Long-term outcomes following antenatal exposure to low-dose aspirin: study protocol for the 4-year follow-up of the APRIL randomised controlled trial

Anadeijda J E M C Landman 1,2, Emilie V J van Limburg Stirum 2,3, Janneke van ‘t Hooft 2,3, Aleid G Leemhuis 4, Martijn J J Finken 5, Anneloes L van Baar 6, Tessa J Roseboom 2,3,7, Anita C J Ravelli 8, Madelon van Wely 2,3, Jaap Oosterlaan 2,4,5, Rebecca C Painter 2,3, Eva Pajkrt 2,3, Martijn A Oudijk 2,3, Marjon A de Boer 1,2

ABSTRACT

Introduction The use of low-dose aspirin by pregnant women to prevent preterm pre-eclampsia is gradually increasing. The administration of aspirin during pregnancy improves perinatal outcome, which could translate into improved child outcome in the long term. However, antenatal exposure to aspirin could have adverse effects on child development that may manifest later in life. The aim of this follow-up study is to assess the long-term effects of antenatal exposure to low-dose aspirin compared with placebo on survival, (neuro)development, behaviour and general health at 4 years corrected age.

Methods and analysis This is a follow-up study of the Dutch double-blind randomised controlled APRIL trial which assessed the effectiveness of treatment with aspirin (80 mg daily) compared with placebo for the prevention of preterm birth in women with a previous spontaneous preterm birth. Treatment was initiated before 16 weeks of gestation and continued until 36 weeks or birth. We aim to follow-up all 379 children born to women who participated in the APRIL trial and survived the neonatal period, at the corrected age of 4 years. The main outcomes are (neuro)development as assessed by the Ages and Stages Questionnaire, and behaviour as assessed by the Strength and Difficulties Questionnaire. Additional outcomes include mortality, growth and general health from birth up to 4 years, and a composite outcome including mortality, abnormal (neuro)development and problem behaviour. Analyses will be performed by intention-to-treat using a superiority design.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The main strength of the study is the long-term follow-up of a randomised trial with a placebo-controlled design.
⇒ The focus on (neuro)development and behaviour as outcomes is a strength, as these domains were deemed most important by patient groups.
⇒ A challenge of this study will be to minimise attrition and to obtain complete data of participants.
⇒ Questionnaires have the advantage that they are feasible and relatively inexpensive; however, these screening tools may be less sensitive in their ability to detect mild problems.

INTRODUCTION

Low-dose aspirin is administered during pregnancy for the prevention of preterm pre-eclampsia and it also reduces the risk of perinatal mortality, preterm birth and small-for-gestational-age birth.1 2 The National Institute for Health and Care Excellence recommends to start prophylaxis with low-dose aspirin 75–150 mg at 12 weeks of gestation in women at risk of pre-eclampsia, and to continue treatment until delivery.3 Given the substantial and increasing proportion of women using low-dose aspirin during pregnancy, and the current debate on potential universal use of aspirin in pregnant women, it is of utmost importance to assess the long-term health of exposed children.4

Aspirin passes the uteroplacental barrier to the fetus and its developing organs.5 7 Aspirin is thought to improve early placentation, thereby improving the flow of nutrients and oxygen to the developing fetus. Improved placentation could offer a range of advantages for later life by reducing the risks of
preterm birth and low birth weight. Furthermore, aspirin has anti-inflammatory properties, which may reduce fetal brain injury caused by maternal inflammation.

An observational cohort study of high-risk pregnancies embedded in the French EPIDAGE study compared children of women receiving low-dose aspirin (n=125) and no-aspirin use (n=447) and found no differences in mortality, cerebral lesions and global cognitive impairment at the age of 5. In fact, there was a trend towards a reduction of total behavioural difficulties and hyperactivity in the low-dose aspirin group. The Danish MOBAND cohort including 185617 children found an increased risk of bilateral spastic cerebral palsy in children (n=9/5737) antenatally exposed to aspirin (adjusted OR (aOR) 2.4, 95%CI 1.1 to 5.3), although data on aspirin dose and frequency of use were lacking. Other observational studies showed that higher doses of aspirin (>300 mg) were associated with an increased risk of asthma at 7 years of age and reduced risk of high childhood blood pressure. However, observational studies may suffer from confounding by indication, precluding any firm conclusions.

A systematic review performed by our team identified two published follow-up studies of randomised controlled trials (RCTs) providing information on aspirin use in pregnancy. In individual studies, a potential benefit on post-neonatal survival at 12 months (Relative Risk (RR) 0.28, 95% CI 0.08 to 0.99) and motor development at 18 months (RR 0.49, 95% CI 0.26 to 0.91) was seen. No differences were found in terms of child growth, general health or development (eg, language comprehension). These RCTs, however, used relatively low doses of aspirin (up to 60 mg daily) and had a shorter duration of exposure (mean gestational age at initiation of therapy of approximately 20 weeks), with a maximum follow-up period of 18 months.

Taken together, the evidence is insufficient to inform current aspirin prescribers in terms of long-term effects on children. In light of the increasing use of prophylactic low-dose aspirin during pregnancy, it is crucial to obtain more long-term data to exclude potential harm and determine possible benefits in the long term. We will perform a follow-up study of children who were exposed to aspirin 80 mg daily versus placebo from 8 to 16 weeks of gestation until 36 weeks as part of the APRIL trial, which included women with a history of spontaneous preterm birth. We aim to evaluate the effects of antenatal low-dose aspirin exposure on (neuro)development, behaviour, mortality, growth and general health of children at 4 years corrected age.

METHODS AND ANALYSIS
Design and setting RCT
This is a follow-up study of the multicentre, double-blind, placebo-controlled randomised controlled APRIL trial. The APRIL trial included women with a singleton pregnancy between 8 and 16 weeks gestation with a history of spontaneous preterm birth of a singleton between 22 and 37 weeks of gestation. Inclusions took place between May 2016 and June 2019 in 8 tertiary care and 26 secondary care hospitals in the Netherlands.

The APRIL trial was randomised in a 1:1 ratio and allocation was blinded for participants, healthcare professionals and the investigators. After informed consent, mothers of eligible children were allocated to low-dose aspirin (80 mg daily) or placebo. Treatment was started between 8 and 16 weeks of gestation and continued until 36 weeks or birth. Compliance with medication was assessed by pill counts and a self-reported medication diary. Other medication, such as progesterone, tocolysis and corticosteroids for fetal lung maturation, could be used according to local protocols.

There were no significant differences in preterm birth rate, maternal outcomes or neonatal outcomes between intervention groups. The median gestational age at birth of children was 38 weeks (IQR 37–39) in the aspirin group and 38 weeks (IQR 37–39) in the placebo group. Mean birth weight was 3102 g (±SD 648) in the aspirin group and 3126 g (±SD 678) in the placebo group. A detailed description of the methods and results can be found in the published protocol and trial results.

Design and setting follow-up
The APRIL follow-up study will focus on survival, (neuro)development, behaviour and general health of children born from participants from the APRIL trial at 4 years corrected age. Recruitment started in September 2020 and is expected to be finalised in March 2024. The APRIL follow-up study will be carried out within the Dutch Consortium for Healthcare Evaluation and Research in Obstetrics and Gynaecology (www.zorgevaluatieerel.nl). The follow-up study has been registered in the Dutch trial register (NL8950). The WHO Trial Registration Data Set (https://www.who.int/clinical-trials-registry-platform/network/who-data-set) can be found in the online supplemental appendix S1. We used the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist as a guide for reporting this study protocol.

Participants
The study population consists of the children born to women who participated in the APRIL trial (n=387; figure 1). All infants who were alive at the corrected age of 3 months (n=379) will be eligible for follow-up assessment at the corrected age of 4 years (n=188 in the aspirin group and n=191 in the placebo group). Non-Dutch-speaking participants will be excluded, as we will only use the Dutch version of the questionnaires to ensure the validity of our results.

Blinding
In the APRIL follow-up study, the investigators involved in data collection and analyses will be blinded for treatment allocation. Women who request to be unblinded will be...
offered unblinding information after the completion of the present follow-up study.

**Study procedures**

Standardised questionnaires will be used to gain information on (neuro)development and behaviour, with an additional questionnaire on general health. All questionnaires will be directed to the parents or caretakers. Table 1 provides an overview of all outcomes and definitions.

**Ages and Stages Questionnaire**

The Ages and Stages Questionnaire (ASQ) is a screening questionnaire for parents/caretakers to assess general development. We will use a validated Dutch translation of the third edition of the 48-month ASQ (range 3.75–4.25 years). The questionnaire consists of six questions regarding important milestones for each of the following five domains: communication, gross motor, fine motor, problem solving and personal social. Possible scores on each item include ‘yes’ (score=10), ‘sometimes’ (score=5) or ‘not yet’ (score=0). The manual provides instructions on how to deal with missing data. Scores on the five domains may range from 0 to 60, with lower scores indicating less attainment of developmental milestones. We will report the score on all five domains and the total problem score, which is a sum of all five domains. A score between ≥1 SD and <2 SD below the normative data in one of the developmental domains will be considered mildly abnormal. The manual advises these children to be provided with developmental activities, after which the child should be rescreened or referred for further evaluation. The results of the questionnaires will be considered abnormal if the child receives a score ≥2 SD below the normative data on any domain or ≥1 SD below the normative data on multiple domains. The manual advises immediate referral for further evaluation in case of an abnormal score.

**Strengths and Difficulties Questionnaire**

The Strengths and Difficulties Questionnaire (SDQ) assesses behavioural, emotional and social functioning as rated by parents. The SDQ can be used for ages from 4 to 17. The questionnaire consists of five questions on the following five dimensions: Conduct problems, Emotional symptoms, Hyperactivity, Peer relationships and Prosocial behaviour. Children are rated on a 3-point scale ranging from 0 (not true) to 2 (certainly true). The Total Difficulties Score can be calculated by adding up all the subscales except for the subscale Prosocial behaviour. The questionnaire has been validated for the Dutch population and normative data have been collected for a large representative sample of 1174 children. A mildly abnormal score is defined as a score >80th centile (Total Difficulties Score 11–14 at 4–7 years) and an abnormal score is defined as a score >90th centile (Total Difficulties Score ≥15 at 4–7 years). A score of ≥11 indicates potential psychosocial problems in need of further assessment. In addition, the scores of the subscales will be reported. Behavioural problems on the Emotional and Conduct subscale are indicated by a score >90th centile (Emotional Problem Score ≥4 and Conduct Problem Score ≥3). There are no generally accepted definitions of an abnormal score of the subscales hyperactivity, peer relationships and prosocial behaviour, and the validity of these separate subscales is unknown.

**Figure 1** Flow diagram of participants eligible for follow-up.
Table 1  Overview of outcomes, tools and definitions

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Tool</th>
<th>Definition</th>
<th>Unit of measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Neuro)development</td>
<td>Ages and Stages Questionnaire</td>
<td>Total problem score</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Five domains:</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>► Communication</td>
<td>Mildly abnormal:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>► Gross motor</td>
<td>≥1 and &lt;2 SD in one domain below mean</td>
</tr>
<tr>
<td></td>
<td></td>
<td>► Fine motor</td>
<td>Abnormal:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>► Problem solving</td>
<td>≥2 SD in any domain or multiple domains &lt;1 SD below mean</td>
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<tr>
<td></td>
<td></td>
<td>► Personal social</td>
<td></td>
</tr>
<tr>
<td>Behaviour</td>
<td>Strength and Difficulties Questionnaire</td>
<td>Total Difficulties Score</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Five subscales:</td>
<td>Mildly abnormal:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>► Conduct problems</td>
<td>&gt;80th centile below mean</td>
</tr>
<tr>
<td></td>
<td></td>
<td>► Emotional symptoms</td>
<td>Abnormal:</td>
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<tr>
<td></td>
<td></td>
<td>► Hyperactivity</td>
<td>&gt;90th centile below mean</td>
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<td></td>
<td></td>
<td>► Peer relationships</td>
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<td></td>
<td></td>
<td>► Prosocial behaviour</td>
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<tr>
<td></td>
<td></td>
<td>Subscales:*</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>► Emotional problem score</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>► Conduct problem score</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>Medical records, Dutch population register</td>
<td>Perinatal death and child death up to 4 years of age</td>
<td>Number (%)</td>
</tr>
<tr>
<td>General health and sociodemographic information</td>
<td>General health and sociodemographic information</td>
<td>For example, the need for a medical specialist and/or developmental care, medication use in the past and present, hospital admissions and need for surgery</td>
<td>Number (%)</td>
</tr>
<tr>
<td>Growth</td>
<td>Growth book from Child Healthcare Centres</td>
<td>► Height of child</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>► Height of biological parents for calculation of target height</td>
<td>Abnormal: 1.6 SDS above or below target height range</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BMI (kg/m²)</td>
<td>Underweight, Overweight, Obesity</td>
</tr>
<tr>
<td>Composite of mortality and abnormal outcome</td>
<td>Tools as described above</td>
<td>Composite of:</td>
<td>Components as defined above</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1. Perinatal death and child death up to 4 years corrected age</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>2. Abnormal (neuro)development</td>
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<td></td>
<td></td>
<td>3. Problem behaviour</td>
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</tbody>
</table>

*There are no definitions of an abnormal score of the subscales hyperactivity, peer relationships and prosocial behaviour, and the validity of these separate subscales is unknown.

ASQ, Ages and Stages Questionnaire; BMI, body mass index; SDQ, Strength and Difficulties Questionnaire; SDS, Standard Deviation Score.

Mortality data of the children will include death from randomisation up to the corrected age of 4. Data will be retrieved from medical records in the participating centres and by searching the Dutch population register.

General health and sociodemographic information

Our research team has developed a health questionnaire which was used in several previous follow-up studies performed within the Dutch Consortium for Healthcare Evaluation and Research in Obstetrics and Gynaecology. This questionnaire includes questions regarding the child’s current and past health (eg, medical
conditions, the need for consulting a medical specialist and/or developmental care, medication use in the past and present, hospital admissions and need for surgery). Health-related problems will be clustered in different categories (0, 1–2 and ≥3 hospital admissions; 0, 1–2 and ≥3 medication used; and 0, 1–2 and ≥3 surgeries needed) to provide insight into the range of these problems. Children with ≥3 hospital admissions and/or ≥3 surgeries between discharge after birth and 4 years corrected age were classified as abnormal. The questionnaire also includes demographical questions concerning the parents/caretakers.

Growth
Parents/caretakers will be asked to provide longitudinal height and weight measurements obtained at regular visits at Children’s Healthcare Centres. In addition, the height of the biological parents will be assessed to allow calculation of the child’s target height and accompanying CI. Children’s height will be presented as SD Scores (SDS) based on national reference values, and as 1.6 SDS above or below the target height range (±10 cm for girls and ±11 cm for boys). Furthermore, the body mass index of the children will be calculated. We will report body mass index as a continuous value, and also the proportion of children who are overweight, obese or obese based on the reference data of Cole et al, in line with Dutch practice guidelines in youth healthcare.35 36

Outcomes
The main outcomes of the APRIL follow-up study are (1) delay in (neuro)development (mildly abnormal ASQ, one domain between 1 and 2 SD) and (2) behavioural problems (mildly abnormal SDQ >80th centile) at children’s corrected age of 4 years. Additional outcomes will include child mortality including perinatal death and child death up to 4 years of age, the incidence of health-related problems as described above and child’s growth. Furthermore, we will evaluate a composite outcome of mortality up to 4 years of age and abnormal child outcome (abnormal ASQ <2 SD in any domain or <1 SD in multiple domains; and/or abnormal SDQ >90th centile). Combining data of mortality and survival with abnormal child outcome will provide a broader scope of relevant outcomes from the start of randomisation until 4 years of age.

Sample size calculation
In line with the original trial, this follow-up has a superiority design. Since the sample size is determined by the power calculation of the original trial, the maximum number of participants in the follow-up study is fixed: 188 in the aspirin group and 191 in the placebo group.19 20 We calculated the minimum number of participants needed to find a significant difference (for a medium effect size with 80% power, α=0.05 and β=0.2) for the two main outcomes: (neuro)development and behaviour. Based on a previous study, we expect to find 20.7% mildly abnormal ASQ scores in our study population.30 To find an OR of 2.5 comparing aspirin to placebo, a sample of 93 children per group would be required, and for an OR of 3.0a sample of 63 per group. For the SDQ, we expect to find to find a mildly abnormal score in 11.6% of our population.37 To find an OR of 2.5 comparing aspirin to placebo, a sample of 135 children per group would be required and for an OR of 3.0a sample of 90 per group.

Data analysis plan
Differences in demographic characteristics of maternal, short-term pregnancy and perinatal outcomes from APRIL follow-up participants will be compared for the aspirin and placebo group using the independent samples t-test, Mann Whitney U test, χ² test or Fisher’s exact test when appropriate. To estimate any relevant attrition bias factors, we will also perform these comparisons between follow-up participants and the ones that were lost to follow-up.

For the main outcome (neuro)development, we will report mean scores (with SDs) and (mildly) abnormal scores on all five domains and the total problem score of the ASQ. For the main outcome behaviour, we will report mean scores (with SDs) and (mildly) abnormal scores of the subscales and Total Difficulties Score of the SDQ. For the outcome health-related problems, only one predetermined analysis will be performed in each health-related category (≥3 admissions/medication/surgeries) to reduce the number of tests. For mortality up to 4 years, the denominator has to be changed in the analysis. All randomised participants will be included in the denominator, rather than follow-up participants only.

In case of a loss to follow-up rate ≤20%, we will perform multiple imputation with 10 datasets using the following variables as predictors: maternal characteristics (ie, ethnicity, maternal age, smoking during pregnancy and education) and neonatal outcomes (ie, gestational age at birth, birth weight, sex, neonatal sepsis, infant respiratory distress syndrome, intraventricular haemorrhage and necrotising enterocolitis). In case of a loss to follow-up rate >20%, we will perform a best-case and worst-case scenario analysis assuming children lost to follow-up either have a normal child outcome (best case) or abnormal child outcome (worst case). In addition, we will perform a simple case extrapolation scenario, assuming children lost to follow-up have the same percentage of disability as the group that was followed.

For the comparisons between the aspirin and the placebo group, a directed acyclic graph analysis will give insight to potential confounders to make decisions on corrections. In case confounders are identified and corrections are needed, linear regression will be performed for continuous outcomes and logistic regression for dichotomous outcomes. In case no corrections are needed, an independent samples t-test, Mann Whitney U test, χ² test or Fisher’s exact test will be used when appropriate. Analyses will be performed according to the intention-to-treat principle and a two-sided p-value ≤0.05 will indicate statistical significance. No correction for multiple testing will
be applied due to the nature of the hypothesis-generating analysis. However, the number of statistical tests will be restricted as much as possible and we will use predefined cut-offs for all tests.

Additional analyses
We will perform five exploratory subgroup analyses for the main outcomes abnormal (neuro)development and problem behaviour:
1. Children of women with ≥80% compliance to study medication compared with women with compliance <80%.
2. Prenatal exposure to progesterone in addition to study medication (low-dose aspirin or placebo) compared with no progesterone exposure.
5. Placental insufficiency versus no placental insufficiency in the index pregnancy.

We will also compare baseline variables of the groups that are compared in the subgroup analyses because differences in baseline variables (that have impact on long-term outcomes, eg, smoking, socioeconomic factors) between the groups compared may introduce bias.

Data collection
A detailed flow diagram of the contact mechanisms is shown in figure 2. We will only contact women who have consented to be approached for future research on the original trial consent form. Before contacting parents/caretakers, we will gain information on the vital status of the mother and the child. Research nurses from the NVOG consortium in participating centres will be asked to scrutinise the medical records to track the possible occurrence of death of mother or child. In addition, the research team will search the Dutch population register. When both mother and child are alive, we will send out a letter including written information about the APRIL follow-up study that is easily understood. Each subject will be informed that participation is voluntary, and that withdrawal of consent will not have any consequences. Trial participants who decline participation in the APRIL follow-up study can make this clear easily by opting out with the attached return slip or an email. These children will be considered lost to follow-up. The trial participants who do not respond to the initial letter will be contacted again by the research team within 4 weeks. Those that wish to participate in the follow-up study can contact the research team. During a telephone call, parents/caretakers will receive further information regarding the study and will have the opportunity to ask questions. Both parents/caretakers have to sign the informed consent form and can send the hardcopy to the research team by post in a freepost envelope. After informed consent is received by the research team, the study procedures will be planned. If parents/caretakers experience difficulties with completing the questionnaires, the research team will offer their assistance.

Data management
Data of the follow-up study will be handled confidentially by using a unique subject identification code. The key to this code is safeguarded by the investigator. Handling of personal data will comply with the EU General Data Protection Act (wet Algemene Verordening Gegevensbescherming, AVG). Electronic case report forms are linked to the unique identification code and will be used for data collection and documentation. All questionnaires are filled out through the same data management system and directly linked to the individual participant. All data will be stored securely at the Amsterdam UMC for fifteen years, according to national guidelines. The research team will have access to the final dataset.

Patient involvement
Our research team has involved patients in the preparation of several follow-up studies that assessed the long-term outcome of children from obstetric intervention studies, mostly interventions for the prevention of preterm birth. The Dutch association for parents of incubator children (Care4Neo.nl) participated in an online survey on long-term development and follow-up research of preterm born children. A majority of the responders had concerns about their child’s long-term development, mostly regarding their general health and future school achievements. A total of 95% would be willing to participate in follow-up research. In addition, our research group held a focus group meeting with mothers of preterm born children to explore the different aspects of their children’s development, and their opinion on the most relevant outcomes that should be assessed in future follow-up studies. We used the input from the focus group in our study design by focusing on (neuro)development and behaviour, as these domains were deemed most important by focus group participants.

ETHICS AND DISSEMINATION
Institutional review board approval was obtained from the Medical Research Ethics Committee from Amsterdam Medical Centre (no. W20 289#20,925). The parents of children who died after hospital discharge will not be contacted. If the child is alive, we will contact mothers who have consented to be approached for further research to participate in the APRIL follow-up study. Parents/caregivers will be made aware that participation is voluntary and that they may withdraw consent from the study at any time. Informed consent will be obtained from all parents/caretakers before inclusion in the study.

Within our team of experts (paediatricians, psychologists and clinical researchers with experience in follow-up studies), we have carefully balanced the information each questionnaire provides, and the time investment these questionnaires require. Each of these questionnaires...
Figure 2  Tracing and contact mechanisms of eligible participants.
(except for the general health questionnaire) are internationally validated as well as translated and validated for Dutch children. If any of the questionnaires has an abnormal score result, the child will be discussed with a neonatologist and/or (neuro)psychologist from our research team and parents will be advised through the telephone to contact their general practitioner for further assistance and referral.

This protocol is published before recruitment is completed. After completion of the study, the results will be published in a peer-reviewed journal and presented at conferences to disseminate the results within the field of obstetrics. We will also share the results with the participants and Care4Neo, the Dutch association for parents with preterm born children.

**DISCUSSION**

Long-term follow-up of children who were exposed to an intervention during pregnancy is important to determine the safety and persistence of neonatal therapeutic effects. Nevertheless, only a minority of RCTs evaluating perinatal interventions perform long-term follow-up. Long-term neurodevelopmental morbidity is one of the core outcomes of studies evaluating the prevention of preterm birth. However, there is no core outcome set for the entire scope of relevant long-term outcomes following interventions during pregnancy, nor are there standardised applied measurement tools. In our study, we will evaluate (neuro)developmental outcome as well as child’s survival, behaviour and general health to obtain a complete overview of the benefits and risks of aspirin exposure during pregnancy.

Children will be assessed at 4 years corrected age. At this age, we expect to obtain an adequate impression of child development and health, and to identify possible difficulties. Whereas, at a younger age, some possible long-term effects may not have become apparent yet.

Compared with questionnaires, an examiner-led clinical assessment may be more sensitive to detect mild problems and would be less susceptible to the parental opinion of their child. However, questionnaires have the advantage that they are feasible, relatively inexpensive and are less of a burden for the child and their family. The questionnaires we will use to detect developmental and behavioural problems are internationally validated.

Our study population is limited to the Dutch population. Since the Netherlands is a high-income country, results of our follow-up may not be generalisable to all populations. In low-income countries, other factors may influence child development (eg, nutrition and inflammation). The ASPIRIN trial, which was performed in low-income and middle-income countries and evaluated low-dose aspirin (81 mg) versus placebo for the prevention of preterm birth, is currently performing follow-up at children’s mean age of 3 years (NCT04888577). The results of the APRIL and ASPIRIN follow-up study will give us more insight into the long-term effects and safety of antenatal exposure to low-dose aspirin. As a substantial and increasing proportion of women use low-dose aspirin prophylactically during pregnancy, this information is relevant to healthcare professionals as well as pregnant women.

**Author affiliations**

1. Amsterdam UMC location Vrije Universiteit Amsterdam, Department of Obstetrics and Gynaecology, De Boelelaan 1117, Amsterdam, The Netherlands
2. Amsterdam Reproduction and Development, Amsterdam, The Netherlands
3. Amsterdam UMC location University of Amsterdam, Department of Obstetrics and Gynaecology, Meibergdreef 9, Amsterdam, The Netherlands
4. Amsterdam UMC location University of Amsterdam, Emma Children’s Hospital, Department of Neonatology and Paediatrics, Meibergdreef 9, Amsterdam, The Netherlands
5. Amsterdam UMC location Amsterdam UMC, Emma Children’s Hospital, Department of Paediatric Endocrinology, De Boelelaan 1117, Amsterdam, The Netherlands
6. Utrecht University, Department of Child and Adolescent Studies, Utrecht, The Netherlands
7. Department of Clinical Epidemiology, Biostatistics and Bioinformatics, Amsterdam UMC Locatie AMC, Amsterdam, The Netherlands
8. Department of Medical Informatics, Amsterdam UMC location University of Amsterdam, Department of Clinical Epidemiology, Biostatistics and Bioinformatics, Meibergdreef 9, Amsterdam, The Netherlands
9. Amsterdam UMC location University of Amsterdam, Amsterdam UMC FollowMe program & Emma Neuroscience Group, Meibergdreef 9, Amsterdam, The Netherlands

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ORCID iDs
Anadeija J E C Landman http://orcid.org/0000-0002-6354-3489
Emile V Jan van Lib urn Strum http://orcid.org/0000-0003-2381-0332
Janneke van ’t Hoof http://orcid.org/0000-0001-5303-1503
Aleid G Leehuis http://orcid.org/0000-0002-4414-9451
Marjita J Jinken http://orcid.org/0000-0002-6589-9788
Anneloes L van Baar http://orcid.org/0000-0002-3447-8836
Maarten van Wely http://orcid.org/0000-0001-9336-6033
Rebecca C Painter http://orcid.org/0000-0001-9336-6033
Jaap Oosterlaan http://orcid.org/0000-0002-0218-5630

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