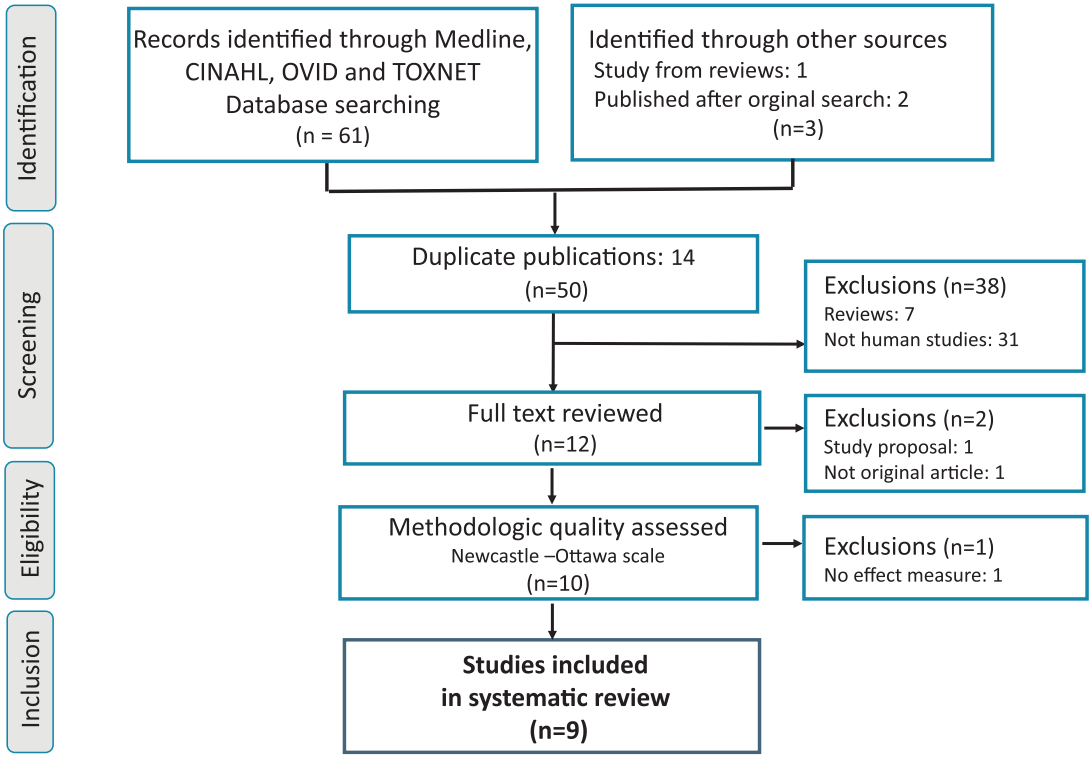

Fig. 1. PRISMA flow diagram. Sixty four records were identified in Medline, CINAHL, TOXNET, PUBMED plus screening of study references. After exclusion of duplicates and non-relevant articles, 12 full-text articles were abstracted, 3 of which were excluded leaving a total of 9 articles included in the review.

by controlling for indication for use, use of other medications and maternal depressive symptoms.

Vlenterie et al. (2016) examined **neurodevelopment problems** at 18 months of age. This second analysis utilized data from 51,200 pregnancies with complete MoBa questionnaire data through 18 months post-partum (Vlenterie et al., 2016). After using propensity score (PS) matching on 23 variables for control of confounding, long-term APAP exposure (> 28 days of APAP use) during pregnancy was modestly associated with delayed motor milestone attainment and with communication problems. Short-term exposure was not associated with increased risk. Sensitivity analysis for several indications for use showed similar effects as the PS-matched analyses, suggesting the identified associations were not due to confounding by indication for use.

3.1.1. Conclusion

This very large study with self-reported APAP exposure at three time points provides strong evidence that prenatal APAP use is associated with multiple neurodevelopmental endpoints. Similar results were found at 18 months and 3 years, except for activity problems and externalizing behaviors identified only at 3 years, an age such problems are more observable. Both studies provide evidence that risk increases with duration of use. The Brandlistuen study evaluated exposure timing and results suggest that exposure during the third trimester may be more critical for these developmental endpoints. Maternal indication for use does not appear to be related to the APAP-outcome association in this population.

3.2. Danish National Birth Cohort – 4 studies

Liew et al. have published four papers reporting on different aspects of neurodevelopment in relation to prenatal APAP exposure in The Danish National Birth Cohort (DNBC). In this nationwide cohort study women were recruited between 6 and 12 weeks of gestation from 1996 to 2002. All analyses were restricted to mothers who answered 3 telephone interviews (at the 12th and 30th gestational weeks and 6 months after birth) that asked whether they had taken any analgesics during pregnancy. Respondents who answered yes were provided with a list of common pain killers, whether available as an OTC or via prescription, including APAP. To address potential confounding by indication, data on diseases or conditions that may trigger use of acetaminophen during pregnancy were collected including muscle and joint diseases, fever, and inflammation or infections. However, these indications were not reported in relation to the use of painkiller. All four analyses examined timing and duration of exposure, confounding by child sex and indication for use.

Liew et al. (2014) examined **ADHD-like behaviors** using the Strengths and Difficulties Questionnaire (SDQ), as well as use of ADHD medications at age 7. This study also examined APAP in relation to diagnosis of hyperkinetic disorders (HKD). These analyses included 64,322 children in the DBNC. Maternal APAP use during pregnancy was associated with a higher risk for HKDs and ADHD-like behaviors, which was greater when use was in both 2nd and 3rd trimesters, increasing with longer duration of use and was not confounded by indication for use. Effect estimates were somewhat higher in girls.

Liew et al. (2016c) examined **ASD risk with and without hyperkinetic disorders** in the same population as Liew et al. (2014). ASD diagnosis was ascertained by linking DNBC to the Danish National Hospital Registry. An ICD-10 diagnosis of hyperkinetic (HKD) disorders was used to classify cases as having HKD. Ever use of APAP during pregnancy was associated with an increased risk of ASD accompanied by HKD (HR = 1.51 95% CI 1.19–1.92). For ASD without HKD effect estimates were higher in girls than boys. For both categories of disease, risk increased with exposure duration. Results did not change when controlling for indication for use or history of maternal psychiatric illness.

Liew et al. (2016a) examined **attention** using Test of Everyday Attention for Children at Five (TEACh-5) and **executive function** in relation to prenatal APAP use using the Behavior Rating Inventory of Executive Function (BRIEF) at age 5 (Liew et al., 2016a). The study

included 1491 mothers and children enrolled in the DNBC. Poorer scores in both attention and executive function were associated with pregnancy APAP use, with detriments increasing with longer exposure, with results largely unchanged when controlling for indication for use. Results for abnormal attention function were similar for boys and girls, but effect estimates for parent-rated executive difficulties were higher for boys.

Liew et al. (2016b) examined three **IQ** scores at 5 year (Liew et al., 2016b). Prenatal APAP was weakly associated with decreased IQ scores in the absence of fever. Conversely, fever was associated with poorer scores in the absence of APAP. No significant decreases were seen in the presence of both fever and APAP use. There was no evidence that duration of use was related to these associations nor that associations differed by sex of the child.

3.2.1. Conclusion

This very large study with self-reported APAP exposure at three time points provides strong evidence that prenatal APAP use is associated with multiple neurodevelopmental endpoints. Three of these four studies provide evidence that risk increases with duration of use, and suggest that the 2nd and third trimesters may be more critical for these developmental endpoints. Only for IQ does maternal indication for use appear to be related to the APAP-outcome association. Findings on modification by sex were inconsistent, with effect estimates higher in girls for ADHD like behaviors and ASD without HKD, higher in boys for executive difficulties and similar in boys and girls for IQ.

3.3. Auckland Birthweight Collaborative Study

Thompson et al. (2014) utilized the New Zealand Auckland Birthweight Collaborative (ABC) Study to investigate associations between medication use in pregnancy and children's **behavioral difficulties and ADHD symptoms** (Thompson et al., 2014). This cohort consisted of 871 mothers and infant pairs of European descent born between 1995 and 1997 disproportionately sampled for small for gestational age. Symptoms of ADHD were evaluated by parent report at age 7 and 11 and child report at age 11 using the SDQ and the Conners' Behavioral Rating Scale Revised (CRS:R-L) scales. Data on medication use were obtained by interviewer-administered maternal questionnaire at one time point soon after the child's birth. Data on indications e.g., fever and inflammatory problems were also collected but not reported in relation to the use of pain killers.

APAP use in pregnancy was associated with marginal differences of total difficulty scores (SDQ) at 7 years (maternal report) and 11 years (child report). On many of the subscales, conduct, hyperactivity, impulsivity and emotional difficulties were more prominent in the exposed children. Specificity to APAP was observed as no statistically significant differences were associated with any of the other drugs investigated.

3.3.1. Conclusion

This small longitudinal study with self-reported APAP exposure at one time point provides some evidence that APAP in pregnancy may increase the risk of ADHD-like behaviors. While the associations remained robust when controlled for confounding including maternal fever, used two independent behavior measures and evaluated multiple medications, this small study has limited generalizability and marginally significant effects.

3.4. Infancia y Merdio Ambiente (INMA) birth cohort

Avella-Garcia et al. (2016) examined both **ADHD related attention function and autism spectrum symptoms** in the Infancia y Merdio Ambiente (INMA) Spanish prospective birth cohort (Avella-Garcia et al., 2016). The cohort included 2644 mother-child pairs recruited during pregnancy between 2004 and 2008. Use of APAP was evaluated in two structured interviews at weeks 12 and 32 of pregnancy. Exposure was classified as ever/never use and frequency of use as never, sporadic (use of any dose in one or two trimesters) and persistent (use of any dose in all three trimesters). If the mother had taken medication, the indication as reported by the mother were collected using open questions. Neurodevelopment outcomes were assessed at one year using the Bayley Scales of Infant Development (BSID). At age five outcomes were assessed using the Childhood Autism Spectrum Test (CAST), Conner's Kiddie Continuous Performance Test (K-CPT), California Preschool Social Competences Scale (CPSCP), McCarthy Scales of Children's Abilities (MCSA) and teacher rated ADHD symptoms using the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) form list. BSID & MSCA were performed by trained psychologist who also administered the CAST questionnaire to the child's parents.

Prenatal APAP was associated with a greater number of autism spectrum symptoms in males, which appear dose dependent with an increase in CAST score of almost two clinical symptoms in those with persistent exposure ($\beta = 1.91$ 95% CI 0.44–3.38). Results were largely unchanged when controlling for indication for use. In contrast, females showed a decrease in autism symptoms and no clear trend by frequency of exposure. In both genders, prenatal APAP exposure was associated with adverse effects on attention related functions of hyperactivity/impulsivity symptoms, with detriments increasing with longer exposure as measured by K-CPT parameters. Attention function was modified by gender. In females, persistent exposure was associated with higher risk of commission errors and poorer detectability scores. Again, results were not significantly different when controlled for indication. The results of the sensitivity analyses suggested separate adverse effects of APAP exposure on ASD and ADHD related outcomes.

3.4.1. Conclusions

This small study with self-reported APAP exposure at 2 time points, used multiple outcome assessments to provide evidence that prenatal APAP was associated with ASD symptoms in boys and ADHD symptom in both genders. Risk increased with duration of exposure and results were largely unchanged when controlling for indication. Effect modification by gender differed on outcome. Prenatal APAP exposure was only associated with a greater number of ASD symptoms in males while ADHD symptoms were more prominent in exposed females. The collection of APAP usage data only through pregnancy week 32 may have led to exposure misclassification and possibly underestimation of effect.

3.5. Avon longitudinal study

Stergiakouli et al. (2016) examined associations between offspring **ADHD related behavioral problems** and maternal prenatal APAP, as well as maternal postnatal APAP use and partner's APAP, as a method to control for familial confounding (Stergiakouli et al., 2016). This study utilized the Avon Longitudinal Study of Parents and Children (ALSPAC) of 7796 mother and child pairs enrolled between 1991 and 1992. APAP use was assessed by maternal questionnaire at 18 and 32 weeks of gestation. Reports of muscle and joint problems, infections (including cold or flu, urinary, or other infections), migraine or headaches were collected at the same time as the medication use. The same questions were asked of the mother and her partner when the child was 61 months old. Children's behavioral problems were assessed by the mother at age 7 using the SDQ. Controlled confounders included maternal ADHD genetic risk scores and self-reported psychiatric illness.

Prenatal APAP use at both 18 and 32 weeks of pregnancy was weakly associated with higher odds of hyperactivity symptoms (aRR = 1.18, 95% CI, 1.01 to 1.38) and (aRR = 1.22, 95% CI 1.04 to 1.43), respectively. At 32 weeks, APAP use was also associated with greater risk of having SDQ total difficulties and conduct problems. Associations between maternal prenatal APAP use and all the SDQ domains were essentially unchanged after mutual adjustment for

maternal postnatal or partner's APAP use. Results were similar when controlled for additional confounders including indication for use.

3.5.1. Conclusions

This study, within an older cohort with self-reported APAP exposure at two time points, provides evidence that prenatal APAP use is associated with increased risk of ADHD related behavioral difficulties. The association did not appear to be explained by indication for use, health care seeking bias or other behavioral and social factors. The collection of exposure data only through pregnancy week 32 may have led to exposure misclassification and underestimation of effects.

4. Discussion

In the nine studies from five cohorts in this review, over 50% of children were exposed to APAP in utero consistent with other estimates of exposure (Kristensen et al., 2016). Because of heterogeneity of study outcomes it was not possible to use meta-analytic methods to provide a quantitative summary estimate of the effects of included studies. There was, however, consistency of results as all nine prospective cohort studies suggested prenatal APAP exposure moderately increased risk of adverse study outcomes (ASD, and ADHD symptoms, and IQ).

ADHD is one of the most common neurodevelopmental disorders, characterized by age-inappropriate inattentiveness and/or increased hyperactivity and impulsivity (American Psychiatric Association, 2000). Less common and more severe, ASD is defined by impaired communication and social interaction as well as repetitive and restricted behaviors and interests (American Psychiatric Association, 2000). ASD and ADHD are considered distinct disorders but are similar in that they share some neuropsychological impairments, are more prevalent in males and prevalence has increased for both in recent years (Leitner, 2014; Chantiluke et al., 2014). ADHD and ASD frequently co-occur, with the presence of ADHD within ASD ranging from 30 to 80%, whereas the presence of ASD in ADHD is estimated at 20–50% (Leitner, 2014; Stevens et al., 2016). It is not yet completely clear whether shared cognitive phenotypes are based on common or different underlying pathophysiology and whether comorbid patients have additive neurofunctional deficits (Mansour et al., 2016).

The cohort studies reviewed here suggest that prenatal exposure to APAP alters neurodevelopment most strongly in relation to hyperactive and attention related phenotypes (Appendix D). Four studies were limited to outcomes related to various ADHD symptomology, (Liew et al., 2016a; Thompson et al., 2014; Stergiakouli et al., 2016; Liew et al., 2014) while Liew et al. (2016c) investigation of ASD only found APAP associated with ASD for those with a comorbid hyperactive behavioral phenotype (HKD) (Liew et al., 2016c). In the Norwegian MoBa studies, at three years of age they found those offspring exposed had increased risk of higher activity levels, externalizing and internalizing behaviors, which can be symptoms of ADHD (Christakis, 2016). On the other hand, communication problems and poor motor development were more common in the exposed at both 18 months and three years, which may be symptomatic of ASD (Vlenterie et al., 2016; Mehling and Tasse, 2016; Brandlistuen et al., 2015). The results of the sensitivity analyses in the Avella-Garcia et al. study, which evaluated both ASD and ADHD related outcomes, suggested separate and adverse effects of APAP exposure on each of the outcomes (Avella-Garcia et al., 2016). Similarly, Liew et al. (2016b) found that the association of APAP on performance IQ was largely independent from the results of their previous study on prenatal APAP and ADHD diagnosis (Liew et al., 2016b; Liew et al., 2014). Taken together these findings suggest ASD and ADHD are distinct disorders, while at the same time, suggest prenatal use of APAP may increase risk most predominantly for hyperactivity and behavioral phenotypes.

Effect modification by gender was investigated in five studies with inconsistent findings (Liew et al., 2016a; Liew et al., 2016b; Avella-Garcia et al., 2016; Liew et al., 2014; Liew et al., 2016c). Both Liew et al., 2014 and Avella-Garcia et al. (2016) found larger effects in girls for ADHD-like behaviors. For ASD, Liew et al. (2016c) found no apparent effect modification by sex for ASD with hyperkinetic symptoms, but for ASD without hyperkinetic symptoms the effect estimates were higher in girls. In contrast, Avella-Garcia only found the increased ASD risk in boys. Effect estimates were higher in boys for executive function and similar in boys and girls for IQ. Caution in interpretation of these findings on gender is warranted as subgroup numbers were small and the confidence intervals wide.

In all studies data on indication for use had been collected. However, misclassification of indication for use may have occurred due to the structure of questions in data collection instruments, where often general health questions were asked, not specifically the indication for each APAP use (Appendix C) with the exception of MOBA (Brandlistuen et al., 2013; Vlenterie et al., 2016) and INMA (Avella-Garcia et al., 2016) studies where indications were collected in relation to the use of APAP. Reported associations between prenatal APAP exposure and health outcomes in children remained in all nine studies after adjustments for indication for use.

Together these nine studies in five cohorts provide a strong body of evidence suggesting neurodevelopmental effects of prenatal APAP exposure. These are all large, validated cohort studies with prospective designs which used a number of analytical methods to control for confounding factors. Several lines of reasoning suggest that bias, confounding and chance are not solely responsible for the observed relationships. First, there is the consistency; all nine studies suggest a moderate increase in risk for those exposed compared to the unexposed. In all studies, results were largely unchanged when controlled for indication for use. There was evidence of a dose-response gradient of increased risk with increasing exposure in all six of the ADHD and ASD symptom studies that investigated the relationship (Vlenterie et al., 2016; Liew et al., 2016a; Avella-Garcia et al., 2016; Liew et al., 2014; Liew et al., 2016c; Brandlistuen et al., 2015). However, the study of IQ tested for a dose-response and did not identify one (Liew et al., 2016b). All but one study (Stergiakouli et al., 2016) controlled for use of other medications. No associations were found with ibuprofen or other analgesic medications, suggested specificity of the association with APAP. However, usage rates of other medications were low, so there may not have been adequate power to detect these associations. All six studies that investigated exposure timing (Liew et al., 2016a; Liew et al., 2016b; Stergiakouli et al., 2016; Liew et al., 2014; Liew et al., 2016c; Brandlistuen et al., 2015) found association to differ by trimester, with stronger associations most often in later pregnancy exposures (primarily during the 3rd trimester), even with two studies not assessing exposure after 32 weeks of pregnancy (Avella-Garcia et al., 2016; Stergiakouli et al., 2016). The exceptions were the study of IQ and executive function which found the highest risk associated with exposure early in pregnancy (Liew et al., 2016a; Liew et al., 2016b).

There are, of course, limitations in these studies which could lead to bias, limiting the ability to make causal inference. The first limitation is inherent to the study of a non-prescription medication and that is reliance on self-report of exposure. The prospective design allowing timely collection of exposure information may reduce recall bias, but all of these studies had limited information on exact dosing and use frequency. Because exposure was assessed before disease, misclassification of exposure should be non-differential with the probability of exposure misclassification not related to disease status —that is, diseased and non-diseased people are equally likely to be misclassified according to exposure. This type of bias usually leads to underestimation of risk, rather than overstatement (Pearce et al., 2007). While assessed using validated, and, in most studies, multiple instruments, outcome misclassification is possible. Four studies relied exclusively on maternal or self-report of outcomes (Vlenterie et al., 2016; Thompson et al., 2014; Stergiakouli et al., 2016; Brandlistuen et al., 2015). Because four of the nine studies utilized the DNBC population and two of the nine studies utilized the MoBa population any systemic bias within these

populations could influence the result of multiple studies. Infant use of APAP is a possible source of residual confounding. Residual confounding by indication is of high concern as maternal immune activation (MIA), infection and fever have been associated independently with ASD development (Flinkkila et al., 2016; Hornig et al., 2017; Brucato et al., 2017).

4.1. Biologic plausibility

Although, APAP has been used for more than one hundred year, its mechanism(s) of action remain unclear and appear to involve a large number of physiologic pathways (Toussaint et al., 2010; Ghanem et al., 2016). APAP readily crosses the placenta (Nitsche et al., 2017) and blood brain barrier (Kumpulainen et al., 2007). In the therapeutic concentration range, APAP is primarily metabolized in the liver mainly by conjugation with glucuronic acid and sulfate which results in the excretion of nontoxic final products. A minor fraction (8–10%) undergoes oxidative metabolism by CYP450, particularly the CYP2E1 isoform generating a reactive and toxic intermediate known as N-acetyl-p-benzoquinone imine (NAPQI). NAPQI is generally normalized by combination with reduced glutathione (GSH), which is converted to non-toxic metabolites that are readily excreted (Toussaint et al., 2010). However, in supratherapeutic doses or in vulnerable individuals cellular GSH stores may be depleted and excessive NAPQI formed which may lead to acute liver failure (ALF) and hepatic encephalopathy (Jetten et al., 2016; Zhao and Pickering, 2011; Butterworth, 2011). It has been demonstrated that APAP can be metabolized by brain cells to produce the toxic reactive intermediate NAPQI in situ (Ghanem et al., 2016). During pregnancy there is a significant increase in APAP clearance, which suggests the therapeutic effects would decrease faster. While no study has been identified investigating differential pregnancy dosing, higher dosing to obtain efficacy would lead to a proportional increase in the formation of toxic oxidative pathways (Allegaert and van den Anker, 2017). Impaired trans-sulfuration and reduced GSH are often seen in those with ASD and ADHD as well as in their parents which may lower the dose threshold for APAP toxicity (Kern et al., 2004; James et al., 2008; Howsmon et al., 2017; Schnackenberg et al., 2009) (Fig.2).

APAP differs from non-steroidal anti-inflammatory drugs (NSAIDS) as it largely lacks peripheral anti-inflammatory action, with its site of pharmacologic action within the central nervous system (Kumpulainen et al., 2007). Its central analgesic effect is mediated through activation of descending serotonergic pathways. The antipyretic effect is believed to occur mainly through central nervous system inhibition of cyclooxygenase (COX) pathways and prostaglandin synthesis (Ghanem et al., 2016). Analgesia is suggested primarily to be produced by acting on the brain as an indirect agonist at cannabinoid receptors through the metabolite p-aminophenol (Ottani et al., 2006). This distinction may be important in determining the specific metabolic pathways involved in ADHD and ASD etiology, as two studies investigating exposure to fever and the relationship to autism, as well as, the Liew et al. (2016b) study of APAP and IQ when fever was the indication, suggest a compensatory protective effect of APAP on neurodevelopmental outcomes (Liew et al., 2016b; Hornig et al., 2017; Zerbo et al., 2013).

There are several hypotheses of the specific mechanism by which APAP may interfere with normal brain development leading to neurodevelopmental disorders in children with genetic and immunologic predispositions. These include excess toxic NAPQI formation, oxidative stress and inflammation induced immune dysregulation, altered brain-derived neurotropic factor (BDNF), endocrine disruption, inhibition of prostaglandin synthesis and cannabinoid receptor effects. These are briefly summarized. (Fig. 3).

4.1.1. Oxidative stress, inflammation and immune activation

One potential mechanism suggests APAP's influences on inflammatory and immunologic mechanisms may predispose to oxidative stress and inflammation (Parker et al., 2017). This inflammatory event may disrupt normal microglia development and their interaction with neurons contributing to the risk of neurological disorders (Hanamsagar and Bilbo, 2017; Bilbo et al., 2015). Strong support comes from an epigenome study in a subpopulation of the MoBa cohort. This study analyzed cord blood samples and found significant differences in DNA methylation in genes involved in oxidative stress and neural transmission pathways in children with ADHD who were exposed long term to APAP in pregnancy compared to controls (Gervin et al., 2017). An additional analysis of cord blood samples from a German longitudinal cohort found prenatal APAP intake, especially in the third trimester, may decrease hematopoietic stem cell frequencies. Thus suggesting a critical period, consistent with the epidemiology, where APAP exposure may influence fetal immune ontogeny (Bremer et al., 2017).

It has been hypothesized two steps may be necessary to trigger adverse health outcomes from APAP: immune activation caused by the illness which was the indication for APAP use; and the APAP itself (Bilbo et al., 2015; Smith and Kriebel, 2010). This hypothesis is consistent with the idea that ASD and ADHD are multifactorial and may be the result of a cumulative load of environmental and genetic contributors (Herbert, 2010). Animal studies suggest MIA and environmental risk factors which impact inflammatory or immune pathways combine to induce ASD-like outcomes (Bilbo et al., 2018).

High dose APAP alone has been show to promotes oxidative stress,

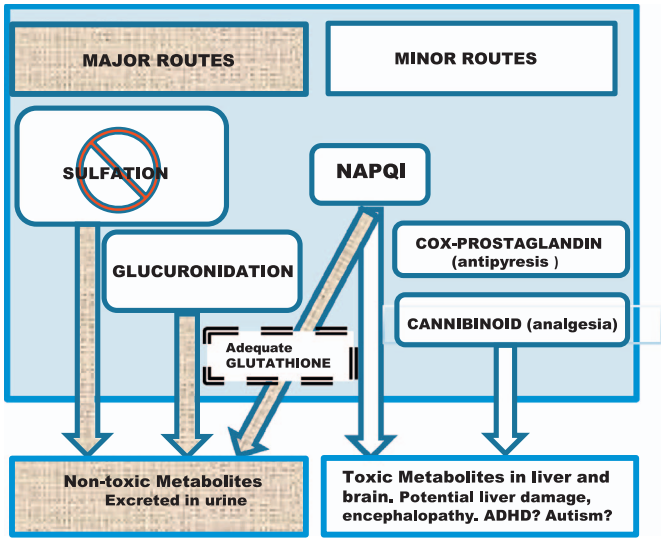

Fig. 2. Simplified APAP Metabolic Clearance Model. APAP is primarily conjugated in the liver through sulfation and glucuronidation. A minor fraction (5–15%) undergoes oxidative metabolism by CYP450 generating the toxic intermediate *N*-acetyl-*p*-benzoquinoneimine (NAPQI). NAPQI is generally normalized by combination with reduced glutathione (GSH) which is converted to non-toxic metabolites that are readily excreted. Overdosing can cause excessive NAPQI formation both in the liver and brain resulting in mitochondrial dysfunction, oxidative stress, immune activation, hepatotoxicity and neurotoxicity. The pharmacological actions of APAP, Cox-dependent production of prostaglandins and activation of the endocannabinoid system, have also been implicated in ADHD and ASD etiology.

	Potential APAP Mechanisms	References
1	Excess toxic NAPQI formation	45,48,50,52,55,58
2	Oxidative stress, inflammation, immune activation	45,59-73
3	Altered Brain-Derived Neurotropic Factor (BDNF)	74,75
4	Endocannabinoid dysfunction	76-79
5	Cox-2 inhibition	80-82
6	Endocrine disruption	10,14,17,83-85

Fig. 3. Potential mechanisms by which APAP may adversely influence neurodevelopment.

increases reactive oxygen species (ROS) production and brain mitochondrial dysfunction in mice (da Silva et al., 2012). A direct toxic effect of APAP in mixed primary cultures of astrocytes and oligodendrocytes has also been reported (Ghanem et al., 2016). Immune dysregulation, oxidative stress and inflammatory responses as identified by elevated levels of the pro-inflammatory cytokines in APAP induced ALF (James et al., 2005; da Rocha et al., 2017; Wang et al., 2013; Li et al., 2010). These same cytokines have also been found to be differentially elevated in pregnant mothers whose children developed ASD (Jones et al., 2017; Goines et al., 2011), the children with ASD or ADHD themselves (Krakowiak et al., 2017; Donfrancesco et al., 2016; Masi et al., 2017; Han et al., 2017) and animal models of ASD and ADHD (Choi et al., 2016; Leffa et al., 2017).

Recent investigations have explored the effects of APAP at therapeutic doses. Jetten and colleagues, found clear indications that the human immune system is triggered and oxidative stress-related gene responses occur even after intake of low doses of APAP (MJA et al., 2012). Similarly, Prill et al. in an experiment in human liver cells found transient loss of mitochondrial respiration identified below the threshold of APAP toxicity with the authors suggesting the APAP therapeutic index may be much narrower than previously believed (Prill et al., 2016).

Several animal studies have investigated the effects of therapeutic APAP doses on the brain and behavior. One of the earliest studies in rats identified a direct neurotoxic action by APAP both in vivo and in vitro at doses below those required to produce hepatotoxicity (Posadas et al., 2010). A number of studies by Blecharz-Klin et al. have investigated effects on various brain regions of Wistar rats at therapeutic APAP doses during development (Blecharz-Klin et al., 2013a, 2013b, 2015a, 2015b, 2016, 2017). Overall their studies demonstrate that APAP exposure during fetal and early post-natal life change cognitive function, spatial working memory and motor performance in a dose-dependent manner by inducing significant change in neurotransmission in brain structures involved in cognitive processes. The changes have primarily been related to dopaminergic neurotransmission in the striatum, the cortical serotonergic system, as well as, the noradrenergic system in the cerebellum and other regions. At the same time, administration of APAP in early life results in significant changes in amino acid levels. This included considerable decrease of the content of amino acids in the striatum (glutamine, glutamic acid, taurine, alanine, aspartic acid) and hypothalamus (glycine) between groups treated with APAP compared to the control. In the prefrontal cortex APAP increased the level of gamma-aminobutyric acid (GABA). Disturbances to the neurological function of these same systems have been implicated in ASD and ADHD etiology (Quaak et al., 2013; Lee et al., 2017; Oblak et al., 2013; Pezze et al., 2014; Ming et al., 2012; Harada et al., 2011; Naaijen et al., 2015).

Additional supportive evidence of adverse neurodevelopmental outcomes from APAP comes from an experiment by Viberg et al. (2014)) Long-lasting effects on cognitive function and behavior in mouse adulthood were observed after subcutaneous administration of two clinically relevant doses of APAP on postnatal day 10. No effect was observed for ibuprofen (Philippot et al., 2016). Postnatal day (PND) 10 in mice is considered to be near the peak of the brain growth spurt (BGS). The BGS is a vulnerable period in brain development characterized by a series of rapid and fundamental changes, including maturation of dendritic and axonal outgrowth, synaptogenesis, establishment of neuronal connections, proliferation of glia cells and myelination (Kolb and Whishaw, 1989). In humans, the BGS begins in the third trimester of pregnancy and continues throughout the first two years of life, with a peak around birth (Philippot et al., 2016). In an additional experiment, this group further defined the critical exposure window in mice. Adverse effects on adult behavior and cognitive function occurred in both male and female mice exposed to APAP on PND 3 and 10, but not when exposed on PND 19 (Philippot et al., 2017). The authors suggested the long-lasting effects were likely due to APAP-induced changes in brain-derived neurotrophic factor (BDNF) levels in key brain regions at a critical time in development (Viberg et al., 2014). BDNF is widely expressed in the brain, particularly during the BGS, and is involved in several important processes in neurodevelopment. It plays a critical role in synaptic plasticity and long-term potentiation and is involved in learning, memory, and attention (Garcia et al., 2012). Several studies have implicated dysregulation of BDNF in ASD and ADHD (Bryn et al., 2015; Liu et al., 2015).

4.1.2. The endocannabinoid system

BDNF has been shown to interact with the endocannabinoid system (Zhong et al., 2015). Modulation of the endocannabinoid system is a proposed mechanism of analgesic action of APAP (Ghanem et al., 2016). Researchers have suggested that APAP produces analgesia by acting on the brain as an indirect agonist at cannabinoid receptors through the metabolite p-aminophenol (Ottani et al., 2006). At the same time, the endocannabinoid system plays an important role in the developing brain with dysfunction implicated in the development of ASD (Foldy et al., 2013; Brigida et al., 2017; Zamberletti et al., 2017). There are the two predominate types of cannabinoid receptors. The cannabinoid receptors1 (CB1) are important for neuron differentiation, proper axonal migration, and establishment of neuronal connectivity, interference during critical times has been suggested to adversely impact brain development (Doenni et al., 2016; Basavarajappa et al., 2009). It has been suggested the abnormal brain connectivity seen in children with ASD could be due to lack of CB1 axon guidance (Schultz and Gould, 2016; Schultz, 2010; McFadden and Minshew, 2013). The cannabinoid receptors2 (CB2) are abundant in immune and microglial cells and primarily play a role in immune system regulation (Ranieri et al., 2016). Siniscalco et al. demonstrated that CB2, but not CB1, is upregulated in peripheral blood mononuclear cells of children affected by ASD compared to controls (Siniscalco et al., 2013).

It has been demonstrated that the APAP metabolites p-aminophenol and AM404 are toxic to mouse embryonic cortical neurons (Schultz et al., 2012). AM404 increases brain endocannabinoid levels by decreasing the re-uptake of anandamide (Bertolini et al., 2006). An experiment with adult male mice involving acute intraperitoneal administration of APAP demonstrated differential changes in social behaviors in adult male and tan brachury tufted (BTBR) mice, a commonly used mouse model of autism-like behavior (Gould et al., 2012). This was associated with corresponding elevations in cortical levels of endocannabinoids. In a subsequent experiment this lab demonstrated that APAP produced long-lasting immune system changes (Schultz and Gould, 2016).

4.1.3. Cox-2 and prostaglandin E2

The anti-pyretic action of APAP is suggested to involve inhibition of cyclooxygenase-2 (Cox-2) dependent production of prostaglandins (Graham et al., 2013). Prostaglandins mediate the generation of fever but also are involved with neuronal development, synaptic plasticity, calcium regulation and masculinization (Dean et al., 2012; Wong et al., 2015; Hay-Schmidt et al., 2017). It has been postulated that exposure to exogenous agents that disrupt signaling of the prostaglandin E2 (PGE2) pathway may contribute to ASD (Wong et al., 2015). The study by Dean et al. exposed rats to APAP and other Cox-2 inhibitors during postnatal day 10, at the peak of the BGS, at the equivalent of clinically relevant doses in humans and demonstrated that disrupting PGE2 synthesis alters cerebellar Purkinje cell development, resulting initially in increased dendritic growth in both sexes. They showed that this later results in cerebellar atrophy in males only, resulting in a sex-specific loss of cerebellar volume. Further, although performance in motor tasks was spared, social interaction and the sensory threshold were altered in males (Dean et al., 2012). Early life damage to the cerebellum, including Purkinje cell atrophy (Wang et al., 2014), is among the strongest identified risk factor for developing ASD symptoms (an approximate forty fold increase in risk) (Limperopoulos et al., 2007). Subsequent work from this group suggested that this insult must occur

during a sensitive time period when the cerebellum is developing critical capacities, during the peak of the BGS (Hoffman et al., 2016). These findings on APAP are consistent with investigations of other exposures, which suggest differing effects based on exposure timing with the peak of the BGS identified as most developmentally critical (Hoffman et al., 2016; Wang et al., 2014; Hornig, 2013; Shi et al., 2009).

The findings of the epidemiology studies summarized earlier are consistent with the animal models in suggesting the dose and timing of exposure is important. An additional investigation in mice exposed to the equivalent of a maximum human dose of APAP throughout pregnancy, but not in early life, found no evidence of behavioral changes, which may also suggest exposure needs to occur at the BGS to induce detrimental effects (Saad et al., 2016).

4.1.4. Endocrine disruption

It has been proposed that endocrine-disrupting pharmaceuticals may interrupt maternal hormone signaling that regulates offspring brain development (Frye et al., 2012). Research shows that endocrine disruptors may pose the greatest risk during prenatal and early postnatal development, with some chemicals suggested to alter neural transmission and the developmental formation of neuronal networks (Kajta and Wojtowicz, 2013). Animal and human studies have found that APAP is anti-androgenic and may causes endocrine disturbances altering reproductive function (Kristensen et al., 2016; Fisher et al., 2016; Holm et al., 2016; Smarr et al., 2017). Further, APAP was demonstrated to decrease maternal progesterone levels in pregnant mice and interfere with pregnancy by altering placenta function and affecting maternal immune adaptation (Thiele et al., 2015).

One interesting investigation of different mixtures of thirteen suspect endocrine disrupting chemicals (EDC) sought to characterize endocrine activity in the developing brain and to determine which developmental processes were preferentially targeted by analyzing induced gene expression patterns (Lichtensteiger et al., 2015). Four EDC mixtures - an anti-androgenic mixture, an estrogenic mixture, a complex mixture containing the estrogenic and anti-androgenic chemicals plus APAP, and just APAP alone, were administered at high dose by oral gavage to rat dams from gestation day 7 until weaning. Gene expression was analyzed on postnatal day 6, during sexual brain differentiation. All mixtures had a strong, mixture-specific impact on genes encoding for excitatory glutamatergic synapses and those controlling migration of glutamatergic and GABAergic neurons, as well as other genes linked with increased risk of ASD. Of important note, the effects of the analgesic drug APAP alone, were almost identical to the complex mixture suggesting APAP may have exerted an important influence on the mixture of all thirteen chemicals combined. While APAP exhibited anti-androgenic activity on reproductive endpoints, the effects on the genes in the brain differed from the anti-androgenic mixture. The authors suggest that in the brain other actions of APAP, e.g. prostaglandin or cannabinoid pathways, may have prevailed over indirect effects of inhibition of testosterone synthesis.

In sum, evidence from these studies suggests that behavior and cognition may be impacted by therapeutic doses of APAP during early development. These studies suggest that in rodents the most sensitive window is equivalent to the third trimester of pregnancy through the first months of life in humans, consistent with the epidemiology. While no definitive conclusion can be drawn from these studies on the neuromodulation abilities of APAP, several plausible biologic mechanisms have been proposed. These effects may be mediated by interference of APAP with immune, BDNF, endocrine, prostaglandin or endocannabinoid regulation.

5. Conclusions

There were consistent findings in the nine prospective cohort studies within five cohorts suggesting adverse neurodevelopmental outcomes in children following APAP use in pregnancy. These findings suggest APAP alters neurodevelopment most strongly in relation to a hyperactive and attention related functions. The greatest risk of ASD and ADHD symptoms appeared to be from prolonged exposure late in pregnancy. The relatively modest risks may be the result of residual confounding but the identification of dose-response gradients, trimester effects, specificity to APAP, biologic plausibility as well as the findings that show associations are not confounded by indication for use argue against a spurious association.

Fever in pregnancy has its own associated risks (Dreier et al., 2014) and currently APAP is considered the best option for fever mitigation during pregnancy, particularly in the third trimester when NSAIDS are contraindicated (Bloor and Paech, 2013). Among the populations in this review, fever mitigation use ranged from < 5% to 37% of total use. Headache, migraine, muscle pain, back pain, and infection, for which limited efficacy has been suggested, accounted for the majority of reported pregnancy APAP use (Stephens et al., 2016; Saragiotto et al., 2016; Jefferies et al., 2016; Ennis et al., 2016; Nazarko, 2014) (Appendix C).

Further epidemiologic studies are urgently needed with; precise assessment of exposure, indication for use and accurate data on timing of use both in utero and early infancy. The use of multiple exposure models should be considered to investigate gene-environment and immune-environment interactions. Additional studies are needed to elucidate the underlying biologic mechanisms and to develop safer analgesics.

Research on infant APAP exposure should be a top priority. Without the protection afforded by the mother's liver and the placenta, other neurotoxins such as lead and arsenic pose their greatest neurologic risk, not from prenatal exposure but rather from direct exposure to the child (Rodriguez-Barranco et al., 2013; Heyer and Meredith, 2016). The majority of U.S. infants are given at least one medication in any given week, with APAP, by far the most common of these (Vernacchio et al., 2009). APAP has been demonstrated to reduce antibody response to vaccine antigens providing evidence of influence on infant immune response (Prymula et al., 2009). There is weak but suggestive evidence of an APAP-ASD association from a small case-control study of use after the measles-mumps-rubella vaccination (Schultz et al., 2008) and a number of additional studies, which taken together suggest a possible relationship to APAP use at the time of male circumcision (Bauer and Kriebel, 2013; Frisch and Simonsen, 2015; Raz et al., 2015; Ben Chaim et al., 2005; Yegane et al., 2006)

Pregnant women should be cautioned against indiscriminate use of this medication. Exposure to APAP is so commonplace that the public health implications of even a modest elevation in adverse neurodevelopmental risk are substantial.

Acknowledgements

Ian Kinreich for observations on the Israeli population.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not for profit sectors.

Appendix A. Confounding control

Study	Outcome measure	Other meds	Indication	Maternal psychiatric issues	Genetic confounding	List of all confounders evaluated	Confounding control methodology/sensitivity analyses/comments
Brandlistuen et al. (2013)	Adverse neurodeve-lopment (ASQ, CBCL)	Yes	Yes	Yes (sibling design), maternal psychological distress using Hopkin Symptom Checklist	Partially (sibling design)	Different adjusted variables by outcome based effect estimate change. May include maternal health before and during pregnancy including infections (respiratory, urinary tract/bladder, genital, diarrhea, gastric flu, fever back pain, headache/ migraine. Concomitant use of NSAIDS, triptans, opioids, other analgesics, benzodiazepines, antidepressants, antipsychotics, antiepileptic drugs. Maternal psychological distress using Hopkins Symptom Checklist. Maternal age, years between pregnancies, parity, smoking, alcohol use. In full cohort analysis, maternal education and chronic diseases.	Sibling Control Design controls for familial confounders and 50% of genetic confounders, tested effect of sibling order (no effect), strong evidence of shared familial confounding by sibling interclass correlation. Effect essentially unchanged by control of indication and other medications.
Vlenterie et al. (2016)	Adverse neurodeve-lopment (ASQ, CBCL)	Yes	Yes	Yes, maternal depressive symptoms, Hopkins Symptom checklist	Education	Maternal age, BMI, parity, marital status, maternal education, smoking, alcohol, folic acid supplementation. Maternal depressive symptoms, infections (genital, urinary and respiratory), fever, headache or migraine, pelvic girdle pain, back pain, neck pain, abdominal pain, other pain. Concomitant medications-NSAIDS, anti-epileptics, antidepressants, triptans and benzodiazepines.	Propensity score match on 23 potential confounding variables using the nearest neighbor approach. Results similar in sensitivity analyses when analysis restricted to women with the health conditions of headache or migraine, fever and infection.
Liew et al. (2014)	ADHD and Hyper kinetic disorder (SDQ), ICD-10 HKD, ADHD med	Yes	Yes	Yes	Education, SES	Child's year of birth, birthweight, sex, maternal age, parity, gestational age, SES, smoking, alcohol use, prepregnancy BMI, mother's self-reported psychiatric illness, self-reported ADHD, father's age at birth, Apgar score, season of conception. Disease or conditions that may trigger APAP use-muscle & joint pain, fever, inflammation or infection.	Results similar in sensitivity analyses when restricted to mothers who did not report psychiatric illness, fever, inflammation and infection during pregnancy. Stratified analyses by SDQ scores reported by mothers only, hospital type, child's sex, most common NSAIDS (Ibuprofen, aspirin).

Liew et al. (2016c)	Autism & Autism with hyperkinetic symptoms, ICD-10 ASD, HKD	Yes	Yes	Yes	SES, maternal ADHD	Child's year of birth, birthweight, sex, maternal age, SES, smoking, alcohol use, prepregnancy BMI, mother's self-reported psychiatric illness, education, father's age at birth, Apgar score, season of conception. Disease or conditions that may trigger APAP use-muscle & joint pain, fever, inflammation or infection. Other medications NSAIDS, Folic acid supplements, antibiotics, sleep meds, anti-depressants. Birthweight and gestational age were potential mediators and not included in final models.	Results similar when restricted to mothers who did not report psychiatric illness, fever, inflammation, infection or musculo-skeletal during pregnancy. Results unchanged when controlled use of other meds, antibiotics, folate & antidepressants
Liew et al. (2016a)	IQ (WPPSI-R)	Yes pain meds	Yes	No	Maternal IQ, education	Child's sex, parity, paternal education, total years of education both parents, maternal IQ, smoking, alcohol, indications for use including inflammation, infections, fever, diseases of muscles or joints. Use of NAIDS.	Created Inverse probability weights combining the probabilities of sampling and participation and then performed weighted regression to account for subject selection oversampling of high alcohol intake and the probability of selective non-participation in this DNBC subgroup analysis. Adjusted for a priori selected confounders. No apparent effect modification by sex. No heterogeneity of effect found between APAP and maternal inflammation or joint/ muscle disease during pregnancy. Sensitivity analyses excluding high alcohol drinkers, those with extreme child IQ values and those later diagnosed with ADHD, with no change in results.
Liew et al. (2016b)	Attention and executive function (BRIEF, TEACh-5)	Yes	Yes	Yes, mental health issue reported Y/N		Child's sex, parity, paternal education, total years of education both parents, maternal IQ, smoking, alcohol, indications for use including inflammation, infections, fever, diseases of muscles or joints. Use of NAIDS. Include an indicator for each tester to address potential variation in assessment. Paternal age, prenatal use of anti-depressants, folic acid supplementation, marital status evaluated but not in final models	As w/ Liew et al. (2016a, 2016b)) utilized inverse probability weights combining the probabilities of sampling and participation. Subgroup analyses by indications of fever, inflammation or infection, and pain or muscular skeletal diseases with minimal change in outcome. Subgroup analyses by sex found similar abnormal attention by sex, but parent rated executive function appeared to be larger in boys.

Thompson et al. (2014)	ADHD Behavior (SDQ)	Yes	Yes	Yes	SES, maternal education	Small for gestation age status, sex, maternal age left school, maternal smoking, paternal smoking, marital status, SES, pre-pregnancy BMI, maternal stress last month of pregnancy, alcohol 1st trimester, living w/ father age 3.5, child's activity level at 3.5 yrs, maternal high fever, visiting GP or taking meds for psychological conditions including depression and anxiety.	Regression covariates. High fever only indication related covariate
Avella-Garcia et al. (2016)	Autism and attention function (CAST) (K-CPT) (ADHD-DSM-IV)	Yes	Yes	Yes, maternal and paternal mental health at child age 14 months, 4–5 years	Education, SES	Child variables: Birth weight, small for gestational age, birth height, head circumference, gestational age, preterm birth, duration of breastfeeding, day care, main caregiver, psychopathology at age 4–5, Maternal variables: age at conception, use of any medications during pregnancy, origin, lives with spouse, mental health at child age 14 months and age 4-5 yrs, attachment to child at 1 yr, parity, working during pregnancy, smoking, passive smoke, folic acid supplementation, alcohol use, illegal drug use, complications during pregnancy such as vaginal liquid, blood leakage, abnormal contractions, allergy. Paternal variables: age at conception, attachment to child at 1 yr, mental health at child age 14 months & 4–5 yrs.	Sensitivity analyses excluding mothers with fever, chronic illness, UTI, or other meds obtained similar effect estimates
Stergiakouli et al. (2016)	ADHD behavior (SDQ)	No	Yes	Yes	Yes (genotype data used to make score)	Maternal age, parity, SES, smoking, alcohol, pre-pregnancy BMI, maternal self-reported psychiatric illness, possible indications for APAP use- including cold or flu, urinary or other infection, migraine or headache in previous 3 months. Composite scores of ADHD molecular genetic risk factors to make a polygenic risk score	Compared offspring behavior problems to prenatal maternal APAP and found association. No association to POSTNATAL maternal use and partner's APAP use. Concluded association was not due to unmeasured behavior or social factors.

Appendix B. Quality assessment

Newcastle- Ottawa quality assessment scale	Brandlistuen et al. (2013)	Vlenterie et al. (2016)	Liew et al. (2014)	Liew et al. (2016c)	Liew et al. (2016a)	Liew et al. (2016b)	Thompson et al. (2014)	Avella-Garcia et al. (2016)	Stergiakouli et al. (2016)
Cohort studies: a study can be awarded a maximum of 1 star for each numbered item within the Selection & Outcome categories. Max of 2 for Comparability	Norwegian MoBa	Norwegian MoBa	Danish National Birth Cohort	Danish National Birth Cohort	Danish National Birth Cohort	Danish National Birth Cohort	Auckland Birthweight Collaborative Study	INMA Spanish Birth Cohort	Avon Longitudinal Study Parents & Children (ALSPAC)
Overall Quality Assessment	7	7	9	9	9	9	5	9	5
Selection/outcome/ comparability	***_/**/_**	***_/**/_**	****/**/***	****/**/***	****/**/***	****/**/***	_***/*_/_*_	****/**/***	***_/*_/_*_
Selection									
1) Representativeness of the exposed cohort									
a) truly representative of the average _____ (describe) in the community *									
b) somewhat representative of the average _____ in the community*	*	*	*	*	*	*		*	*
c) selected group of users e.g. nurses, volunteer					Oversampled for high alcohol exposure, did subgroup analysis excluding heavy drinkers w/ same effect	Oversampled high alcohol exposure, made adjustments by inverse probability weighting	_ oversampled for small for gestational age, European only		
d) no description of the derivation of the cohort									
2) Selection of the non-exposed cohort	*	*	*	*	*	*	*	*	*

a) drawn from the same community as the exposed cohort *									
b) drawn from a different source									
c) no description of the derivation of the non-exposed cohort									
3) Ascertainment of exposure									
a) secure record (e.g. surgical records)*									
b) structured interview*			*Phone	*phone	*Phone	*Phone	*Interview	*Structured interviews	
c) written self report	_3 questionnaires by mail	_3 questionnaires by mail							_questionnaire
d) no description									
4) Demonstration that outcome of interest was not present at start of study									
a) yes *	*	*	*	*	*	*	*	*	*
b) no									
Comparability (can be two points)									
1) Comparability of cohorts on the basis of the design or analysis									
a) study controls for _____ (select the most important factor)* (indication)	*	*Propensity score matched	*	*	*	*	_ (only fever)	*	*
b) study controls for any additional factor * (maternal psychiatric issues, other meds)	*	*	*	*	*	*	*	*	_other medications not controlled
(This criteria could be modified to indicate specific control for a second important factor.)									
Outcome									
1) Assessment of outcome									
a) independent blind assessment *					*Psychologist administered	*Psychologist administered		*BSID, MSCA, CAST by psychologist	

b) Record linkage*			*Hospital, pharmacy	*Hospital, psychiatric					
c) Self report	_parent report	_parent report	Also parent report			Also parent & teacher report	_parent, child report	Teacher rating DSM-IV, CPSCS	_parent report
d) No description									
2) Was follow up long enough for outcome to occur									
a) Yes (select an adequate follow up period for outcome of interest)*	*	*	*	*	*	*	*	*	*
b) No									
3) Adequacy of follow up of cohorts									
a) Complete follow up all subjects accounted for*									
b) Subjects lost to follow up unlikely to introduce bias* small number lost > ___ % (select an adequate %) follow up, or description provided of those lost)	*Sibling design makes less likely to bias	*49% lost to follow up, differences assessed, found limited	*Similar HKD rates in those missing interviews	*Similar ASD rates in those missing interview	*Described, statistical adjustments for non-participation in study sample	*Described, statistical adjustments for non-participation in study sample	_differed on SES, education, smoking, age, unknown ADHD status of lost to followup	*Lost persons described, younger, lower SES, more smoking, less breast feeding, unknown ASD status	
Small number lost > ___ %	64% lost to follow up in sibling cohort	49% lost to follow up	31% lost		16% missed interview		30–41%	11% at 1 yr, 20% at 5 yrs	43% missed questionnaire
c) Follow up rate < ___% (select an adequate %) and no description of those lost					_lost persons not described				_lost persons not described
d) No statement									

Appendix C. Indication for use

Study	Outcome	Data collection methodology	APAP use % of total population	Fever indication %	Headache/ migraine indication %	Infection indication %	Back, muscle or joint pain Indication %	Notes:
Brandlistuen et al. (2013)	Adverse neurodevelop-ment 3 years	Self-report In 3 questionnaires. Possible indications were listed, for each indication the women could specify the specific exposure window and name medications taken	46%	19.5%	63.4%	12.2% (flu, cold)	19.5%	Indication % of those who used APAP for > 28 days
Vlenterie et al. (2016)	Adverse neurodevelop-ment 18 months	Same as Brandlistuen et al. (2013) above	41%	25%	80%	53% (often in combo w/ fever)	Back pain 66%, pelvic girdle pain 50%	Indication % are for those who used APAP for > 28 days, 78.9% reported more than one indication
Liew et al. (2014)	ADHD and Hyperkinetic disorder	Self reported APAP use in 3 telephone interviews, asked about any pain killer use, weeks of use on a week by week basis. Adjusted in analyses for indications associated with APAP use but exact reason for APAP use was unknown.	56%	33%	n/a	11%	11%	Two independent questions 1) APAP use 2) Illnesses, fever or pain in last 3 months
Liew et al. (2016c)	Autism (with hyperkinetic disorder)	Same as Liew et al. (2014) above	56%	33%	n/a	11%	11%	Same as Liew et al. (2014) above
Liew et al. (2016a)	Intelligence Quotient (WPPSI-R)	Same as Liew et al. (2014) above	59%	31%	n/a	11%	10%	Same as Liew et al. (2014) above
Liew et al. (2016b)	Attention and executive function	Same as Liew et al. (2014) above	59%	31%	n/a	11%	10%	Same as Liew et al. (2014) above
Thompson et al. (2014)	ADHD Behavior		50%	< 5%		Did adjust but % n/a		
Avella-Garcia et al. (2016)	Autism and ADHD related Attention Function	In 2 structured interviews at gestation weeks 12 & 32 mothers were ask “have you taken any medications since 1 month before pregnancy or during pregnancy?” If answer was positive asked medication name, dose, duration of use, timing and indication	41–43%	9%		Urinary tract 13%		Analgesia was main indication-66%
Stergiakouli et al. (2016)	ADHD behavior	In 2 questionnaires administered at 18 and 32 weeks gestation, mothers asked if they had muscle and joint problems, infections, migraine or headache in the last 3 months. The indication question was asked separately from question on APAP use.	53% @ 18 wks 42% @ 32wks		Did adjust but % n/a	Did adjust but % n/a	Did adjust but % n/a	

Appendix D. Findings of hyperactivity and attention

Study	Prospective cohort study	Outcome and assessment tools	Ever exposed pregnancy	Prolonged exposure
Brandlistuen et al. (2013)	Norwegian MoBA	**Adverse neurodevelopment-3 yrs**		**More than 28 days**
		1) Externalizing behaviors - Child Behavior Checklist (CBCL 11/2-5/LDS)		1) β = 0.28 (0.15–0.42)
		2) Activity level -EAS questionnaire		2) β = 0.24 (0.11–0.38)
Liew et al. (2014)	Danish DNBC	**ADHD/hyperkinetic disorder(HKD)-7 yrs**		**All 3 trimesters**
		1) HKD diagnosis	1) HR 1.37 (1.19–1.59)	1) 1.61 (1.30–2.01)
		2) ADHD medication 2 +	2) HR 1.29 (1.15–1.44)	2) 1.44 (1.21–1.72)
		3) Parent report- (SDQ) total difficulties	3) HR 1.13 (1.01–1.27)	3) 1.24 (1.03–1.40)
Liew et al. (2016c)	Danish DNBC	**Autism spectrum disorders (ASD) 12.7 yr followup**		**All 3 trimesters**
		1) ASD w/ HKD symptoms ICD-10	1) HR 1.51 (1.19–1.92)	1) HR 1.77 (1.24–2.53)
		2) Infantile autism w/ HKD ICD-10	2) HR 1.55 (0.98–2.45)	2) HR 2.45 (1.32–4.53)
Liew et al. (2016b)	Danish DNBC	**Attention & executive function at 5 yrs** Psychologist assessed with TEACh-5		
		1) 1st trimester overall attention	1) Mean dif = −0.34 (−0.63–0.05)	
		2) 1st trimester selective attention	2) Mean dif = −0.25 (−0.50–0.01)	
		3) Subnormal overall attention	3) OR = 1.5 (1.0–2.5)	
		4) Selective attention difficulties	4) OR = 1.5 (1.0–2.4)	
		5) 1st trimester sustained attention	5) OR = 2.8 (1.5–5.5)	
Thompson et al. (2014)	New Zealand ABC	**ADHD symptoms at 7 & 11 yrs**	Adjusted mean difference	
		1) DSM hyperactive/impulsive-parent@7	1) β = 2.0 (0.3–3.6)	
		2) SDQ hyperactivity-child-11 yrs	2)β = 0.4 (0.0–0.8)	
Avella-Garcia et al. (2016)	Spanish INMA	**Attention function symptoms 5 yrs**		**Persistent use**
		1) DSM-IV hyperactivity/impulsivity	1) IRR 1.41 (1.01–1.98)	1) IRR 2.01 (0.95–4.24)
		2) Conner's (K-CPT) commission errors	2) IRR 1.14 (1.03–1.26) females	2) IRR 1.32 (1.05–1.66) Females
		3) K-CPT lower detectability/reaction	3) β = −0.10 (−0.18 to −0.02) females	3) β = −0.18 (−0.36–0.00)Females
Stergiakouli et al. (2016)	English ALSPAC	**ADHD symptoms at age 7**	**Ever used at 18 weeks**	**Ever used at 32 weeks-** last 3 months
		1) SDQ-hyperactivity	1) RR 1.18 (1.01–1.38)	1) RR 1.22 (1.04–1.43)
		2) SDQ -total difficulties	2) RR 1.01 (0.79–1.27)	2) RR 1.37 (1.07–1.75)
		3) SDQ conduct problems	3) RR1.13 (0.96–1.32)	3) RR 1.35 (1.13–1.60)

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