



# BMJ Open Prenatal iodine supplementation and early childhood neurodevelopment: the PoppiE trial – study protocol for a multicentre randomised controlled trial

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## ABSTRACT

**Introduction** Observational studies suggest both low and high iodine intakes in pregnancy are associated with poorer neurodevelopmental outcomes in children. This raises concern that current universal iodine supplement recommendations for pregnant women in populations considered to be iodine sufficient may negatively impact child neurodevelopment. We aim to determine the effect of reducing iodine intake from supplements for women who have adequate iodine intake from food on the cognitive development of children at 24 months of age.

**Methods and analysis** A multicentre, randomised, controlled, clinician, researcher and participant blinded trial with two parallel groups. Using a hybrid decentralised clinical trial model, 754 women (377 per group) less than 13 weeks' gestation with an iodine intake of  $\geq 165 \mu\text{g/day}$  from food will be randomised to receive either a low iodine (20  $\mu\text{g/day}$ ) multivitamin and mineral supplement or an identical supplement containing 200  $\mu\text{g/day}$  (amount commonly used in prenatal supplements in Australia), from enrolment until delivery. The primary outcome is the developmental quotient of infants at 24 months of age assessed with the Cognitive Scale of the Bayley Scales of Infant Development, fourth edition. Secondary outcomes include infant language and motor development; behavioural and emotional development; maternal and infant clinical outcomes and health service utilisation of children. Cognitive scores will be compared between groups using linear regression, with adjustment for location of enrolment and the treatment effect described as a mean difference with 95% CI.

**Ethics and dissemination** Ethical approval has been granted from the Women's and Children's Health Network Research Ethics Committee (HREC/17/WCHN/187). The results of this trial will be presented at scientific conferences and published in peer-reviewed journals.

**Trial registration number** NCT04586348.

## INTRODUCTION

Inadequate iodine intake during pregnancy can affect the synthesis of thyroid hormones

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This is the first randomised controlled trial to investigate childhood neurodevelopmental outcomes following reduced prenatal iodine supplementation in an iodine sufficient population.
- ⇒ This trial is being conducted in seven different areas of Australia ensuring results are representative of the general pregnant population.
- ⇒ Utilisation of a decentralised trial design including online digital marking campaigns for screening and recruitment will optimise enrolment and facilitate sample size attainment.
- ⇒ The selection of our iodine sufficient population is based on maternal reported iodine intake from food for ease of screening and because urinary biomarkers are not an accurate measure of individual intake.
- ⇒ Non-compliance with supplementation and/or lost to follow-up at the 24-month primary outcome assessment may contribute to risk of bias.

and impair fetal brain development.<sup>1</sup> Severe iodine deficiency leads to profound intellectual disability in the child and is the most common cause of preventable brain damage globally.<sup>2</sup> Cohort studies from the late 1990s and early 2000s suggested that mild-to-moderate iodine deficiency was also associated with poorer developmental outcomes in the children.<sup>3–6</sup> In 2009 following results of a national survey indicating that mild-to-moderate iodine deficiency had re-emerged in parts of Australia,<sup>7</sup> the Australian Government mandated the addition of iodine to salt used in bread making to increase population intake. In addition, the Australian National Health and Medical Research Council recommended that pregnant women take an iodine supplement containing 150  $\mu\text{g/day}$ . This dose was chosen to make up the difference



between the average iodine intake from food and the recommended iodine intake (220 µg/day) for pregnant women in Australia. Since this time, several cohort studies have suggested that excess iodine intake during pregnancy may be associated with poorer developmental outcomes in the offspring.<sup>8–10</sup> Our 2018 cohort study including 800 mother–infant pairs showed that maternal iodine intake at both the lowest and highest quartiles is associated with lower cognitive and language scores and higher odds of cognitive delay compared with infants of mothers with an iodine intake in the second quartile.<sup>11</sup> Further analyses indicated that the inflection points that drove the association between lower iodine intake in pregnancy and poorer childhood neurodevelopmental scores was around 185 µg/day with the upper limit for similarly poor neurodevelopment being 350 µg/day.<sup>11</sup> Since 2010, one adequately powered randomised controlled trial of iodine supplementation and child neurodevelopment has been conducted in India and Thailand, areas with mild to moderate iodine deficiency. No differences in neurodevelopment at 5–6 years of age were reported in children whose mothers' received iodine versus placebo during pregnancy.<sup>12</sup>

Australia is one of few countries to implement a combined policy of iodine fortification and supplementation. Furthermore, many prenatal micronutrient supplements provide more than the recommended 150 µg/day, with common supplements providing 200–220 µg/day iodine. Current evidence suggests that the margin of safety between iodine deficiency and excess in pregnancy and child neurodevelopmental outcomes is narrower than once thought, and hence randomised controlled trial evidence in iodine sufficient populations is essential. Our trial will only include women known to have sufficient iodine intake from food alone. We aim to provide evidence as to whether current iodine supplementation practices during pregnancy should continue or a more targeted approach is required based on individual iodine intake.

### Hypotheses

We hypothesise that reducing iodine intake from prenatal supplements for women with sufficient iodine intake from food will improve the cognitive scores of children at 24 months of age compared with standard recommended supplementation.

## METHODS AND ANALYSIS

### Trial design

The Prenatal Iodine Supplementation and Early Childhood Neurodevelopment (PoppiE) trial is a randomised, controlled, clinician, researcher and participant/family blinded, multicentre trial with two parallel groups.

### Participating centres

The Sponsoring Institution and Trial Coordinating Centre is the South Australian Health and Medical

Research Institute (SAHMRI) based at the Women's and Children's Hospital. The study will take place in seven locations in Australia (South Australia, Victoria, New South Wales, Queensland, Western Australia, Australian Capital Territory and Tasmania) using a hybrid, decentralised clinical trial design. All screening, enrolment, randomisation and study visits up until the 24-month assessment are managed remotely by the coordinating centre (SAHMRI). The following centres will participate in the completion of the 24-month infant neurodevelopmental assessment; Women's and Children's Hospital and Flinders Medical Centre, South Australia; Royal Women's Hospital, Victoria; Mater Mothers' Hospital, Queensland; Royal North Shore Hospital, New South Wales; Telethon Kids Institute, Western Australia. Twenty-four-month assessments in locations without a participating centre will be administered by trained personnel sourced and trained by the coordinating centre.

### Study population

Pregnant women over the age of 16 years who are 13 weeks' gestation or less ( $\leq 13$  weeks).

### Eligibility criteria

#### Inclusion criteria

- ▶  $\leq 13$  weeks' gestation.
- ▶ Consume greater than 165 µg/day of iodine from food alone based on our validated Iodine Specific Food Frequency Questionnaire (I-FFQ).<sup>13</sup>
- ▶ English as the main language spoken at home (neurodevelopmental assessment across language barriers is significantly limited with marked and unwanted variability).

#### Exclusion criteria

- ▶ Current treatment for thyroid disease (eg, taking thyroxine) or had all or part of thyroid gland removed.
- ▶ Previous child diagnosed with thyroid dysfunction.
- ▶ Carrying a fetus with a known or suspected congenital abnormality likely to adversely affect neurodevelopment.

### Study treatments

Participants will be randomised to receive a prenatal multivitamin and mineral supplement (PreNuro) with a reduced amount of iodine (20 µg/day—intervention) or a standard prenatal multivitamin and mineral supplement with 200 µg/day of iodine (control). A multivitamin and mineral supplement was used as there are no prenatal supplements available in Australia that contain iodine only. Moreover, most women in Australia take a supplement that contains multivitamins and minerals throughout pregnancy; women in our consumer group indicated that they would give up iodine but did not to stop taking other vitamins and minerals. The control supplement was designed to match the amount of iodine contained in most commonly used prenatal multivitamin and mineral supplements in Australia. The amount of other minerals and vitamins in the study supplements are

formulated to approximate the current leading brands of prenatal multivitamin and mineral supplements. Participants will be instructed to take one supplement per day orally, from randomisation ( $\leq 13$  weeks' gestation) until delivery of their baby. Study supplements are manufactured and packaged in a licensed facility in accordance with the Code of Good Manufacturing Practice for Medicinal Products and have been donated to the trial by Factors Group of Nutritional Companies Inc, Burnaby, British Columbia, Canada. The supplement labelling includes an individual product identifier, batch number, expiry date and the statement 'for clinical trial use only'. Supplement supplies are maintained by a Central Depot and issued to women via express post. Dispensing of study product is recorded in a Researcher Electronic Data Capture (REDCap) database<sup>14</sup> to ensure an accurate record of the dispensing of study product.

### Monitoring adherence to study treatment

SAHMRI Research Personnel will maintain regular contact with participating women by automated short

message service (SMS), email and telephone to monitor and encourage supplement adherence and compliance with the study protocol (table 1).

At each contact, women will be asked if they have missed any supplements in the past week and if so, how many have been missed. Women will be supplied with excess supplements and asked to count and relay the number of unused supplements (at birth) during the postnatal telephone Call. A mid-pregnancy urine sample will also be collected to determine urinary iodine concentration (UIC) between intervention and control groups. A quarterly newsletter will be emailed to participants to keep them informed of study progress and optimise retention. All clinical care for women involved in this trial will be undertaken by her designated pregnancy care provider.

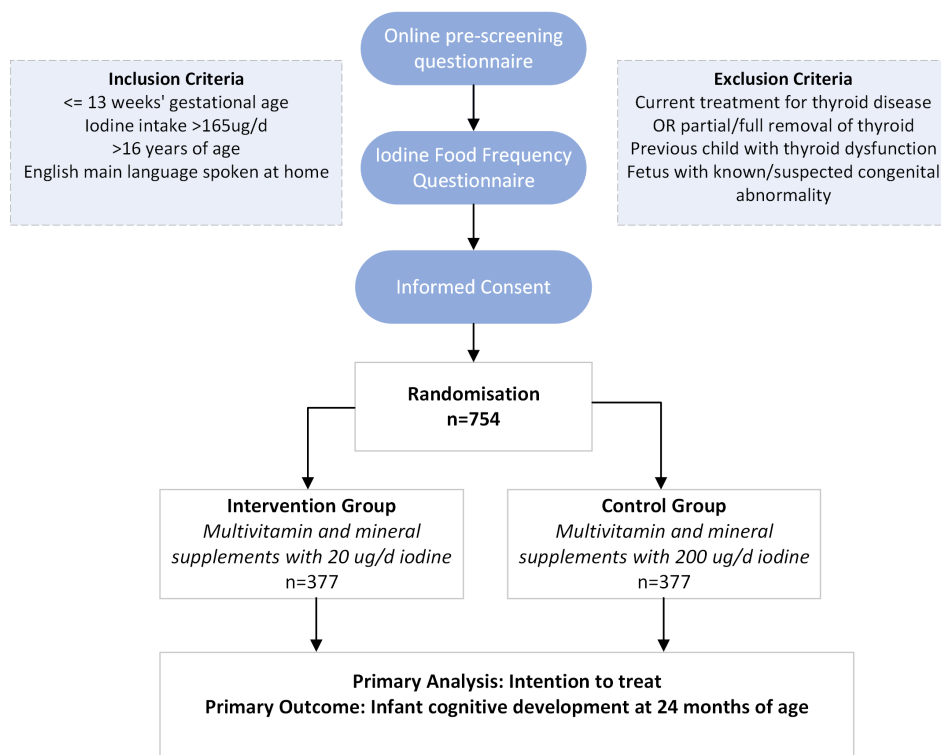
### Participant recruitment and study timeline

Enrolment of women commenced in January 2021 and is expected to complete by October 2023. Developmental assessments of children at 24 months of age will commence in July 2023 and are expected to be completed by September

**Table 1** Schedule of visits

Event	Maternal visits				Infant follow-up visits		
	Enrolment	7 days postenrolment, 16 weeks, 22 weeks, 36 weeks GA	28 weeks GA	42 weeks PMA	3 months, 12 months	6 months, 18 months	24 months
	Phone call	Phone call, SMS or email	Phone call	Phone call	SMS or email	Phone call	Clinic visit
Informed consent	X						
Randomisation/allocation	X						
Maternal demographics	X						
Pregnancy data	X						
Maternal delivery data				X			
Contact details	X	X	X	X	X	X	X
Supplement adherence		X	X	X			
Adverse events		X	X	X			X
Serious adverse events		X	X	X		X	X
I-FFQ	X		X				
UIC	X		X				
Infant birth data				X			
Infant anthropometrics				X			X
Infant feeding				X	X	X	X
Infant supplementation				X	X	X	X
Childcare attendance							X
Bayley-IV							X
ITSEA							X
HSQ							X
MBS/PBS consent							X

Bayley-IV, Bayley Scales of Infant Development, fourth edition; GA, gestational age; HSQ, Home Screening Questionnaire; I-FFQ, iodine specific food frequency questionnaire; ITSEA, Infant Toddler Social Emotional Assessment; MBS, Medicare Benefits Scheme; PBS, Pharmaceutical Benefits Scheme; PMA, postmenstrual age; SMS, short message service; UIC, urinary iodine concentration.



**Figure 1** Participant flow throughout the study.

2026. Women will be recruited using a digital marketing campaign and online prescreening survey. Advertising and recruitment of women may also occur in antenatal clinics at participating centres, GP Clinics and/or local public or private healthcare settings or community events. Women who pass initial obstetric and clinical inclusion and exclusion criteria are invited to complete a validated I-FFQ to determine their iodine intake<sup>13</sup> (figure 1). Women with an estimated iodine intake of >165 µg/day from food alone are considered eligible for the trial and are invited to proceed to a phone screening appointment with a member of the SAHMRI Research team. Once eligibility has been confirmed, study staff will conduct the informed consent discussion and email or text the participant information sheet which will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation and advised that they are free to decline any aspect of the study or withdraw from the study at any time without prejudice. Informed consent will be obtained from each participant and documented using electronic signature via REDCap e-consent module. A copy of the signed consent form will be provided to women and filed in the REDCap repository.

At enrolment women will be asked to cease any iodine containing supplements at enrolment and for the length of the study intervention period (enrolment to delivery). The following clinical and demographic information will be collected to describe characteristics of the sample, determine baseline differences between the groups and for possible inclusion as covariates for adjustment in the (preplanned) analyses; proposed delivery location, expected date of delivery, self-reported cultural ethnicity,

gravidity, parity, age, preconception and current supplement use, weight, height, maternal highest level of education, occupation and maternal smoking status. A baseline median UIC by location of enrolment will be determined to confirm state differences in iodine status that have been previously identified and to determine balance between the two treatment groups.

Prenatal study visits will be completed by phone in addition to brief SMS surveys. At 2 weeks post women's estimated due date (42 weeks' post menstrual age), women will be contacted by telephone for the postnatal study visit and collection of birth details. During the infant follow-up phase, families will be contacted 6 monthly by phone and SMS survey (table 1). Families will bring their infant to a clinic appointment at 24 months of age for the Bayley Scales of Infant Development, fourth edition (Bayley-IV) assessment. Where necessary, families will be offered appointments at the family's home. Parents/caregivers will receive a report with the results of the assessment and will be offered the opportunity to discuss the results with a study psychologist. If the test reveals a possible disability such as cognitive impairment, or if the caregiver is concerned about the child's performance or abilities, the family will be offered a referral to appropriate services.

## Outcomes and measures

### Primary outcome

The primary outcome is the infant developmental quotient (DQ) at 24 months of age as assessed with the Cognitive Scale of the Bayley-IV. The Bayley-IV is a widely used test of global development for children up to 42 months of age. The Cognitive Scale is administered by



a psychologist, trained health professional or trained technician, and evaluates sensorimotor development, exploration, manipulation, object relatedness, concept formation, memory and simple problem-solving. All raw scores are age-standardised to scale scores with a mean of 100 and SD of 15. Standardised scores range from 50 to 150 and can be classified as within the normal range of development (85–115), delayed performance (<85) or accelerated development (>115).

### Secondary outcomes

#### *Developmental outcomes*

Language and motor scores from the Bayley-IV will be included as secondary outcomes. The Language Scale is a composite of receptive communication (verbal comprehension, vocabulary) and expressive communication (babbling, gesturing and utterances) abilities. The Motor Scale evaluates both gross (big, large movements such as rolling over or walking) and fine (small movements and manipulations using small muscles, such as the fingers or lips) motor functioning.

Behavioural and emotional development of infants will be assessed using The Infant Toddler Social Emotional Assessment (ITSEA). The ITSEA will be completed by parents at the time of the Bayley-IV assessment. The ITSEA measures four domains (externalising, internalising, dysregulation and competence) and is the most comprehensive measure of a variety of social-emotional and behavioural problems as well as competencies, and is age standardised for young children.<sup>15</sup> ITSEA scores for each domain are age-standardised to a mean of 50 (SD 10) and can be categorised as typical, or as 'of concern' indicating a possible behavioural or emotional problem warranting further follow-up and investigation.

#### *Infant health outcomes*

Secondary infant outcomes will be collected via parental report and information recorded in the infant's 'Health and Development Record' booklet provided to parents by the birthing hospital. A photograph of this record will be sought at the postnatal telephone call and uploaded to the study database. Infant outcomes include length of gestation; birth weight, length and head circumference; admission to special care nursery; infant feeding (breast, formula, commencement of solids) and supplement use; height, weight and head circumference at 24 months. Thyroid-stimulating hormone levels will be obtained from routine neonatal screening tests (South Australian participants only).

#### *Maternal outcomes*

Maternal outcomes will include pregnancy complications (pre-eclampsia, gestational diabetes, postpartum haemorrhage), initiation of labour (spontaneous or induction) and mode of delivery (vaginal/caesarean).

#### *Background information and characteristics*

Background information will be collected at enrolment to describe the clinical and demographic characteristics

of women and will include self-reported cultural ethnicity, gravida, parity, age, preconception and current supplement use, weight, height, maternal highest level of education, occupation, maternal smoking status. Stimulation within the home environment has an important role in the cognitive, social and emotional developmental outcomes of infants and will be assessed at 24 months of age with a revised version of the Home Screening Questionnaire.<sup>16</sup>

#### *Safety outcomes*

Safety outcomes including side effects and tolerability of supplements will be assessed through routine data collection by maternal report. Serious adverse events will be assessed and include major congenital anomalies; fetal, infant or maternal mortality; maternal admission to an intensive care unit during the intervention period and infant admission to intensive care (birth to study completion).

#### *Economic evaluation analysis*

Taking a health system perspective, a within-trial cost-effectiveness analysis will be conducted. In addition, cost of interventions, direct costs associated with health service utilisation of children up to 3 years of age will be assessed through data linkage of the Australian Government Medicare Benefits Schedule (MBS) and Pharmaceutical Benefits Scheme (PBS). The incremental cost-effectiveness ratio will be reported with respect to differences in the clinical outcomes. A bootstrapping approach will be applied to represent the uncertainty around mean estimates and deterministic sensitivity analysis undertaken to test the sensitivity of the results to variation in inputs into economic evaluation. Health service utilisation of children up to 3 years of age will be assessed through data linkage of the Australian Government MBS and PBS to evaluate the cost-effectiveness of the intervention. This analysis will be reported after publication of the primary and secondary outcome comparisons.

#### *Patient and public involvement*

Members of the public were involved at several stages of the trial, including the design, management and conduct of the trial. We received input from our SAHMRI Women and Kids consumer group comprising women with young children. We also consulted with members of the Health Translation South Australia Community Interest Register who been pregnant during the previous 12 months. We carefully assessed the burden of the trial and all participant communication material. We intend to disseminate the main results to trial participants and will seek patient and public involvement in the development of an appropriate method of dissemination.

#### *Sample size*

To detect a mean difference of 4 points in the Cognitive Scale of the Bayley-IV with 90% power (SD=15 points, two-tailed  $\alpha=0.05$ ), a sample size of 297 women per group is required. No adjustment will be made for multiple births in sample size calculations, as the proportion of women

expected to have a multiple birth is just 1.8% in this population and the inclusion of women with a multiple birth will increase the effective sample size for the number of children. Assuming 6% perinatal losses and allowing a further 15% lost to follow-up to 24 months, a total of 754 women (377 per group) will be randomised. A four-point difference in the Cognitive Scale of the Bayley-IV is realistic based on the results of our cohort study<sup>11</sup> and would constitute a difference considered clinically important by developmental paediatricians. Similar effects on DQs have prompted public health authorities to promote strategies to prevent iron deficiency anaemia and remove lead from petrol and paint.<sup>17 18</sup>

### Randomisation

An independent statistician not otherwise involved in the study or data analysis will generate and keep the randomisation schedule. The computer-generated schedule will allocate women to intervention or control groups in the ratio of 1:1 using randomly permuted blocks of varying sizes, with stratification for location of enrolment. Block sizes will not be disclosed to ensure allocation concealment. Randomisations will be performed by approved study staff via a secure web-based randomisation module designed in REDCap. Women will be allocated a random, unique, reidentifiable randomisation identification number (ID). According to their assigned treatment, women will be issued with study supplements labelled with a unique product ID.

### Data management and analysis plan

A purpose-built REDCap database will be used for data capture and workflow management and hosted on secure servers with SAHMRI. Data are collected by trained research personnel and entered directly into REDCap, with logic checks used to ensure data quality, or submitted directly into REDCap by participants via survey. REDCap uses a MySQL database via a secure web interface and includes a complete suite of features to support the Health Insurance Portability and Accountability Act of 1996 compliance, including a full audit trail, user-based privileges and integration with the institutional Lightweight Directory Access Protocol server.<sup>14</sup> A record of all women approached, screened for eligibility and consented will be recorded.

### Statistical analysis methods

All outcomes will be analysed on an intention-to-treat basis according to a prespecified statistical analysis plan. Cognitive scores of the Bayley-IV will be compared between groups using a linear regression model, with adjustment for location of enrolment and using generalised estimating equations with an independence working correlation structure to account for multiple births. The effect of treatment will be described as a mean difference with a 95% CI. Further secondary outcomes will be analysed using linear and logistic regression models for continuous and binary outcomes, respectively, with generalised

estimating equations used for infant-level outcomes to account for multiple births. Planned subgroup analyses of the primary outcome will test for evidence of effect modification by location of enrolment and baseline iodine intake. In all analyses, missing outcome data will be addressed using multiple imputation, performed separately by randomised group using chained equations.

### Economic analysis methods

Economic outcomes will be analysed using generalised linear models fitted to estimate and compare costs between the two study groups. Goodness-of-fit tests including the modified Park, Pregibon link and modified Hosmer and Lemeshow tests will assist in specifying an appropriate functional form for the generalised linear model. The incremental cost-effectiveness ratio will be reported with respect to the primary clinical outcomes including mean differences in cognitive and language scores and the proportion of children with delayed development (scores <85). To handle parameter uncertainty, we will use non-parametric bootstrapping to generate 5000 bootstrap replicates of the cost and outcome variables.

### Data monitoring and safety

The trial coordinating centre will perform ongoing monitoring via weekly reports of participants screened/enrolled/randomised, visits due/overdue/missed, adverse and serious adverse events, product inventory and dispense records, sample collection logs, and participant communication logs. Reports are scrutinised at monthly trial management meetings of the PoppiE Executive Management Team and quarterly trial steering committee meetings involving all trial investigators. An independent data safety and monitoring board (DSMB) comprising an independent obstetrician, neonatologist and biostatistician has been appointed to safeguard the interests of trial participants. The DSMB will conduct annual reviews of recruitment progress, retention, adherence with the intervention, serious adverse events and general study progress. A formal charter has been developed to assist with the running of the DSMB. No interim analyses are planned.

### Ethics and dissemination

This study will be conducted in accordance with the approved version of the Study Protocol and in compliance with the Australian National Statement on Ethical Conduct in Research Involving Humans which builds on the ethical codes of the Declaration of Helsinki and the Principles of International Conference on Harmonisation Good Clinical Practice (as adopted in Australia). All procedures and study materials have been reviewed and approved by the Women's and Children's Health Network Human Research Ethics Committee (HREC/17/WCHN/187), as well as the research governance officers at each collaborating centre. Any change to the protocol or informed consent form that affects the scientific intent, study design, patient safety or may affect

a participant's willingness to continue participation in the study is considered an amendment, and therefore, will be written and filed as an amendment to this protocol and/or informed consent form. All such amendments will be submitted to the HREC, for approval prior to becoming effective.

The primary and secondary objectives will be analysed and reported first without waiting for the health economic or longer-term outcome data linkage and analysis. Study findings will be submitted for peer-reviewed publication and for presentation at appropriate local and international conferences. In addition, study findings will be disseminated to participants through a one-page lay summary. Results will be made available to the wider community through social media avenues and the SAHMRI website. No participants will be identified in the dissemination of study results and data collected will be treated with confidence.

### Access to data

Individual participant data, including data dictionaries, may be shared after deidentification on reasonable request. Proposals to access the data must be scientifically and methodologically sound and must be reviewed and approved by the PoppiE trial steering committee and the Women's and Children's Human Research Ethics Committee. To gain access, data requestors will need to sign a data access agreement. Proposals should be directed to the Chair of the PoppiE Steering Committee, KPB via email (karen.best@sahmri.com).

### Participant and public involvement

The study was supported by a consumer advisory group which provided input to the design of the protocol. A consumer representative from the SAHMRI Women and Kids Consumer Advisory Group partnered with us for the design of the study, informational material to support the intervention and the burden of the intervention from the participant's perspective. We will meet with the consumer representative/s for this trial and the full consumer advisory group on a regular basis for the duration of the study. At the end of the study, the consumer advisory group will be given the opportunity to comment on the findings and contribute to the dissemination plan. Study participants are kept informed about study progress with bimonthly PoppiE participant newsletters.

### Perspectives

This the first randomised controlled trial to examine the effect of prenatal iodine supplementation, for women known to have sufficient iodine intake from food, on early childhood neurodevelopment. The PoppiE trial will provide evidence as to whether current routine iodine supplementation practices during pregnancy should continue or a more targeted approach is required based on individual iodine intake. If the PoppiE trial shows that cognitive and language development of young children is improved by limiting iodine supplementation for

pregnant women with already adequate intakes, this will necessitate rapid action to change the universal recommendation of iodine supplementation for pregnant women. Should we find no differences in childhood neurodevelopment between the randomised groups, this provides the necessary reassurance for pregnant women, health professionals and policy-makers internationally that current policies are not harmful.

### Trial status

The PoppiE trial began on 21 January 2021. As of 23 December 2022, 500 participants have been randomised.

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**Contributors** KPB, TG, JFG and MM conceived the trial and proposed the trial design. TS and EK advised on sample size calculations, trial design and analysis. KPB and TG wrote the first draft of the study protocol, JFG, MM, TS, JC, SJZ, SK, HS, AS, LWD, AJM, TACN, HHAA; RG, DM, EK. SW contributed to refinement of the study protocol, revision of drafts and approval of the final protocol manuscript.

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**Disclaimer** The funder/s have no role in the study design; collection, management, analysis and interpretation of data; writing of the report; and the decision to submit the report for publication and have no authority over any of these activities.

**Competing interests** SW serves as a consultant at InovoBiologic, AB, Canada.



**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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