

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

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To cite: Landman AJEMC, van Limburg Stirum EVJ, van 't Hooft J, *et al.* Long-term outcomes following antenatal exposure to low-dose aspirin: study protocol for the 4-year follow-up of the APRIL randomised controlled trial. *BMJ Open* 2022;**12**:e060632. doi:10.1136/bmjopen-2021-060632

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2021-060632>).

Received 29 December 2021
Accepted 06 July 2022



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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.

Ethics and dissemination Institutional Review Board approval was obtained from the Medical Research Ethics Committee from Amsterdam Medical Center (no. W20 289#20.325). The results will be published in a peer-reviewed journal and presented at conferences.

Trial registration number The APRIL trial (NTR5675, NL5553; EudraCT number 2015-003220-31) and the APRIL follow-up study (NL8950) are registered in the Dutch trial register. The study is funded by the Amsterdam Reproduction & Development research institute.

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.¹ Furthermore, aspirin has anti-inflammatory properties, which may reduce fetal brain injury caused by maternal inflammation.^{8–11}

An observational cohort study of high-risk pregnancies embedded in the French EPIPAGE 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.¹² The Danish MOBAND cohort including 185 617 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.¹³ 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.^{14 15} 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.¹⁶ 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.^{17 18} 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.¹⁹ 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.²⁰ The median gestational age at birth of children was 38⁺¹ weeks (IQR 37⁺¹–39⁺¹) in the aspirin group and 38⁺¹ weeks (IQR 37⁺⁰–39⁺⁰) in the placebo group. Mean birth weight was 3102 g (\pm SD 648) in the aspirin group and 3126 g (\pm SD 678) in the placebo group. A detailed description of the methods and results can be found in the published protocol and trial results.^{19 20}

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.zorgevaluatienederland.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-registration-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.²¹

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

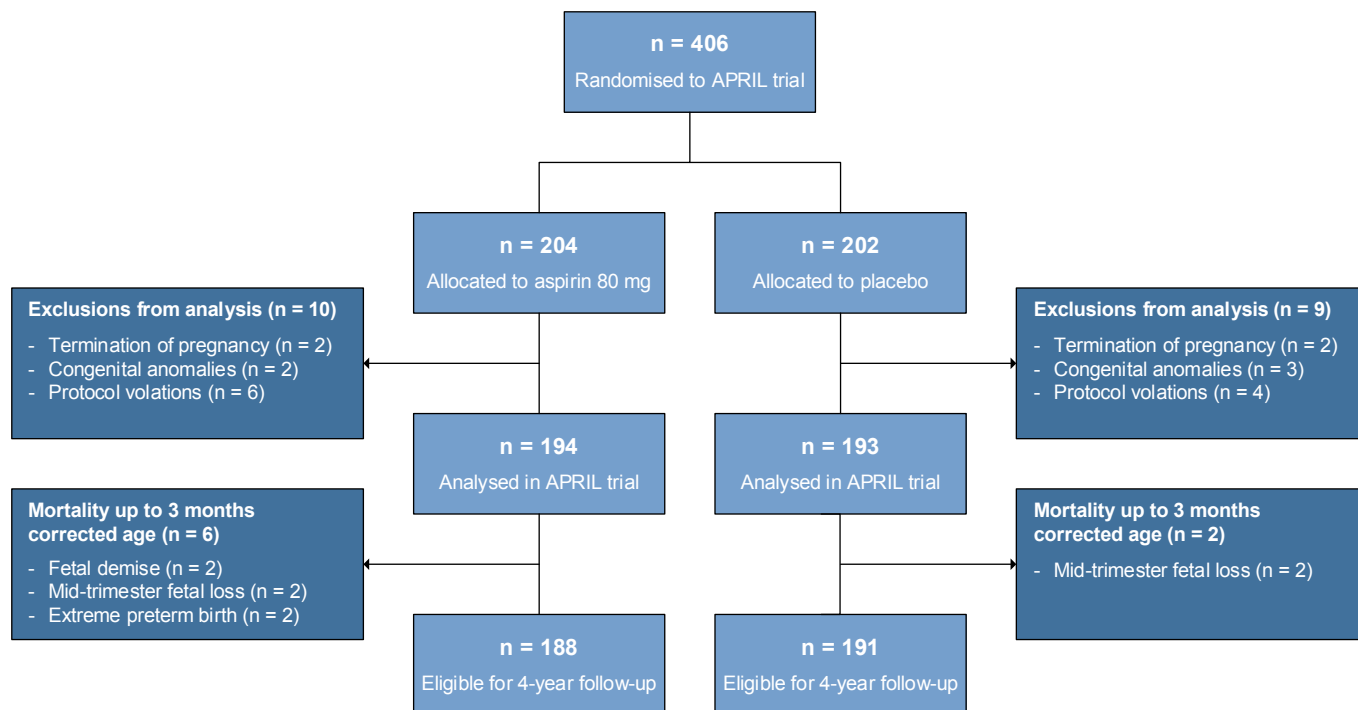


Figure 1 Flow diagram of participants eligible for follow-up.

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.²² We will use a validated Dutch translation of the third edition of the 48-month ASQ (range 3.75–4.25 years).²³ 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 questionnaire 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.²³ The manual advises immediate referral for further evaluation in case of an abnormal score.²²

Strength and Difficulties Questionnaire

The Strengths and Difficulties Questionnaire (SDQ) assesses behavioural, emotional and social functioning as rated by parents.²⁴ 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.^{25–27} A mildly abnormal score is defined as a score > 80 th centile (Total Difficulties Score 11–14 at 4–7 years) and an abnormal score is defined as a score > 90 th 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 > 90 th 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.^{25 26}

Table 1 Overview of outcomes, tools and definitions

Outcome	Tool	Definition	Unit of measurement
(Neuro)development	Ages and Stages Questionnaire	Total problem score	Mean (SD)
		Five domains: <ul style="list-style-type: none"> ▶ Communication ▶ Gross motor ▶ Fine motor ▶ Problem solving ▶ Personal social 	Mean (SD) Mildly abnormal: ≥1 and <2 SD in one domain below mean Abnormal: ≥2 SD in any domain or multiple domains <1 SD below mean
Behaviour	Strength and Difficulties Questionnaire	Total Difficulties Score	Mean (SD) Mildly abnormal: >80th centile below mean Abnormal: >90th centile below mean
		Five subscales: <ul style="list-style-type: none"> ▶ Conduct problems ▶ Emotional symptoms ▶ Hyperactivity ▶ Peer relationships ▶ Prosocial behaviour 	Mean (SD)
		Subscales:* <ul style="list-style-type: none"> ▶ Emotional problem score ▶ Conduct problem score 	Abnormal: >90th centile
Mortality	Medical records, Dutch population register	Perinatal death and child death up to 4 years of age	Number (%) All randomised children as the denominator
General health and sociodemographic information	General health and sociodemographic information	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	Number (%) Follow-up population as the denominator
Growth	Growth book from Child Healthcare Centres	<ul style="list-style-type: none"> ▶ Height of child ▶ Height of biological parents for calculation of target height 	Mean (SD) Abnormal: 1.6 SDS above or below target height range
		BMI (kg/m ²)	Mean (SD) Abnormal: <ul style="list-style-type: none"> ▶ Underweight ▶ Overweight ▶ Obesity
Composite of mortality and abnormal outcome	Tools as described above	Composite of: <ol style="list-style-type: none"> 1. Perinatal death and child death up to 4 years corrected age 2. Abnormal (neuro)development 3. Problem behaviour 	Components as defined above

*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

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.^{28–30} 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).^{31–34} 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 underweight, overweight 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, >80 th 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 >90 th 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, $\alpha=0.05$ and $\beta=0.2$) 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 3.0 a 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 3.0 a 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, χ^2 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 $\leq 20\%$, 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, χ^2 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 $\geq 80\%$ 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.
3. Preterm born children < 37 weeks of gestation versus children born ≥ 37 weeks.
4. Small-for-gestational-age children < 10 th centile versus children ≥ 10 th centile at birth.
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#20.325). 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/caretakers 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

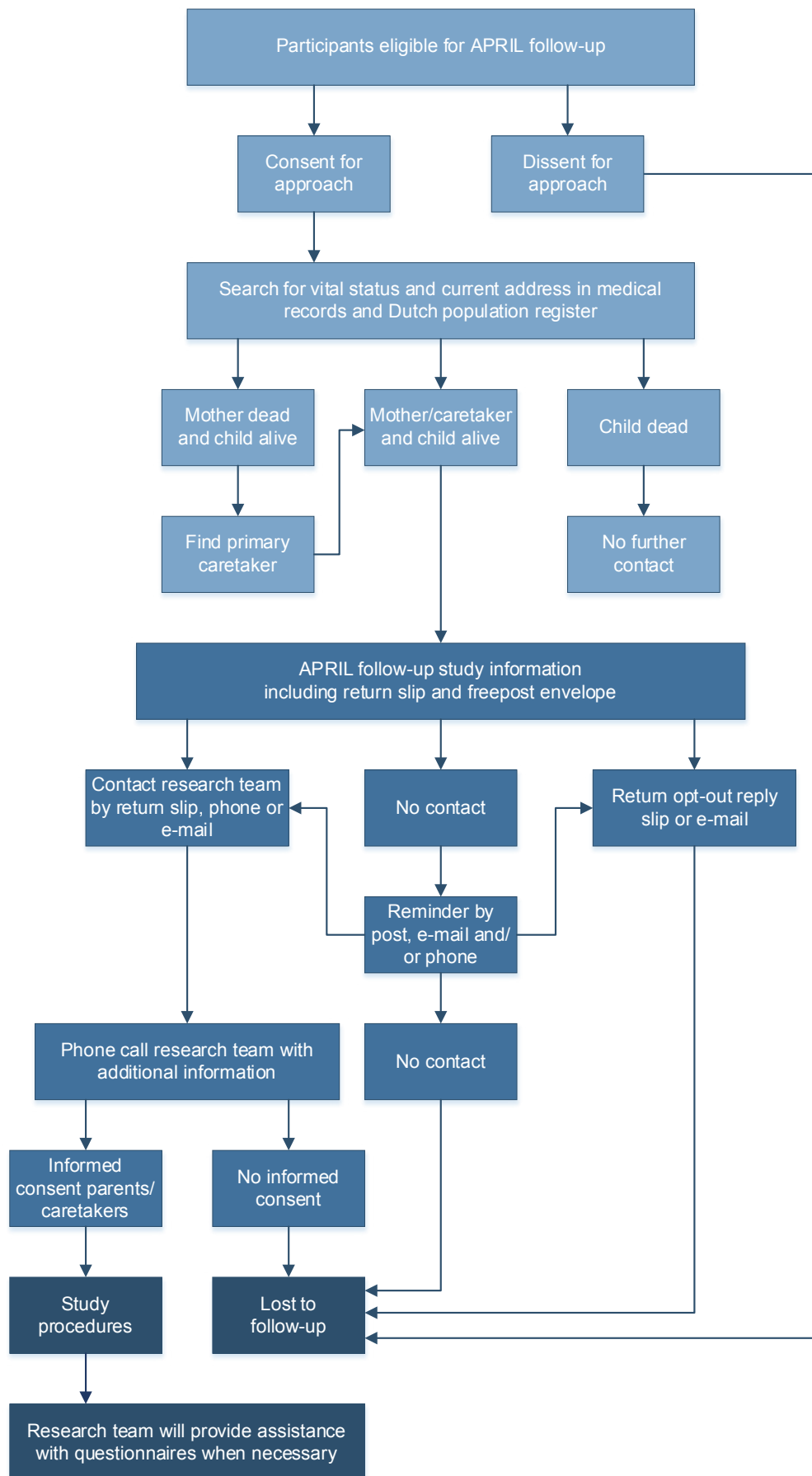


Figure 2 Tracing and contact mechanisms of eligible participants.

(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.³⁸ Nevertheless, only a minority of RCTs evaluating perinatal interventions perform long-term follow-up.³⁹ Long-term neurodevelopmental morbidity is one of the core outcomes of studies evaluating the prevention of preterm birth.⁴⁰ 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.^{39 41–43} 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.⁴⁴

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).^{45 46} 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 (NCT04888377).² 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.

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Acknowledgements We would like to thank the participants of the study, the research nurses and research midwives from the Dutch Consortium for Healthcare Evaluation and Research in Obstetrics and Gynaecology (NVOG Consortium), the staff from the Dutch Consortium Trialbureau and the members of the APRIL study group: CJM de Groot, BW Mol, L Visser, TAJ Nijman, MAC Hemels, JOEH van Laar, DNM Papatsonis, MN Bekker, J van Drongelen, MG van Pampus, M Sueters, DP van der Ham, JM Sikkema, JJ Zwart, AJM Huisjes, ME van Huizen, G Kleiverda, J Boon, MTM Franssen, W Hermes, H Visser, KC Vollebregt, EMA Boormans, HA Bremer, E Tuinman, J Langenveld, F van der Made, RJP Rijnders, HAAM van Vliet, LM Freeman, WM Moninckx, J Blaauw, I Krabbendam, R van de Laar, MFG Verberg and HCJ Scheepers. We also thank the Dutch association for parents of incubator children and the mothers who participated in the focus groups for their contribution.

Contributors All authors are members of the APRIL follow-up study group and were involved in the conception and design of the study. AL, JvH, MADb and MAO are grant holders and planned this follow-up. AL, EVJvLS, JvH, MADb and MAO drafted the manuscript. AGvW-L, MJJF, AvB, TJR, AR, MvW, JO, RC and EP critically reviewed the study proposal and provided scientific advice. EVJvLS is coordinating the study and will perform the analyses under supervision of MvW. Final data interpretation will be done by EVJvLS, JvH, MAO and MADb. All authors approved the final manuscript.

Funding This work was supported by Amsterdam Reproduction & Development (AR&D) research institute (<https://www.amsterdamumc.org/en/research/institutes/amsterdam-reproduction-development.htm>). AR&D has no influence on study design, data collection, management, analysis, and interpretation of data, writing of the report and the decision to submit the report for publication. They do not have ultimate authority over any of these activities.

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES

- Duley L, Meher S, Hunter KE, *et al*. Antiplatelet agents for preventing pre-eclampsia and its complications. *Cochrane Database Syst Rev* 2019;2019.
- Hoffman MK, Goudar SS, Kodkany BS, *et al*. Low-dose aspirin for the prevention of preterm delivery in nulliparous women with a singleton pregnancy (aspirin): a randomised, double-blind, placebo-controlled trial. *The Lancet* 2020;395:285–93.
- National Institute for Health and Care Excellence. Hypertension in pregnancy: diagnosis and management (NICE guideline 133, 2011. Available: <https://www.nice.org.uk/guidance/ng133>
- Ayala NK, Rouse DJ. A Nudge toward universal aspirin for preeclampsia prevention. *Obstet Gynecol* 2019;133:725–8.
- Jacobson RL, Brewer A, Eis A, *et al*. Transfer of aspirin across the perfused human placental cotyledon. *Am J Obstet Gynecol* 1991;165:939–44.
- Levy G, Garrettson LK. Kinetics of salicylate elimination by newborn infants of mothers who ingested aspirin before delivery. *Pediatrics* 1974;53:201–10.
- Levy G, Procknal JA, Garrettson LK. Distribution of salicylate between neonatal and maternal serum at diffusion equilibrium. *Clinical pharmacology and therapeutics* 1975;18:210–4.
- Degos V, Favrais G, Kaindl AM, *et al*. Inflammation processes in perinatal brain damage. *J Neural Transm* 2010;117:1009–17.
- Hagberg H, Gressens P, Mallard C. Inflammation during fetal and neonatal life: implications for neurologic and neuropsychiatric disease in children and adults. *Ann Neurol* 2012;71:444–57.
- Hagberg H, Mallard C, Ferrero DM, *et al*. The role of inflammation in perinatal brain injury. *Nat Rev Neurol* 2015;11:192–208.
- Shiow LR, Favrais G, Schirmer L, *et al*. Reactive astrocyte COX2-PGE2 production inhibits oligodendrocyte maturation in neonatal white matter injury. *Glia* 2017;65:2024–37.
- Marret Stéphane, Marchand L, Kaminski M, *et al*. Prenatal low-dose aspirin and neurobehavioral outcomes of children born very preterm. *Pediatrics* 2010;125:e29–34.
- Petersen TG, Liew Z, Andersen A-MN, *et al*. Use of paracetamol, ibuprofen or aspirin in pregnancy and risk of cerebral palsy in the child. *Int J Epidemiol* 2018;47:121–30.
- Chen Y, Zhao D, Wang B, *et al*. Association of intrauterine exposure to aspirin and blood pressure at 7 years of age: a secondary analysis. *BJOG* 2019;126:599–607.
- Chu S, Huang L, Bao Y, *et al*. In utero exposure to aspirin and risk of asthma in childhood. *Epidemiology* 2016;27:726–31.
- Landman AJEMC, van Limburg Stirum EVJ, de Boer MA, *et al*. 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. *Eur J Obstet Gynecol Reprod Biol* 2021;267:213–20.
- CLASP Collaborative Group CLASP Coordinating Centre, Radcliffe Infirmary, Oxford. Low dose aspirin in pregnancy and early childhood development: follow up of the Collaborative low dose aspirin study in pregnancy. *BJOG: An International Journal of Obstetrics & Gynaecology* 1995;102:861–8.
- Parazzini F, Bortolus R, Chatenoud L, *et al*. Follow-up of children in the Italian study of aspirin in pregnancy. *The Lancet* 1994;343:1235.
- Visser L, de Boer MA, de Groot CJM, *et al*. Low dose aspirin in the prevention of recurrent spontaneous preterm labour – the April study: a multicenter randomized placebo controlled trial. *BMC Pregnancy Childbirth* 2017;17:223.
- AJEMC L, De Boer MA, Visser L. Evaluation of low-dose aspirin for the prevention of recurrent spontaneous preterm labour (the April study): a multicentre, randomised, double-blinded, placebo-controlled trial. *PLoS Med* 2021.
- Chan A-W, Tetzlaff JM, Altman DG, *et al*. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med* 2013;158:200–7.
- Squires JBD. Ages & stages questionnaires®. In: (ASQ®-3): a Parent-Completed child monitoring system. 3rd edn. Baltimore: Brookes Publishing Co., Inc, 2009.
- Kerstjens JM, Bos AF, ten Vergert EMJ, *et al*. Support for the global feasibility of the ages and stages questionnaire as developmental screener. *Early Hum Dev* 2009;85:443–7.
- Goodman R. The strengths and difficulties questionnaire: a research note. *J Child Psychol Psychiatry* 1997;38:581–6.
- Stone LL, Janssens JMAM, Vermulst AA, *et al*. The strengths and difficulties questionnaire: psychometric properties of the parent and teacher version in children aged 4–7. *BMC Psychol* 2015;3:4.
- TheunissenMHCdWM, van Grieken A, Mieloo C. *Handleiding voor Het gebruik van de strengths and difficulties questionnaire binnen de Jeugdgezondheidszorg*. TNO: Leiden, 2016.
- Maurice-Stam H, Haverman L, Splinter A, *et al*. Dutch norms for the Strengths and Difficulties Questionnaire (SDQ) – parent form for children aged 2–18 years. *Health Qual Life Outcomes* 2018;16:123.
- Cuijpers CJJ, van 't Hooft J, Schneeberger C. Progesterone for preterm birth prevention in women with short cervical length: outcomes in children at 2 years. *Ultrasound Obstet Gynecol* 2020 (published Online First: 2020/09/23).
- de Ruigh AA, Simons NE, van 't Hooft J. Child outcomes after amniocentesis compared with no intervention in women with second-trimester rupture of membranes: a long-term follow-up study of the PROMEXIL-III trial. *BJOG* 2020 (published Online First: 2020/01/28).
- Simons NE, Beek C, Lee JH, *et al*. Child outcomes after placement of a cervical pessary in women with a multiple pregnancy: a 4-year follow-up of the ProTWIN trial. *Acta Obstet Gynecol Scand* 2019;98:1292–300.
- Netherlands Organisation for applied scientific research (TNO). JGZ-Richtlijn Lengtegroei [Dutch], 2019. Available: <https://www.ncj.nl/richtlijnen/alle-richtlijnen/richtlijn/lengtegroei-2019> [Accessed Cited 2021 Mar 24].
- de Wilde JA, van Dommelen P, van Buuren S, *et al*. Height of South Asian children in the Netherlands aged 0–20 years: secular trends and comparisons with current Asian Indian, Dutch and who references. *Ann Hum Biol* 2015;42:38–44.
- Schönbeck Y, Talma H, van Dommelen P, *et al*. The world's tallest nation has stopped growing taller: the height of Dutch children from 1955 to 2009. *Pediatr Res* 2013;73:371–7.
- Schönbeck Y, van Dommelen P, HiraSing RA, *et al*. Trend in height of Turkish and Moroccan children living in the Netherlands. *PLoS One* 2015;10:e0124686.
- Cole TJ *et al*. Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ* 2000;320:1240–3.
- Cole TJ, Flegal KM, Nicholls D, *et al*. Body mass index cut offs to define thinness in children and adolescents: international survey. *BMJ* 2007;335:194.
- de Laat SAA, Essink-Bot M-L, van Wassenaer-Leemhuis AG, *et al*. Effect of socioeconomic status on psychosocial problems in 5- to 6-year-old preterm- and term-born children: the ABCD study. *Eur Child Adolesc Psychiatry* 2016;25:757–67.
- Marlow N, Doyle LW, Anderson P, *et al*. Assessment of long-term neurodevelopmental outcome following trials of medicinal products in newborn infants. *Pediatr Res* 2019;86:567–72.
- Teune MJ, van Wassenaer AG, Malin GL, *et al*. Long-term child follow-up after large obstetric randomised controlled trials for the evaluation of perinatal interventions: a systematic review of the literature. *BJOG* 2013;120:15–22.
- van 't Hooft J, Duffy JMN, Daly M, *et al*. A core outcome set for evaluation of interventions to prevent preterm birth. *Obstet Gynecol* 2016;127:49–58.



- 41 Khan K, O'Donovan P. The CROWN initiative: journal editors invite researchers to develop core outcomes in women's health. *BMC Pregnancy Childbirth* 2014;14:199.
- 42 Olmedo-Requena R, Amezcua-Prieto C, Al Wattar BH, *et al.* Variations in long-term outcome reporting among offspring followed up after lifestyle interventions in pregnancy: a systematic review. *J Perinat Med* 2020;48:89–95.
- 43 Williamson PR, Altman DG, Blazeby JM, *et al.* The comet (core outcome measures in effectiveness trials) initiative. *Trials* 2011;12:A70.
- 44 National Institute for Health and Care Excellence. Developmental follow-up of children and young people born preterm quality standard NICE, 2011. NICE Quality Standard [QS169]. Available: <https://www.nice.org.uk/guidance/qs169> [Accessed 24 Jun 2021].
- 45 Kutlesic V, Brewinski Isaacs M, Freund LS, *et al.* Executive summary: research gaps at the intersection of pediatric neurodevelopment, nutrition, and inflammation in low-resource settings. *Pediatrics* 2017;139:S1–11.
- 46 Suchdev PS, Boivin MJ, Forsyth BW, *et al.* Assessment of neurodevelopment, nutrition, and inflammation from fetal life to adolescence in low-resource settings. *Pediatrics* 2017;139:S23–37.