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Review article

Long-term health and neurodevelopment in children after antenatal exposure to low-dose aspirin for the prevention of preeclampsia and fetal growth restriction: A systematic review of randomized controlled trials

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ABSTRACT

Objective: To evaluate the long-term effects of antenatal aspirin exposure on child health and neurodevelopmental outcome beyond the perinatal period.

Study design: PubMed, Embase.com, the Cochrane Library and Web of Science were systematically searched from inception through 5 November 2020. We performed a cited-reference search and ClinicalTrials.gov was searched on 20 October 2020 to identify trial results that were not reported elsewhere. We included randomized controlled trials reporting on health-related outcomes in children (aged > 28 days) exposed to aspirin versus placebo or no treatment during pregnancy. Studies with any dose or duration of aspirin use were included. We excluded studies evaluating other antiplatelet agents or non-steroidal inflammatory drugs. Two authors independently performed study selection, data extraction and quality assessment. Quality assessment was performed using the Cochrane RoB2 tool for the original randomized controlled trials and the QUIPS for the follow-up studies. Results are presented as relative risks (RR) with 95% confidence intervals (95%CI).

Results: The search yielded 6,907 unique records. Two studies were included, containing 4,168 children at age 12 months and 5,153 children at 18 months. Children were exposed to aspirin 50–60 mg versus placebo or no treatment. At 12 months, post-neonatal mortality was lower after allocation to aspirin (0.2% versus 0.5%; RR 0.28, 95%CI 0.08–0.99) in a single study. At 18 months, fewer children were found to have (gross and fine) motor problems (RR 0.49, 95%CI 0.26–0.91) after antenatal aspirin exposure in one study. No differences were found in mortality rate; the proportion of children with a short stature or low weight; or respiratory, hearing or visual problems at 18 months. Both included studies had a high risk of bias.

Conclusion: The two included studies showed evidence of potential benefit of antenatal low-dose aspirin on mortality and neurodevelopment up to the age of 18 months. Our findings support the current application of low-dose aspirin in pregnant women at risk for preeclampsia and fetal growth restriction. However, further follow-up research of children who were exposed to low-dose aspirin during pregnancy is of utmost importance to exclude potential long-term harm.

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Contents

Introduction

Prophylactic treatment with low-dose aspirin starting < 16 weeks of gestation reduces the risks of preeclampsia, small-for-gestational-age infants and preterm birth [1]. International guidelines recommend that pregnant women at increased risk of preeclampsia take low-dose aspirin throughout pregnancy [2–4]. A substantial and increasing proportion of fetuses is exposed to low-dose aspirin, raising the question of long-term effects on child health.

Aspirin inhibits platelet aggregation and has anti-inflammatory properties through the inhibition of cyclo-oxygenase (COX) [5,6]. Aspirin passes the uteroplacental barrier and enters the fetal circulation even at low doses [7–9]. No differences in intracranial hemorrhage or other neonatal harms have been found for doses up to 150 mg in a systematic review from the US Preventive Services Task Force [10]. However, when considering the pharmacodynamics of aspirin, permanent effects on cell and tissue development and, consequently, long-term health and neurodevelopment can be anticipated. A previous study demonstrated that the absence of adverse effects on the short term does not guarantee absence of adverse effect in the long-term [11].

Antenatal exposure to low-dose aspirin may also be beneficial in the long term. Preeclampsia is associated with adverse neonatal outcomes, in particular preterm birth and small-for-gestational-age infants. These conditions have also been associated with long-term morbidities in children [12–17]. Prevention of these conditions by low-dose aspirin may translate into improved outcomes for children later in life by improving short-term outcome, as well as by diminishing the long-term sequelae of these complications on long-term health.

Long-term follow-up of children exposed to an intervention during pregnancy is important to determine the persistence of short-term neonatal benefits and long-term safety [18]. There is no overview of the evidence on long-term effects of antenatal exposure to aspirin on the health of children based on randomized controlled trials (RCTs). Therefore, our objective was to systematically review the effects of antenatal aspirin exposure on children's outcomes beyond the direct perinatal period from RCTs.

Material and methods

Protocol and registration

The review was registered in the Prospero database (ID: CRD42020162088). No changes have been made to the registered details during the conduct of this systematic review. We followed Cochrane Handbook for Systematic Reviews of Interventions and reported according to the PRISMA statement [19,20]. The study received funding from the Amsterdam Reproduction & Development research institute, which had no role in the establishment of the study.

Information sources and search strategy

A systematic search was performed from inception up to 5 November 2020 in PubMed, Embase.com, Wiley/Cochrane Library

and Clarivate Analytics/Web of Science Core Collection by a medical information specialist (JCFK) in collaboration with one of the first authors (AL). The search included keywords and free-text terms for [1] 'pregnancy' or [2] 'children' combined with [3] 'acetylsalicylic acid'. A search filter was applied to identify RCTs and systematic reviews. No language or publication date restrictions were applied. The complete search strategies can be found in the Supplementary information (Appendix A). We performed a cited-reference search and ClinicalTrials.gov was searched on 20 Oct 2020 to identify trial results that were not reported elsewhere.

Outcome measures

The outcomes of this systematic review were child health-related or neurodevelopmental outcomes beyond the perinatal period (aged > 28 days) following aspirin exposure during pregnancy versus placebo or no treatment. As, at present, a specific core outcome set for follow-up studies is not available, we defined the following principal domains of health-related outcomes: survival, general health, cardiovascular health, development, behavior and mental health.

Eligibility and study selection

We included studies with any dose or duration of aspirin use, and irrespective of the indication for its use. Studies evaluating other antiplatelet agents or non-steroidal inflammatory drugs were excluded. Any measure of these outcomes was eligible for inclusion. Unpublished as well as published data in any language were eligible for inclusion. Two authors (AL and EvLS) independently screened titles and abstracts of all potential articles. In case of disagreement regarding eligibility between authors, the full article text was screened. The same authors independently screened the full text of the remaining articles to determine the final selection using the predefined inclusion criteria. Disagreements on eligibility were resolved by discussion or consulting a third author (RP).

Data extraction

Two authors (AL and EvLS) independently extracted data from the included articles using a piloted data extraction form. Disagreements were resolved by consulting a third author (RP). Accuracy of the data extraction was assessed at a separate occasion. We collected data on author, year, and source of publication; baseline characteristics and demographics from original trial and follow-up study; definitions of health-related outcomes; sample size and attrition from original trial; the timing, duration and dose of aspirin use; indication for aspirin use; publication status; start date and end date; ethical approval; key conclusions and type and source of funding. Corresponding authors of the included articles were contacted for further information if relevant data were not presented in the original publication.

Assessment of risk of bias

Cochrane Collaboration's tool for assessing the risk of bias (RoB2) was used to evaluate the validity of included RCTs and to assign a judgement of low risk, some concerns or high risk of bias [21]. We used the Quality In Prognosis Studies (QUIPS) to appraise the included follow-up studies [22]. As the QUIPS tool is designed for prognostic studies, we made some alterations to make it applicable to the included studies (Appendix B). The studies were assigned a judgement of low, moderate or high risk of bias. Furthermore, the GRADE approach was used to assess the certainty of the evidence for the key outcomes (post-neonatal) mortality and neurodevelopmental impairment (i.e. cognitive impairment, motor impairment, or neurosensory impairment). We planned to use a funnel plot to assess publication bias. Risk of bias assessment was performed independently by two authors (AL and EvLS) and discrepancies were resolved by consulting a third author (RP). We did not exclude studies based on quality assessment.

Data synthesis and analysis

We presented the results of dichotomous outcomes from the individual studies as relative risks (RR) and 95% confidence intervals (95%CI). In case of sufficient studies, we planned to conduct meta-analysis and subgroup analyses of studies comparing aspirin dose; gestational age at initiation of therapy; duration of therapy during pregnancy; indication for aspirin use; and follow-up duration of studies. Statistical analyses were performed using Review Manager by two authors (AL and EvLS) (RevMan 5.3.5) [23].

Results

Study selection

The search yielded 6,907 unique articles which were assessed for eligibility (see Fig. 1). Two articles, encompassing the data of 4,168 children at 12 months and of 5,153 children at 18 months of age, met the criteria for inclusion [24,25]. No additional studies were identified by cited-reference search or in the trial registry. Corresponding authors of both studies were contacted to retrieve additional information on baseline characteristics and outcomes, but could not supply the required data upon our enquiry.

Study characteristics of original studies

The two included studies were follow-up studies from RCTs performed between 1988 and 1992: the Collaborative Low-dose Aspirin Study in Pregnancy (CLASP) trial and the Italian Study of Aspirin in Pregnancy (ISAP) [26,27]. The CLASP trial randomized 9,364 women between aspirin 60 mg and placebo in 213 centers in 16 countries [26]. The ISAP trial randomized 1,106 women between aspirin 50 mg and no treatment in 81 Italian centres [25]. Characteristics of participants from the original RCTs are summarized in Table 1. Both trials included singleton and twin pregnancies. Low-dose aspirin was administered for the prevention or treatment of fetal growth restriction and preeclampsia, and was initiated between 12 and 32 weeks of gestation and continued until delivery.

Study characteristics of follow-up studies

Characteristics of the included follow-up studies are presented in Table 2. The CLASP trial performed follow-up of 4,168 children at 12 months of age (43.3% from original trial) through questionnaires directed to their general practitioner, and of 4,365 children at 18 months (45.3% from original trial) through parental questionnaires [24]. Characteristics of women and their birth outcomes from the original trial were similar to the characteristics and outcomes of those mothers whose children were assessed at 12 and 18 months. Parents and general practitioners remained unaware of treatment allocation at follow-up [24]. The ISAP trial performed follow-up at 18 months corrected age of 788 children (65.8% from original trial) through parental questionnaires [24,25]. The authors stated that there were no differences in maternal characteristics and birth outcomes between the responders and those who were

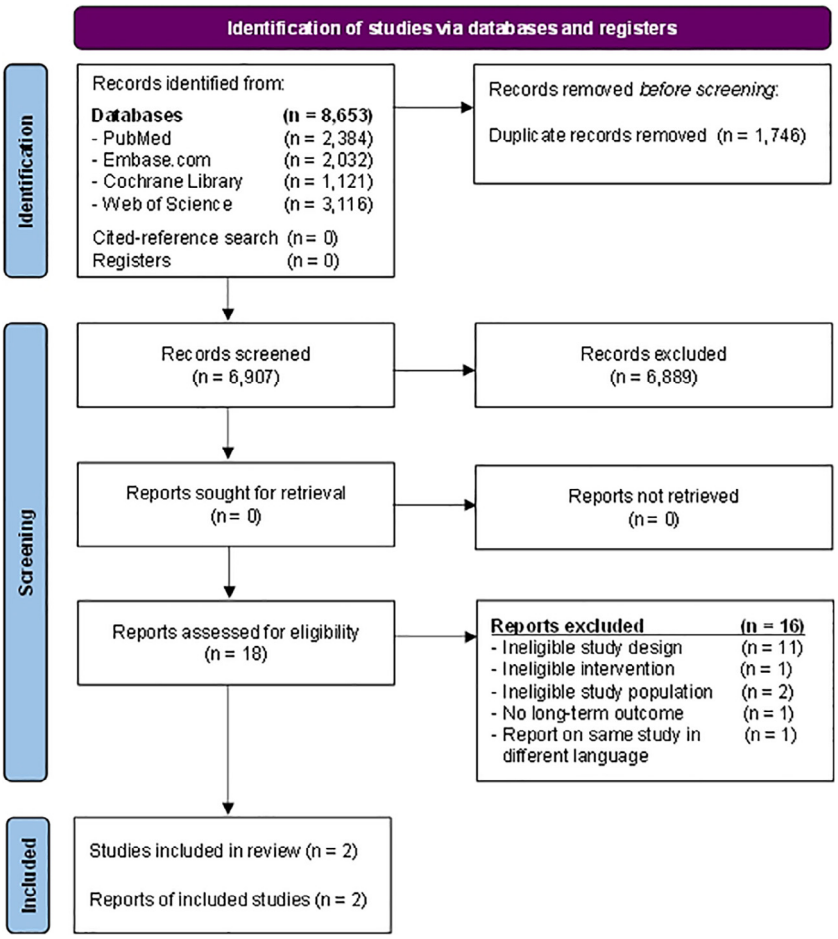

Fig. 1. PRISMA flow diagram.

lost to follow-up, however, quantitative data were not published. No comparison of baseline characteristics and obstetric outcomes was made between the study population from the original trial and the follow-up study [25]. Neither follow-up study reported important obstetric outcome data (e.g. gestational age at birth and birth weight) stratified per intervention at baseline, nor adjusted for these data in their analyses.

Risk of bias of included studies

Risk of bias assessment of the original trials using the Cochrane tool is presented in Fig. S1. The CLASP trial had a low risk of bias and there were some concerns regarding the ISAP [26,27]. Based on the QUIPS tool, both follow-up studies had an overall high risk of bias. Details of our judgement are provided in Appendix C and Fig. S2. We were unable to compile a funnel plot to assess publication bias due to the limited number of studies. A summary of the GRADE evaluation can be found in Appendix D. The results of (post-neonatal) mortality were classified as low quality. No GRADE evaluation on the outcome neurodevelopmental impairment could be made.

Data synthesis

Due to the limited number of included studies with substantial heterogeneity of the outcome definitions used in both studies, planned meta, subgroup and sensitivity analyses were not performed.

Post-neonatal mortality

The total mortality rate, including perinatal mortality, was not reported in both studies. The CLASP follow-up reported on the mortality rate between hospital discharge and follow-up at 12 and 18 months. Information on child's vital status was gathered through general practitioners and the UK National Health Service Central Registry. The ISAP follow-up reported mortality between eight days after birth and follow-up of all responders at 18 months [25].

The 12-month mortality rate was lower in the aspirin group than in the placebo group (0.2% versus 0.5%; RR 0.28, 95%CI 0.08–0.99) [24]. Causes of death at 12 months were not reported. At 18 months, no difference in mortality rate was measured in either study (Table 3). Causes of death in the aspirin group (n = 7) were prematurity (n = 1), sudden infant death syndrome (n = 4), infection (n = 1) and pulmonary problems (n = 1). Causes of death in the placebo group (n = 13) were sudden infant death syndrome (n = 8), congenital anomalies (n = 3), pulmonary problems (n = 1) and infection (n = 1).

Child neurodevelopment

Both included studies reported on several domains of development [24,25]. The development-related questions were mainly based on the questionnaire from Sonnander et al. that included questions from the Griffiths Developmental scales [28,29]. Age-related norms were used to determine developmental problems

Table 1
Characteristics original trials reporting on aspirin use in pregnancy among women at high risk of preeclampsia or fetal growth restriction.

Original trial	Type of treatment	Sample size, randomized pregnant women		Sample size, pregnant women with outcome data available		Sample size, babies including live births and fetal losses > 12 weeks		Prophylactic treatment for women at risk of PE and IUGR (%)*	Therapy for IUGR or PE (%)*	Initiation of treatment in weeks (mean ± SD)	Cessation of treatment	Maternal age at randomization, mean (±SD)	Nulliparous women (%)*
CLASP 1994	Aspirin 60 mg	9,364	4,683	9,309	4,659	9,631	4,810	4,013 (85.7%)†	670 (14.3%)‡	12–32 (19.4 ± 5.6)	delivery	28.5 (±5.4)	1,310 (28%)
	Placebo		4681		4,650		4,821	4,008 (85.6%)†	673 (14.4%)‡			28.5 (±5.5)	1,309 (28%)
ISAP 1993	Aspirin 50 mg	1,106	583	1,042	565	1,171	633	448 (76.8%)§	117 (20.1%)¥	16–32 (21.4 ± 5.3)	delivery	30.7 (±6.4)	NR
	No treatment		523		477		538	374 (71.5%)§	103 (19.7%)¥			30.5 (±6.7)	

IUGR: intra-uterine growth restriction, **NR**: not reported, **PE**: preeclampsia.
* Percentage is based on the sample size of the randomized women
† History of preeclampsia or IUGR, chronic hypertension, renal disease, or other risk factors, such as maternal age, family history, or multiple pregnancy.
‡ Women with signs or symptoms of preeclampsia or IUGR in the current pregnancy.
§ Age < 18 or > 40 years, mild or moderate chronic hypertension (diastolic pressure between 90 and 110 mmHg), nephropathy with normal renal function and normal blood pressure, history of pregnancy-induced hypertension with or without proteinuria developing after week 32 of a previous pregnancy, history of IUGR (<10th centile), and twin pregnancy.
¥ Pregnancy-induced hypertension (diastolic pressure between 90 and 110 mm Hg) in this pregnancy or early signs of IUGR (mean fetal abdominal circumference < 2 SD for gestational age).

Table 2
Characteristics follow-up studies reporting on long-term health and neurodevelopment in children after antenatal exposure to low-dose aspirin for the prevention of preeclampsia and fetal growth restriction.

Follow-up study	Selection for follow-up	Planned age of follow-up assessment	Time period of follow-up	Origin of population	Type of assessment	Maternal treatment during gestation	Alive children approached for follow-up (% of original trial)		Children with follow-up data (response rate %)		Follow-up rate from original trial	Sex of children (male, %)	Gestational age at birth, weeks (±SD)	Birth weight, g (±SD)
CLASP follow-up 1995	women recruited for trial < January 1st 1992	12 months§	NR	UK	general practitioner questionnaire	Aspirin 60 mg	4,675 (48.5%)	2,329	4,168	2,069 (88.8%)	43.3%	NR	38.6 (±2.7)	3,057 (±739)
						Placebo		2,346		2,099 (89.5%)				
		18 months§	NR	UK + Ottawa (Canada)	parental questionnaire	Aspirin 60 mg	5,081 (52.8%)	2,524	4,365	2,146 (85.0%)	45.3%	NR	38.5 (±2.7)	3,058 (±745)
						Placebo		2,557		2,219 (86.8%)				
ISAP follow-up 1994	infants born > February 1989	18 months§	NR	Italy	parental questionnaire	Aspirin 50 mg	1,083 (90.4%)	590*	788	427 (72.4%)	65.8%	NR	NR	NR
						No treatment		493*		361 (73.2%)				

NR *not reported*; **UK** *United Kingdom*.
* Infants who died after the first week of life are not excluded.
§ Exact age range of children at follow-up (including SD) is not reported.

Table 3
Mortality, neurodevelopment, anthropometrics, and health outcomes of children at 18 months of age after antenatal exposure to low-dose aspirin.

Outcome	Study	Aspirin group			Control group			RR (95%CI)	*p* value
		n	total	%	n	total	%		
Mortality	CLASP follow-up 1995	5	2,529	0.2%	12	2,569	0.5%	0.42 (0.15 – 1.20)	0.11
	ISAP follow-up 1994	2	427	0.5%	1	361	0.3%	1.69 (0.15 – 18.6)	0.67
Gross motor abnormal	CLASP follow-up 1995	9	2,146	0.4%	10	2,219	0.5%	0.93 (0.38–2.29)	0.88
	ISAP follow-up 1994	–	–	–	–	–	–	–	–
Fine motor abnormal	CLASP follow-up 1995	28	2,146	1.3%	39	2,219	1.8%	0.74 (0.46–1.20)	0.23
	ISAP follow-up 1994	–	–	–	–	–	–	–	–
Gross and fine motor problems	CLASP follow-up 1995	–	–	–	–	–	–	–	–
	ISAP follow-up 1994	15	427	3.5%	26	361	7.2%	0.49 (0.26–0.91)	0.02
Language problems	CLASP follow-up 1995	124	2,146	5.8%	136	2,219	6.1%	0.94 (0.74–1.19)	0.62
	ISAP follow-up 1994	55	427	12.9%	47	361	13.0%	0.99 (0.69–1.42)	0.95
Hearing problems	CLASP follow-up 1995	20	2,146	0.9%	25	2,219	1.1%	0.83 (0.46–1.48)	0.53
	ISAP follow-up 1994	1	427	0.2%	0	361	0%	–	–
Vision problems	CLASP follow-up 1995	9	2,146	0.4%	18	2,219	0.8%	0.52 (0.23–1.15)	0.11
	ISAP follow-up 1994	5	427	1.2%	5	361	1.4%	0.85 (0.25–2.90)	0.79
Short stature	CLASP follow-up 1995*	236	2,146	11.0%	248	2,219	11.2%	0.98 (0.83–1.16)	0.85
	ISAP follow-up 1994§	36	427	8.4%	44	361	12.2%	0.69 (0.46–1.05)	0.08
Low weight	CLASP follow-up 1995*	112	2,146	5.2%	129	2,219	5.8%	0.90 (0.70–1.15)	0.39
	ISAP follow-up 1994§	76	427	17.8%	60	361	16.6%	1.07 (0.79–1.46)	0.66
Respiratory problems	CLASP follow-up 1995	45	2,146	2.1%	46	2,219	2.1%	1.01 (0.67–1.52)	0.96
	ISAP follow-up 1994	56	427	13.1%	32	361	8.9%	1.48 (0.98–2.23)	0.06

* <3rd centile.
§ <10th centile.

and difficulties [30]. Results above the 90th centile were considered abnormal [24,25].

Results of child neurodevelopment are shown in Table 3. In the CLASP follow-up at 18 months, abnormal gross motor development (0.4% versus 0.5%; RR 0.93, 95%CI 0.38–2.29) and abnormal fine motor development (RR 0.74, 95%CI 0.46–1.20) of children was similar between the aspirin group and the control group. The CLASP follow-up also reported no differences in specific aspects of development and health at 18 months of age (Table S1) [24]. In the ISAP follow-up at 18 months, there were fewer children with gross and fine motor problems in the aspirin group (3.5% versus 7.2%; RR 0.49, 95%CI 0.26–0.91) [25]. There were no differences in abnormal language development, and hearing or vision problems in either one of the follow-up studies.

Anthropometrics

Both studies reported on a parental measure of height and weight at the age of 18 months. An abnormal value of height or weight was defined as < 3rd centile in the CLASP follow-up study and < 10th centile in the ISAP follow-up study [24,25]. Neither study reported a significant difference in the prevalence of short stature or low weight between the aspirin and control group (Table 3).

Respiratory problems

In the CLASP follow-up, respiratory problems were defined as frequent coughs and wheezes as reported by parents, and the ISAP follow-up provided no definition. Neither study reported a significant difference in respiratory problems between treatment groups (Table 3).

Healthcare consumption

In the CLASP follow-up, fewer children in the aspirin group visited the hospital for developmental delay compared to the placebo group (0.7% versus 1.4%; RR 0.47, 95%CI 0.25–0.89) at 12 months (Table S2) [24]. Hospital visits and admissions, and nonroutine consultations with the general practitioner at 12 and 18 months did not differ between groups. The ISAP follow-up did not report on healthcare consumption.

Discussion

We found that children antenatally exposed to maternal low-dose aspirin for the prophylaxis or treatment of preeclampsia or fetal growth restriction had lower mortality until the age of 12 months. Furthermore, there were fewer hospital visits for developmental delay at 12 months along with improved gross and fine motor function (as assessed from the achievement of specific developmental milestones) at 18 months. There were no differences in other neurodevelopmental outcomes (i.e. language, hearing and/or vision problems), respiratory problems and the proportion of children with a short stature and/or low weight between treatment groups at 18 months of age.

In the CLASP follow-up, the mortality rate from hospital discharge to children's age of 12 months was significantly lower in the aspirin group than in the placebo group [24]. This is in line with other evidence suggesting that prophylaxis with low-dose aspirin in pregnancy reduces the perinatal mortality rate [1]. The reduced mortality rate may be a direct result of improved short-term perinatal outcome, achieved by the reduction of preeclampsia, small-for-gestational-age and/or preterm birth, all of which have been reported to be robustly improved by antenatal low-dose aspirin [1], and are risk factors for long-term morbidity [12–17]. It seems plausible that the prevention of these obstetric complications by low-dose aspirin may not only reduce mortality and morbidity in the short-term but also in the longer term. However, mortality rate at 18 months did not differ between groups in either of the included studies and a causal relationship between aspirin and reduced post-neonatal mortality could not be demonstrated based on these data.

In our review, children exposed to low-dose aspirin during pregnancy had a lower likelihood of gross and fine motor problems, and hospital visits for developmental delay. One cohort study among 584 5-year-old children born between 22 and 32 completed weeks of gestation also found possible beneficial effects of antenatal exposure to low-dose aspirin on neurodevelopment: a reduction in problem behavior and hyperactivity, but

not in cognitive impairments [15]. We speculate that antenatal exposure to low-dose aspirin could have a direct neuroprotective effect translating into improved long-term outcome. For example, by prevention of damage caused to the developing fetal brain by intrauterine inflammation [31–34]. On the other hand, concerns have been raised regarding the safety of antenatal low-dose aspirin exposure for the developing fetal brain [35]. A Scandinavian retrospective study showed increased risk (aOR 2.4, 95%CI 1.1–5.3) for cerebral palsy in children up to 6 years ever exposed to 80–500 mg aspirin (n = 5,746) during pregnancy compared to those who were not exposed (n = 138,763) [36]. A likely explanation for these conflicting findings is that observational studies suffer from confounding by indication, with women at higher risk of perinatal poor outcome, and therefore of poor neurodevelopmental outcome in the long term, being more likely to receive antenatal low-dose aspirin.

Considering the important functions of the COX enzyme and prostaglandins throughout the human body, delayed effects from antenatal exposure to aspirin could arise in other organ systems as well. In our study, we did not identify such delayed effects in other organ systems, e.g. the respiratory system. In contrast, follow-up from the Collaborative Perinatal Project, including 19,928 children at the age of 7, found an increased risk of asthma among children with antenatal exposure to aspirin. These children were antenatally exposed to therapeutic doses of aspirin > 300 mg [37]. Another study using the same cohort also found aspirin might be beneficial with regards to children's blood pressure at 7 years of age [38]. We did not identify data of RCTs assessing cardiovascular outcomes.

Notably, both included studies assessed aspirin up to 60 mg started relatively late in pregnancy, while current practice advises doses up to 150 mg a day starting before 16 weeks of gestation [39]. It can be assumed from the dose–response effect of aspirin that longer duration of antenatal exposure to a higher dose of aspirin would have more impact on child development. This impact could be either positive or negative. Many large RCTs have assessed the effect of low-dose aspirin 75–150 mg initiated early in pregnancy on obstetric complications. Long-term follow up among children born in these trials could provide valuable information to current prescribing practice. Considering the large variations in long-term outcome reporting in follow-up studies [40], we encourage standardization of the applied measurement tools and development of a core outcome set to facilitate comparability of future studies [41,42].

Strengths of our study include the broad search strategy and robust methodology, as well as the clinical relevance of the question we attempted to answer. The main limitation of our findings is the limited number of studies, preventing us from drawing firm conclusions. Furthermore, the studies date from the early 90's and since that time obstetric and neonatal healthcare has changed substantially, potentially limiting the applicability of the findings to current practice. The included studies were restricted to a follow-up age of 18 months, when infants are still at a very early stage of brain development. Beyond this age, the brain continues to develop rapidly. As early as school age, specific cognitive functions are challenged for the first time so that more subtle effects of antenatal low-dose aspirin exposure can only become manifest with age.

The follow-up studies had a high risk of bias. They were susceptible to selection bias due to high attrition from the original trial, especially in the CLASP trial that followed less than half of the children. The risk of selective attrition may be low, as baseline characteristics and obstetric outcomes of participants in the follow-up studies did not deviate from those in the original studies. However, the included studies did not report important family factors, such as parental socioeconomic status, which are known to influence infant neurodevelopment, as well as being an important source of selective attrition [43,44].

Another limitation may be the fact that included studies used questionnaires administered from parents or caregivers for an assessment of follow-up outcomes rather than a physical assessment. Questionnaires have the advantage of being easily accessible and inexpensive but may be subjective. However, the Griffith survey used in the follow-up studies is a validated questionnaire for assessing general development in high-risk children [29]. Lastly, studies did not adjust for factors associated with perinatal and long-term outcome (e.g. gestational age at birth) in their analyses while gestational age at birth has a large impact on child health and development [45]. As low-dose aspirin has been shown to reduce preterm birth in other studies, gestational age at birth could have modified the observed effects between treatment groups in the studies. Therefore, direct causality between antenatal aspirin exposure and the study outcomes could not be established.

Conclusion

We found possible positive effects of low-dose aspirin administered during pregnancy on post-neonatal mortality and motor development up to 18 months of age. Our findings support the current wide application of preventive low-dose aspirin in pregnancy. However, literature was scarce, had a high-risk of bias and was limited to aspirin doses up to 60 mg and age at follow-up of 18 months. Further follow-up research of children who were exposed to low-dose aspirin during pregnancy is of paramount importance.

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Details of Ethics Approval

Ethical approval was not required for secondary use of data in this systematic review and meta-analysis.

Paper presentation information

N/A.

Disclaimer

N/A.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Registration

PROSPERO ID: CRD42020162088.

Contribution to Authorship

ALa, MdB, MO and RP designed the study as presented in the Prospero database. ALa and JK performed the search. ALa and EvLS

performed study selection, data extraction and risk of bias assessment, and disagreements were resolved by discussion with RP. MF and ALe provided expertise from a paediatric perspective. JvtH and RP provided expertise on long-term follow-up of children from obstetric studies. ALa and EvLS drafted the manuscript under supervision of RP. All authors critically reviewed the manuscript and approved the final version.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejogrb.2021.11.010.

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