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<tr>
<td>ABSoC</td>
<td>Access, barriers, and systems of care</td>
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<tr>
<td>AKU</td>
<td>Aga Khan University, Nairobi</td>
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<tr>
<td>CIMT</td>
<td>Carotid intima-media thickness</td>
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<td>CSDH</td>
<td>Commission on Social Determinants of Health</td>
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<tr>
<td>CVD</td>
<td>Cardiovascular disease</td>
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<tr>
<td>DALY</td>
<td>Disability-adjusted life year</td>
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<tr>
<td>DH</td>
<td>District hospital</td>
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<tr>
<td>DOHaD</td>
<td>Developmental origins of health and disease</td>
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<tr>
<td>FGR</td>
<td>Fetal growth restriction</td>
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<tr>
<td>KCL</td>
<td>King’s College London</td>
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<td>London School of Hygiene and Tropical Medicine</td>
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<td>MSU</td>
<td>Midlands State University</td>
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<tr>
<td>MRCG</td>
<td>Medical Research Council Unit, The Gambia, at LSHTM</td>
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<tr>
<td>MUAC</td>
<td>Mid-upper arm circumference</td>
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<td>NCD</td>
<td>Non-communicable disease</td>
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<td>NDST</td>
<td>Neurodevelopmental screening tool</td>
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<tr>
<td>OR</td>
<td>Odds ratio</td>
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<td>PHC</td>
<td>Primary health centre</td>
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<td>PP</td>
<td>Postpartum</td>
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<td>PTB</td>
<td>Preterm birth</td>
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<tr>
<td>PTSD</td>
<td>Post-traumatic stress disorder</td>
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<tr>
<td>PV</td>
<td><em>Per vaginam</em> (vaginal)</td>
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<tr>
<td>RQ</td>
<td>Research question</td>
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<tr>
<td>SDG</td>
<td>Sustainable Development Goal</td>
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<td>SGUL</td>
<td>St George’s, University of London</td>
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<tr>
<td>SOH-D</td>
<td>State of hygiene determinants</td>
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<td>SOH-V</td>
<td>Visual state of hygiene</td>
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<tr>
<td>SOP</td>
<td>Standard operating procedure</td>
</tr>
<tr>
<td>SpO₂</td>
<td>Oxygen saturation (by pulse oximetry)</td>
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<tr>
<td>ToD</td>
<td>Time of disease (as relevant)</td>
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<tr>
<td>TraCer</td>
<td>Transcerebellar diameter gestational age app</td>
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<tr>
<td>UBC</td>
<td>University of British Columbia</td>
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<td>UL</td>
<td>University of Liverpool</td>
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<td>WASH</td>
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<td>WDS</td>
<td>Washington developmental screen</td>
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<td>WHO</td>
<td>World Health Organization</td>
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<td>WP</td>
<td>Work package</td>
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**Preamble**

The by-line for the proposed PRECISE-DYAD project is, “Health trajectories for mums and their children.” Our interest is in determining the pathways to healthy outcomes for mothers and their children following both normal and complicated pregnancies. In this instance, “health,” as defined by the World Health Organization (WHO), is "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity [1]."

DYAD seeks to expand and extend the PRECISE study (PREgnancy Care Integrating translational Science, Everywhere [PRECISEnetwork.org]) of deeply-phenotyped maternal-fetal/newborn dyads to provide insights into the life course of health and disease. The focus of PRECISE-DYAD is to understand the pathways to either healthy longitudinal outcomes following either healthy pregnancies or those complicated by the placental complications of pregnancy, namely pregnancy hypertension, fetal growth restriction (FGR), and stillbirth, and preterm birth (PTB) (Figure 1).

We plan to follow-up dyads in two sub-Saharan African study sites (Gambian (n=2 primary health centres [PHCs] and one district hospital [DH]) and Kenyan (n=2 DHs)). We will follow-up for three years all Gambian and Kenyan PRECISE dyads (both normal and complicated pregnancies).

![Figure 1. The PRECISE-DYAD deep phenotyping of women and children](image-url)
**DYAD Investigator Team**

Each project lead will bring skills to this collaboration that strengthen the research paradigm beyond the PRECISE project from which DYAD will evolve. These collaborators, and their roles are described briefly below (Table 1).

**Table 1 Co-Investigator expertise and institutions**

<table>
<thead>
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<th>Job Title</th>
<th>Institution/ Organisation</th>
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<td>Database Manager</td>
<td>University of British Columbia</td>
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<tr>
<td>Maggie Woo-Kinshella</td>
<td>PRECISE PhD Student</td>
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Background

Biological sampling and biological banking within pregnancy cohorts are novel, yet currently under-utilised analytical methods for understanding the onset and resulting implications of diseases and treatments within the antenatal and postpartum periods. PRECISE-DYAD will collect health data and biological samples from postpartum women enrolled in PRECISE (H18-02828; HR-17/18-7855; AKU# 2018/REC-74 (v2); MRCG# SCC 1619v1.2) and their infants up to three years postpartum.

PRECISE-DYAD will extend the ongoing PRECISE network study [PRECISEnetwork.org] of pregnant women and their infants (dyads); it will provide a greater epidemiological and mechanistic understanding of health and disease pathways in The Gambia and Kenya, following uncomplicated pregnancies and those complicated by pregnancy hypertension, fetal growth restriction (FGR), preterm birth (PTB), and/or stillbirth (mothers only).

For women, we aim to determine if, and how, these pregnancy events identify those more likely to avoid complications in subsequent pregnancies, mental ill-health, or early onset of cardiometabolic diseases. For their children, we will address the impact of these pregnancy disorders on their physical, mental, and neurodevelopmental health until three years. We will explore the consequences for maternal health trajectories of caring for children with moderate-to-severe neurodevelopmental delay resulting from complicated pregnancies, and will interrogate interactions with social determinants of health, including environmental exposures on maternal and infant health. Also, we will develop a rich database and a large sample biorepository for future studies.

The scope of the placental disorders and their impact

The overlapping incidences of our conditions of particular interest are: pregnancy hypertension [10-11% [2]], FGR [median incidence of small-for-gestational age in sub-Saharan Africa: 24% [3], half of which will be FGR [4]; i.e., 12%], stillbirth [incidence 2-3% [5, 6]]; and PTB (10%) in less-developed sub-Saharan African countries [3].

Annually, pregnancy hypertension, FGR and stillbirth, are associated with 46,000 maternal and 2.5 million fetal, neonatal and infant deaths [7-9]; most of these occur in less-developed countries and >50% in sub-Saharan Africa [7, 9]. PTB (<37 weeks), complicates an approximated 15 million pregnancies annually, with a rate of ≈12% and 9% in The Gambia and Kenya, respectively [10]. PTB is the leading cause of death in children under five, accounting for ≈1 million lives lost annually [11]. In 2010, ≈13 million preterm infants survived beyond 28 days [12]. Of these, an estimated 345,000 (2.7%) and 567,000 (4.4%) developed moderate-to-severe or mild neurodevelopmental disability, respectively, while many more had specific learning, behavioural, physical or mental health impairments [12]. Fewest data are available where the PTB burden is heaviest; a recurrent issue. PTB is responsible for ≈77 million disability-adjusted life years (DALYs); 3.1% of the global total [12]. Historically, the primary aetiology for spontaneous PTB appeared to be infectious. In more-developed countries there is growing recognition that
placental dysfunction may contribute to some 30-75% of spontaneous PTB [13-15], and be confounded by infectious disease and compounded by anaemia [16].

Major morbidities complicate about 20-fold more pregnancies and infancies than lives lost, resulting in 60 million lives threatened and altered by these disorders.

**Developmental origins of health and disease (DOHaD)**

Studies addressing the DOHaD hypothesis in more-developed countries have described the interplay between maternal health, common pregnancy complications, and subsequent maternal and child health trajectories [17-23]. In contrast, in less-developed countries, these investigations have almost exclusively centred on the prolonged influence of maternal nutritional status [24-29]. In sub-Saharan Africa, we know very little of the longer-term health consequence following placental disorders.

**Pregnancy as a maternal biological stress test**

In addition to immediate mortality and severe acute morbidity risks, in more-developed countries, women who have experienced any of the single placental disorders are at increased actuarial risk for developing early-onset cardiovascular (CVD) and metabolic (especially diabetes) disease and mental health problems (e.g., depression, post-traumatic stress disorder [PTSD]) [20, 30-36].

CVD risks are cumulative according to the number of placental complications, so that women who have delivered preterm, of a stillborn and small infant, with hypertension display a risk for premature CVD similar to cigarette smoking [32, 37-39]. Such women are at increased risk of recurrently-complicated pregnancies [20, 40-42]. Other than for South Africa [35, 36], no equivalent data exist for the African context.

**Social determinants of maternal, fetal, and child health**

In less-developed countries with high-risk environments, children are at greater risk of a wide range of exposures that are surmised to influence brain development (e.g., antenatal, perinatal and infectious insults, poverty, exposure to violence, lack of hygiene, lack of stimulation) [43-45]. As more children survive, their risk for longer-term phycial and mental health morbidities will increase steadily. Currently, the pathways to, and exact burden (epidemiology) of, neurodevelopmental disorders in less-developed country settings, including Africa, are unclear. This is in large part due to difficulty conducting well-designed ‘life-course’ studies to track dyads and to look beyong just measuring child development to identifying specific disorders, particularly during infancy [46, 47].

This absence of reliable identification of neurodevelopmental disorders in less-developed countries impairs the context-specific investigation of the underlying aetiologies; a critical gap in developing effective strategies for prevention and intervention.
For all these acute and medium-to-long term consequences of pregnancy complications, the risks borne by families in sub-Saharan Africa are many-fold higher than those in more-developed countries. This disparity in outcomes between less- and more-developed countries represents a human rights issue and provides the opportunity to intervene to enhance development through improved survival and ‘thrive’ of each community’s greatest resource, their people.

An important unfinished agenda within the Millennium Development Goals was the missed opportunity to adequately reduce infant deaths and reverse maternal health inequalities. Underpinned by WHO Global Strategy for Women’s, Children’s and Adolescents’ Health [48], this prompted incorporation of new goals in the 2016 UN Sustainable Development Goal (SDG) 3 to ‘ensure healthy lives and promote well-being for all at all ages’ [49]:

- 3.1 ... reduce the global maternal mortality ratio to less than 70 per 100,000 live births
- 3.2 ... end preventable deaths of newborns and children under 5 years of age, with all countries aiming to reduce neonatal mortality to at least as low as 12 per 1,000 live births and under-5 mortality to at least as low as 25 per 1,000 live births

In addition, SDG3 3.4 aims to reduce by one third premature mortality from non-communicable diseases (NCDs) through prevention and treatment and promote mental health and well-being (pathways to NCDs are a focus of PRECISE-DYAD).

In the UK and China, exposure to particulate matter with an aerodynamic diameter ≤2.5μm (PM$_{2.5}$) and ≤10 μm (PM$_{10}$), and ozone during pregnancy is associated with higher risk for pre-eclampsia, FGR, stillbirth, and PTB [50-53] (59-62). Importantly, exposures to particulate matter and NO$_2$ are inversely associated with placental mitochondrial DNA (mtDNA) content [54]; however, there are no metabolomic or “exposomic” data linking the placenta and prenatal exposure to air pollution [55]. A pregnant woman’s environment can have lasting consequences on health trajectories of mother and child [51, 56-58]. No equivalent African data have been identified; PRECISE-DYAD can confirm findings in Africa and close data gaps.

For water, sanitation and hygiene (WASH), in India, PTB is associated with sharing (vs private) latrines (odds ratio (OR) 1.55 [95% CI 1.01, 2.38]), while Zambian data implicated poor WASH in stillbirth risk [59]. Unimproved, compared with improved water sources, can double maternal mortality risk [60]. Poor WASH conditions are significantly detrimental to child growth and development, due to both sustained exposure to enteric pathogens and wider social and economic mechanisms [61]. Similarly, there are statistically-significant associations between prenatal exposures to NO$_2$, SO$_2$, and PM$_{10}$ and the risk of childhood wheezing and asthma [62].

**The link between PRECISE and PRECISE-DYAD**
Designed to strengthen research capacity in Africa through a shared research project, the UKRI GCRF-funded PRECISE is learning about women in a 360° manner, including their social determinants, physical and mental health, with a biorepository that complements replete clinical and epidemiological data (PRECISEnetwork.org) [63]. PRECISE-DYAD is designed to provide broad follow-up and complementary science for the PRECISE Network (Figures 2 & 3).

**Figure 2. PRECISE-to-PRECISE-DYAD**

**Figure 3. Schematic of cohort activities: PRECISE (blue) & PRECISE-DYAD (green)**

NCD, non-communicable disease; PTB, preterm birth; pp, postpartum; TM, trimester

**Objectives**

a) To understand what happens to mothers and children after pregnancies complicated by:
1. Pregnancy hypertension
2. Fetal growth restriction
3. Stillbirth
4. Preterm birth

b) For women, to determine if these pregnancy events, or caring for children with moderate-to-severe neurodevelopmental delay due to these events, identify women more likely to have repeatedly-complicated pregnancies, mental ill-health, or heart disease or diabetes at an early age.

c) For their children, to understand if these pregnancy events have an impact on physical, mental, and neurodevelopmental health until at least three years of age.

d) To determine how maternal and child health are influenced by internal and exterior air and water quality.

**Research Settings**

African women and their children have multiple social and health challenges that may predispose to, or compound, the common disorders of pregnancy; these include calorie-restricted and variety-limited diets often with seasonal variation, and chronic and acute infections. Also, women often have limited autonomy of decision-making and live in communities prone to poor interior and exterior air quality, poor water and sanitation, floods or drought and often geographically remote from quality health facilities. These factors negatively influence pregnancy outcomes [64, 65].

The pathways to healthy outcomes following common pregnancy complications are probably very different for these sub-Saharan African women, compared with those living in more-developed countries. Yet, it is these women and their children who bear most of the burden of death and illness related to the immediate and long-term sequelae pregnancy complications. PRECISE-DYAD is designed to address this area of neglected global health research through its ability to compare maternal and child health trajectories following normal and complicated pregnancies.

The research settings for PRECISE-DYAD will be:

- **Farafenni District, The Gambia** (3 study sites), and
- **Kilifi County, Kenya** (2 study sites)
**The Gambia**

Our primary partner in The Gambia is the MRC Unit The Gambia at LSHTM (PIs: Umberto D’Alessandro & Anna Roca). The field research will occur at the Maternal Newborn Child and Adolescent Health clinic in Farafenni (urban PHC & Farafenni General Hospital) and associated rural PHCs in Illiasa and Ngayen Sanjal.

![Figure 4. Gambian sites](image)

Figure 4. Gambian sites
Kenya

Our primary partner in Kenya is the Aga Khan University (East Africa) (AKU) (PIs: Marleen Temmerman & Angela Koech). The field research will be conducted through the Mombasa field station, with field activity in Mariakani Subcounty Hospital (urban) and Rabai Health Centre (rural).

Figure 5. Kenyan sites

PRECISE-DYAD Cohort

PRECISE-DYAD is an observational cohort study of women, and, when relevant, their living children, who participated in PRECISE in The Gambia and Kenya. Building upon the detailed pregnancy information and samples established by PRECISE, DYAD will further contribute by collecting data that will assist in the investigation of mechanisms that underpin optimal maternal and child health trajectories following either normal or complicated pregnancy.

Consent process

The women participating in PRECISE will be informed about PRECISE-DYAD follow up during one of the PRECISE visits and/or by contacting participating PRECISE women directly either by phone calls or visiting them in their homes. We will ask for specific consent for follow-up at one of these visits.

Women enrolled in PRECISE-DYAD will have an opportunity to read or be read the informed consent in their native language and have an opportunity to ask the research co-ordinator any questions they may have. It will be explained that participation is voluntary and can be
terminated at any time without reason and without any penalty. If the potential participant has any questions, they will be answered in their native language to ensure that they understand the research and their potential role in it. Consent will be confirmed with the participant’s signature or a thumbprint. In case of thumbprint, a literate witness (other than the member of the research team obtaining consent) will be asked to sign. Finally, the member of the research team obtaining consent will sign the form and give a copy of the information sheet to the participant (Appendix 1).

If a woman has moved outside of the study area but is planning to come back in the region whilst the project is ongoing, or if she doesn’t want to attend the health care facility, we will ask for her consent to conduct a phone interview. During the phone interview, only a subset of the questionnaire will be asked. When the participant is back to the region, or if she is willing to attend the health care facility for a visit, full consent will be taken, and she can proceed with the remaining study visits as per the protocol.

**Confidentiality**

To ensure privacy, all the interviews and consenting will take place in a private room or an area with appropriate space for privacy at the local health facility. Hard copies of the study-related forms will be stored in a locked cabinet in a storage room under supervision of the principal investigators as per policy of the hosting institution. Electronic records will be stored in password-protected computers and tablets and only approved study personnel will have access to entire level of information (i.e., technicians will have access only to a subset of data, thus reducing the risk for major level breach). Access to the entire dataset will be restricted to the main PI and the site PIs, to keep a strict control of the data. All specimens and associated phenotypic data will be de-identified and given a unique participant identifier code and no personal information will be stored in the specimen tracking data management system.

**Number of participants**

We will maintain a cohort of PRECISE dyads, providing follow-up until three years. For sample size calculations, we have estimated that we will achieve 80% follow-up for three years following birth [66-69]. This will result in a cohort of ≈4800 women and ≈4500 children (assuming 6% stillbirths and neonatal/infant deaths). Of the related pregnancies, approximately 960 will have been complicated by a placental disorder.

**Community engagement**

The sites that are participating in PRECISE-DYAD have been working in these communities for many years and have built strong relationships with their communities. Participating communities are already aware of the PRECISE study and have had in-depth discussions about optimal collection strategies for samples that may have cultural or religious significance (e.g.,
blood). Community engagement activities will be conducted in all study sites to ensure the women and communities in which they live are aware of the PRECISE-DYAD programme of work.

We will run ‘PRECISE-DYAD open days’ to connect with study participants, their families and community members. We will dedicate time for interactive learning and discussions about pregnancy and mother and child health. These open days will take place in the communities where the participants live or at the health centre where the study takes place (The Gambia= 3, Kenya= 2). The choice of location will optimize participation by selecting centrally located/convenient locations.

A brief overview of activity is presented (Table 2).

<table>
<thead>
<tr>
<th>Table 2. Community engagement</th>
<th>The Gambia</th>
<th>Kenya</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stakeholders</td>
<td>Religious leaders</td>
<td>Health care workers</td>
</tr>
<tr>
<td></td>
<td>Non-religious community leaders</td>
<td>Community leaders</td>
</tr>
<tr>
<td></td>
<td>Community birth companions</td>
<td>Community health volunteers</td>
</tr>
<tr>
<td></td>
<td>Community health nurses</td>
<td>Community-wide meetings</td>
</tr>
<tr>
<td></td>
<td>Women attending ANC</td>
<td>Pregnant women, partners, family members</td>
</tr>
<tr>
<td>Engagement methods</td>
<td>Community outreach with community leaders</td>
<td>Health talks (baraza)/video loops at ANC</td>
</tr>
<tr>
<td></td>
<td>Health facility open days</td>
<td>Community meetings</td>
</tr>
<tr>
<td></td>
<td>Local radio announcement</td>
<td>Meetings for target audiences (pregnant women, mothers, in-laws, partners)</td>
</tr>
<tr>
<td></td>
<td>DYAD open days</td>
<td>DYAD open days</td>
</tr>
<tr>
<td>Key messages</td>
<td>Introduction to research and informed consent</td>
<td>Introduction to research and informed consent</td>
</tr>
<tr>
<td></td>
<td>When/how/why biobanking</td>
<td>When/how/why biobanking</td>
</tr>
<tr>
<td>Engagement frequency</td>
<td>Sensitisation activities will occur before and during follow-up</td>
<td>Continue PRECISE activities</td>
</tr>
<tr>
<td></td>
<td>Iterative communication of results to the community</td>
<td>Activities will be heightened in communities closest to health facilities (largest number of participants)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Activities will occur monthly</td>
</tr>
</tbody>
</table>

Visit content and data and sample collection

Outcome measures

Dyads will be followed-up at PHCs until three years; contact points: 6 weeks to 6 months, 12 months, 24 months, and, for first year of PRECISE births, 36 months (if applicable within the 2-year data collection). We will follow-up women who have suffered either a stillbirth or child death using the same protocol administered by specifically trained surveillance staff. In addition, we will follow up children who lost their mother after they were born. Following identified deaths
of women or their PRECISE-DYAD children, verbal autopsies will be performed to identify the cause of death at any time within the data collection period.

Non-clinical data will relate to nutritional status of both mothers and children. If a woman has moved since her last visit, we will ask questions about her natural and built environment. In addition, we will check for family care indicators to assess the quality of children's home environment. We will ask questions about the women mode of contraception and pregnancy intention. During the COVID-19 pandemic, we will ask questions related to COVID-19 symptoms and we will capture information about COVID-19 vaccination (including type of vaccine, number of doses, vaccination frequency and date of vaccination) (see Appendix 2).

At each visit, these clinical data will be collected. These data will include limited information about general health, medical history for women and general health and neurodevelopment assessment for children. At every visit, women and children will have their anthropometric measurements, BP and SpO₂ measured (see Appendix 2 & 3).

These data will be collected during each visit for all women and will be entered into the PRECISE-DYAD data platform.

**Visit content**

**Visit 1 at 6 weeks - 6 months (Table 3)**

As we will follow the same cohort of women and children, the women participating in PRECISE will be informed about PRECISE-DYAD follow up during one of the PRECISE visits. Dyads will be contacted by the team and invited to a visit. During the visit, both mother and child(ren) will be asked to provide clinical and non-clinical data mentioned above. In addition to these questions, maternal stress and anxiety following birth will be assessed in a purposefully selected sample of women. We will also evaluate pelvic floor health following childbirth and its impact on everyday life in a nested case-cohort of women. We will ask questions about the quality of care that both the mother and child(ren) received during and after delivery. For the child, in addition to the questions mentioned above, we will score their general movement and development using a video recording, and an observation questionnaire. Child gross and fine motor development and language will be scored using a direct assessment tool or an indirect assessment tool if the assessment is taking place over a telephone interview. Finally, we will assess the quality of maternal-child interactions by videorecording that will include a measure of maternal looking, voice, and touch (see Appendix 2, 3 & 5).
Visit 2 at 12 months (Table 4)
Dyads will be contacted by the team and invited to a visit. During this visit, both mother and child will be asked to provide clinical and non-clinical data mentioned above. Maternal stress, anxiety and depression following birth will be assessed in a randomised sample of women. If a woman couldn’t participate to the first DYAD visit at 6 weeks – 6 months after deliver for any reason, we will ask the quality of care questionnaire at the first follow up visit she attends. In addition, premature maternal cardiovascular aging will be measured using ultrasonic cardiac output monitors (USCOM) and arteriography (see Appendix 2 & 3). Child gross and fine motor development and language will be scored using a direct assessment tool or an indirect assessment tool if the assessment is taking place over a telephone interview (see Appendix 2 & 5).


**Table 4. Data collection and sampling of mothers and children during visit 2**

<table>
<thead>
<tr>
<th>Mother</th>
<th>Child</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Data collection:</strong></td>
<td><strong>Data collection:</strong></td>
</tr>
<tr>
<td>- Profile Form</td>
<td>- General Health (11b)</td>
</tr>
<tr>
<td>- General Information Form</td>
<td>- Nutrition (6c)</td>
</tr>
<tr>
<td>- Medication (1)</td>
<td>- Neurodevelopment (12a)</td>
</tr>
<tr>
<td>- General Health (2)</td>
<td>- Family Care indicators (14)</td>
</tr>
<tr>
<td>- COVID-19 (3)</td>
<td><strong>Clinical assessment</strong></td>
</tr>
</tbody>
</table>
| - Contraception and Pregnancy intentions (4) | - Vital signs (heart rate, blood pressure, 
                                                respiratory rate, pulse oximetry and 
                                                haemoglobin) peak flow |
| - Environment + WASH (5) | - Anthropometry: height, weight, MUAC 
                               and head circumference |
| - Nutrition (6a) | |
| - Mental Health (7b, 7c) | |
| **Cardiology assessment** | **Clinical assessment** |
| - pulse wave velocity and cardiac output | - Vital signs (heart rate, blood pressure, 
                                                respiratory rate, pulse oximetry and 
                                                haemoglobin) peak flow |
| **Clinical assessment** | - Anthropometry: weight, MUAC, waist:hip 
                               circumference ratio |
| - Vital signs (heart rate, blood pressure, 
                                                respiratory rate, pulse oximetry and 
                                                haemoglobin) peak flow | |
| - Anthropometry: weight, MUAC, waist:hip 
                               circumference ratio | |

**Visit 3 at 24 months (Table 5)**

Dyads will be contacted by the team and invited to a visit. During this visit, both mother and child will be asked to provide clinical and no clinical data. We will also evaluate pelvic floor health following childbirth and its impact on everyday life.

Child gross and fine motor development and language will be scored using a direct assessment tool or an indirect assessment tool if the assessment is taking place over a telephone interview and the likelihood of moderate to severe vision, hearing, communication, and motor impairment will be evaluated. Children will be screened for epilepsy and in case they are screened positive, a further questionnaire will be asked to the caregiver. Children with communication and motor impairment will be further assessed for moderate to severe behavioural problems/autism and health-related quality of life. Finally, we will assess the maternal child interaction by video recoding, which includes a measure of maternal looking, voice and touch (see Appendix 2, 3 & 5).
Table 5. Data collection and sampling of mothers and children during visit 3

<table>
<thead>
<tr>
<th>DYAD Visit 3 (24 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mother</strong></td>
</tr>
<tr>
<td><strong>Data collection:</strong></td>
</tr>
<tr>
<td>- Profile Form</td>
</tr>
<tr>
<td>- General Information Form</td>
</tr>
<tr>
<td>- COVID-19 (3)</td>
</tr>
<tr>
<td>- Contraception and Pregnancy intentions (4)</td>
</tr>
<tr>
<td>- Environment + WASH (5)</td>
</tr>
<tr>
<td>- Nutrition (6a)</td>
</tr>
<tr>
<td>- Pelvic Floor health (8a, 8b)</td>
</tr>
<tr>
<td><strong>Clinical assessment</strong></td>
</tr>
<tr>
<td>- Vital signs (heart rate, blood pressure, respiratory rate, pulse oximetry and haemoglobin) peak flow</td>
</tr>
<tr>
<td>- Anthropometry: weight, MUAC</td>
</tr>
<tr>
<td><strong>Child</strong></td>
</tr>
<tr>
<td><strong>Data collection:</strong></td>
</tr>
<tr>
<td>- General Health (11b)</td>
</tr>
<tr>
<td>- Nutrition (6c)</td>
</tr>
<tr>
<td>- Neurodevelopment (12a, 12b, 12c, 12d)</td>
</tr>
<tr>
<td>- Vision screening (12g, 12h)</td>
</tr>
<tr>
<td>- Epilepsy/seizures screening form + Epilepsy history (13a, 13b)</td>
</tr>
<tr>
<td>- Family Care indicators (14)</td>
</tr>
<tr>
<td><strong>Video recording:</strong></td>
</tr>
<tr>
<td>- Observation of maternal child interaction</td>
</tr>
<tr>
<td><strong>Clinical assessment</strong></td>
</tr>
<tr>
<td>- vital signs (heart rate, blood pressure, respiratory rate, pulse oximetry and haemoglobin)</td>
</tr>
<tr>
<td>- Anthropometry: height, weight, MUAC and head circumference</td>
</tr>
</tbody>
</table>

**Visit 4 at 36 months (Table 6)**

Dyads will be contacted by the team and invited to a visit. During this visit, both mother and child will be asked to provide clinical and non-clinical data. Child gross and fine motor development and language will be scored using a direct assessment tool or an indirect assessment tool if the assessment is taking place over a telephone interview and the likelihood of moderate to severe vision, hearing, communication, and motor impairment will be evaluated. Children will be screened for epilepsy and in case they are screened positive, a further questionnaire will be asked to the caregiver. Children with communication and motor impairment will be further assessed for moderate to severe behavioural problems/ASD and health-related quality of life (see Appendix 2, 3 & 5).
Air Quality and WASH

Sub-Saharan Africa presents a particular challenge from both indoor and outdoor air quality due to combined high levels of ambient fine particulate pollution (PM_{2.5}) and dominant use of biomass for cooking [70]. We will randomly select women within the PRECISE cohort from each study health facility. During recruitment, we will screen participants fuel use, via responses to the PRECISE questionnaire to ensure that the sub-sample is representative of the full cohort. If we find a cohort that is not representative, we will enrich this cohort by selecting participants.

In-field indoor/outdoor air quality exposure

The environment can have lasting consequences on maternal and childhood health trajectories. Representative in-field assessment of interior and exterior air quality will be assessed by field measurement campaigns in the dry and rainy seasons. Portable monitors will be situated at the health centres and a random sampling of up to 100 homes/site (n=500). Measurements will be combined with pre-existing PRECISE questionnaire responses and existing databases to extend the sample to the full cohort.

<table>
<thead>
<tr>
<th>Mother</th>
<th>Child</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Data collection:</strong></td>
<td></td>
</tr>
<tr>
<td>- Profile Form</td>
<td></td>
</tr>
<tr>
<td>- General Information Form</td>
<td></td>
</tr>
<tr>
<td>- COVID-19 (3)</td>
<td></td>
</tr>
<tr>
<td>- Contraception and Pregnancy intentions (4)</td>
<td></td>
</tr>
<tr>
<td>- Environment + WASH (5)</td>
<td></td>
</tr>
<tr>
<td>- Nutrition (6a)</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical assessment</strong></td>
<td></td>
</tr>
<tr>
<td>- Vital signs (heart rate, blood pressure, respiratory rate, pulse oximetry and haemoglobin) peak flow</td>
<td></td>
</tr>
<tr>
<td>- Anthropometry: weight, MUAC</td>
<td></td>
</tr>
</tbody>
</table>

| **Data collection:** |
| - General Health (11b) |
| - Nutrition (6c) |
| - Neurodevelopment (12a, 12b, 12c, 12d) |
| - Vision screening (12g, 12h) |
| - Epilepsy screening form + Epilepsy history (13a, 13b) |
| - Family Care indicators (14) |
| **Clinical assessment** |
| - Vital signs (heart rate, blood pressure, respiratory rate, pulse oximetry and haemoglobin) |
| - Anthropometry: height, weight, MUAC and head circumference |
Representative in-field assessment of personal and residential air quality will be made using portable sensor packs (Dyson Technology Ltd, Malmesbury, UK) that continuously monitor PM$_{2.5}$, PM$_{10}$, nitrogen dioxide, temperature, humidity and mobility (accelerometry and GPS location). Measurements are logged every second autonomously for 120 hours. The subset will be selected as representative of the full cohort, based on fuel use informed by the cohort questionnaire. A random sample of women will have a mid-week visit by the fieldworkers as a quality control measure of adherence to the sub-study protocol.

Additional fixed sampling will be carried out continuously for 14 days outside of each recruitment centre (n=5) in order to assess outdoor air quality. The same sampling equipment will be used as for the personal/residential sampling.

In Kenya, a short pilot study will be conducted to inform the messaging around carrying sensors during community engagement sessions. These pilot participants may also be invited to share their experiences during subsequent community meetings.

In-depth interviews with a sample of participants will also be conducted before and after they carry the sensors. The qualitative data obtained on the sensor experience will be used to inform future research involving the same sensors or other wearable devices.

*Water, sanitation and hygiene (WASH)*

WASH assessments will be conducted twice at every facility per country and in 100 participants homes. State of hygiene determinants (SOH-D) and visual state of hygiene (SOH-V) scores, and surface swabs of fomites and water samples (biochemical and metagenomic analysis) will all be measured. Sampling will be repeated in dry and rainy seasons.

These outdoor data, WASH results and personal/indoor exposure measurements will be used to create personal exposure models. Measurements will be combined with questionnaire responses and the WHO Global database of household air pollution measurements (https://www.who.int/airpollution/data/hap-measurements/en/) to extend the sub-sample to the full cohort.

*Health economics*

We will conduct household visits for 100 participants per country within 3 months of them giving birth to ask about the money they spent on their antenatal and postnatal care (see Table 10 in Appendix 2). The women will be selected based on the mode of delivery and outcome: all those who had a caesarean section, all whose babies died in the perinatal period, a selection of women with placental disorders (severe HTN (>160 and >110), Preterm birth <33 weeks, SGA <3rd percentile) and a selection of women with uncomplicated pregnancies and live born children.
**PRECISE in DYAD**

At any DYAD visit, if a participant is pregnant, we will ask her if she wishes to be followed up throughout her pregnancy as was done in the PRECISE study. One of the PRECISE study’s broad objectives was to develop a unique cohort of biologically and contextually characterised pregnant and non-pregnant women of reproductive age in sub-Saharan Africa to support research into placental disorders (hypertension, fetal growth restriction and stillbirth). For the PRECISE in DYAD study, we would like to know if pregnancy events or caring for children with delayed brain development due to these events, can cause similar complications in future pregnancies, influence mental health, or increase the risk of heart or breathing disease or diabetes. We would also like to know, what the effect of these pregnancy outcomes are on decisions around birth spacing and on subsequent healthy pregnancy, as well as the effect of caring for children with moderate-to-severe neurodevelopmental disability (vs those without such disability) on subsequent healthy pregnancy.

We will follow the same visit schedule of up to two visits during pregnancy and then a delivery visit. Data and biological samples will be collected as shown below (also see appendix 6).

<table>
<thead>
<tr>
<th>DYAD Pregnancy visit</th>
<th>Birth visit</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Data</strong></td>
<td><strong>Samples</strong></td>
</tr>
<tr>
<td>Table 1, 2, 3, 4, 12</td>
<td>Blood (16ml) Urine</td>
</tr>
</tbody>
</table>

**Creating the PRECISE-DYAD biorepository (see Appendix 4)**

**Collection of samples**

**Blood**

We anticipate that each participant enrolled in the PRECISE-DYAD cohort will provide four blood samples, one sample at each visit. Each blood draw will be approximately 16mL for women. For children, we will either collect a blood spot using 2 or 3 drops of blood from heel (visit 1) or finger (for children older than 1 year) or collect blood through venepuncture (5 ml for children older than 1 year). The decision on how to collect blood will be up to the participant and the confidence of the staff in collecting the samples. All blood collection is intended to qualify as minimal risk. The total volume and frequency, when considered in the context of the clinical encounter, will not exceed the following parameters (OHRP (45 CFR 46.110):
• For healthy, non-pregnant adults who weigh at least 50kg, the amounts drawn may not exceed 550 mL in an 8-week period and collection may not occur more frequently than 2 times per week
• For other adults and children, the amount drawn may not exceed the lesser of 50 mL or 3 mL per kg in an 8-week period and collection may not occur more frequently than 2 times per week

**Vaginal swabs**
Mid-vaginal swabs will be collected at the DYAD visit 1 (6 weeks-6 months)

**Breastmilk**
In Gambia only, up to 5 ml of breastmilk will be collected at the DYAD visit 1 (6 weeks-6 months).

**Urine sample**
Up to 20 mL of urine will be collected at visits 2 and 3.

**Child stool**
The stool swab will be collected to examine the child microbiome. The stool sample will be collected from the child at DYAD visit 1 and 3.

All samples will be collected, processed and stored in adherence to the PRECISE-DYAD Network Clinical and Biological SOPs across all sites. Study personnel at each site will receive initial and ongoing training as needed to ensure SOPs are followed and samples are of the highest quality.
Table 7. Sampling from Mothers

<table>
<thead>
<tr>
<th>Samples collected</th>
<th>DYAD Visit 1</th>
<th>DYAD Visit 2</th>
<th>DYAD Visit 3</th>
<th>DYAD Visit 4</th>
<th>Total Collections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>16 ml</td>
<td>16 ml</td>
<td>16 ml</td>
<td>16 ml</td>
<td>4</td>
</tr>
<tr>
<td>Breast milk</td>
<td>5 ml</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Vaginal swab</td>
<td>4 swabs</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Urine</td>
<td></td>
<td>20 ml</td>
<td>20 ml</td>
<td></td>
<td>2</td>
</tr>
</tbody>
</table>

Table 8. Sampling from Children

<table>
<thead>
<tr>
<th>Samples collected</th>
<th>DYAD Visit 1</th>
<th>DYAD Visit 2</th>
<th>DYAD Visit 3</th>
<th>DYAD Visit 4</th>
<th>Total Collections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>2-3 drops from heel prick</td>
<td>2-3 drops from finger stick or venepuncture (5 ml)</td>
<td>2-3 drops from finger stick or venepuncture (5 ml)</td>
<td>2-3 drops from finger stick or venepuncture (5 ml)</td>
<td>4</td>
</tr>
<tr>
<td>Stool</td>
<td>2 swabs</td>
<td></td>
<td>2 swabs</td>
<td></td>
<td>2</td>
</tr>
</tbody>
</table>

**Biorepository**

The intention is to use the valuable biorepository of samples collected through PRECISE and PRECISE- DYAD to unravel mechanisms and identify novel biomarkers (with/without clinical data) as predictors of important maternal and child outcomes.

All samples remaining after planned analyses for this initial project will add to the existing PRECISE biorepository collected during pregnancy, birth, and up to three years thereafter to facilitate and accelerate future discoveries on maternal, fetal, neonatal, and child health. This biorepository will be managed and governed by a Data and Samples Access Committee including representatives from each country and owned by each country.

Complementing the extensive PRECISE biorepository, we will sample women (serum, plasma, buffy coat, breast milk, vaginal swabs, urine) and children (blood, stools). With planned leveraged funding, we will use agnostic ‘omics science (proteomics, metabolomics, genomics, epigenomics, metagenomics) to enable pathway recognition.
Where possible, we train local faculty and staff to use in-country-based technologies and complex bioinformatics. Understanding pathways will enable the development of low cost, point-of-care diagnostics, and therapeutics to improve women’s and children’s care.

**Database and Data Management**

The DYAD database will be created to track women and babies. The same participant ID format in PRECISE will be used so that the DYAD dataset can be linked with the PRECISE database.

We have the advantage of access to the recently developed standard pregnancy database (PRECISE). The DYAD platform will be PRECISE-compliant in terms of data dictionary, to facilitate future international collaborations.

**Format and scale of data**

**Qualitative data**

Digital voice recorders and hand-written field notes will be used to record community engagement sessions (as needed), related focus group discussions (FGD) and interviews (IDI). Primary analysis will be conducted in the local language, prior to translation/back translation into English if necessary. Each FGD and IDI will be assigned a unique identifier and photographs taken during data collection and reflection notes attached to transcripts for analysis. All coded transcripts will be cross-checked by the local research team to resolve or clarify any data misinterpretation. Data will be analysed using NVivo software.

**Clinical and laboratory data**

Clinical data will be collected using Android tablets and computers and stored in a MySQL and PostgreSQL database. Core laboratory data will be transmitted into this database from a laboratory management information system (LIMS). The database will store information about individual participants and tracks multiple follow-up visits over time. The database supports secure online data entry on a standard web browser, or offline data collection on a mobile device and data synchronisation with the server over Wi-Fi connection by end users. Data will be able to be downloaded as CSV or Excel files that can be imported to R or other equivalent statistical software.

**Routine automated laboratory methods**

All laboratory data, such as ELISAs and assays on automated clinical analysers, generate data which will be stored in Microsoft Excel. Data generated on automated analysers and from the plate reader for ELISAs, will be transcribed to Excel, from Ascii files generated. Hard copies of results will be retained. After transcription, each result will be checked manually by two separate technicians. Once the dataset is complete, each variable will be range-checked. Data outside the expected range will be verified against the hard copies. Reasons for missing data will be logged.
**Data management, documentation and curation**

**Servers and data storage**

The original database and web servers will be hosted in each country and managed by the local IT team. All data will be stored locally on secure database and file servers on a high-speed network with access control. Servers are to be stored in locked rooms, with extra measures for security including auxiliary power through UPS and/or a diesel generator and system monitoring. A tape backup system is used for backing up the database.

A copy of all blinded anonymous (unidentifiable) qualitative, clinical and laboratory data will be stored on a remote University of British Columbia Server (shared drive with access control) located at the BC Children’s Hospital Research Institute, which is locally and remotely backed up within the institute every day. Servers are stored in a secure locked server room with restricted access to authorised system administrators. The server room is protected by a security keypad and monitored for environmental changes and availability. The servers at BC Children’s Hospital Research Institute are managed by research institute IT team along with IT security policies.

**Software platform management**

The database systems will be hosted and managed by a local IT administrator and/or data manager in each country. The local IT administrator will be responsible for network security and access control, system updates, database backup and recovery and clients’ computer updates. Local IT network, system and security policies and procedures will be followed. The data manager will be responsible for setting up and configuring the database, testing system functionalities, updating metadata and installing/configuring mobile apps on tablets for users. The data manager will also take charge of importing and exporting data, monitoring data updates, audit trails and reports and reporting/resolving data queries within the study team. Executable application programs will be created and run periodically by the data manager for data queries and data transmission between the database systems.

**Data quality control and data query**

To ensure high quality of data, program rules will be added to implement skip logics and cross validation rules will be created for checking inconsistencies. All skip and validation rules along with the data entry forms will be tested to confirm the functionality of the system is behaving as expected and acceptable before starting data collection at sites.

**Data preservation strategy and standards**

Backups of the local databases in each country will be kept on their authorised file storage servers for 10 years and be remotely stored according to local IT policies.

Backups of the UBC central databases will be kept on the network drive and copied onto tapes and kept at an authorised remote location for a minimum 10 years.
Data security and confidentiality of potentially disclosive personal information

General protection

Hard copies of the study-related forms will be stored in a locked cabinet or a storage room under supervision of the principal investigator and/or an authorised study coordinator at each local site. Electronic records will be stored in password-protected computers and only approved study personnel will have access to this information. Only de-identified data (i.e. names, contacts or addresses are excluded) will be transmitted through a secure connection by the local data manager.

Data sharing and access

Data will be dependently available, in view of the limits implied by consent. The Data and Sample Committee will review applications to use the study data. This committee will comprise the PI and co-PIs and named collaborators.

Applications will be considered from academic and, potentially, commercial bodies, all of which must be for bona fide research or for educational purposes. All interested parties will complete a project proforma detailing the rationale for the study and the information required. The forms will be reviewed to ensure compliance with administrative requirements, prior to consideration. Once agreed, and following any requested revision, the form will be signed off by the PI and, following the signing of a data sharing agreement, the data will be made available. A record of the process will be kept and made available for periodic review by an independent assessor. A log will be kept of all studies, each of which will have a unique identifier. All agreements will be subject to a time limit for uptake, and if not met, the agreement will be withdrawn, so that other scientists could use the data for a similar/the same study. Academic researchers will be requested to provide the necessary costs for data retrieval and transfer, with a surcharge to support administration of the Data and Samples Committee.

External users will be bound by data sharing agreements including specification of the dataset(s) to be prepared and released, the purposes for which data are released and the conditions under which the data may be used, particularly in relation to ethics committee approvals. The specific obligations and arrangements to maintain confidentiality and data security will be itemised. The agreement will address handling of intellectual property, publication, authorship, acknowledgement and whether data are provided on an “exclusive” or “non-exclusive” basis to the requester. It will include a requirement that research publications and other outputs based on the data are reported to the PIs and that the UKRI be acknowledged in outputs. The researchers will agree not to transfer data to another unauthorised third-party. The researchers will also be asked to make available a copy of data derived, and details of how the data were derived, after a reasonable delay allowing the researchers to publish their aims and objectives prior to those derived data becoming widely available to other scientists. Arrangements for secure data archiving will be made and the costs of data retrieval detailed.
Relevant policies on data sharing and security

- General Data Protection Regulation (GDPR)
  https://ico.org.uk/for-organisations/guide-to-the-general-data-protection-regulation-
gdpr/
- International Organization for Standardization
  http://www.iso.org/iso/home.html
- King’s College London Research Data Management Policy
  https://www.kcl.ac.uk/governancezone/Research/Research-Data-Management-Policy.aspx
- London School of Hygiene and Tropical Medicine Research Data Management Policy
  http://researchonline.lshtm.ac.uk/612422/
- St George’s, University of London Data Management Policy
- The UK Data Protection Act 2018
- University of Oxford Policy on the Management of Research Data and Records
  http://researchdata.ox.ac.uk/university-of-oxford-policy-on-the-management-of-
  research-data-and-records/

Analytical Approach

Our analytical approach will include both:

1. Mediation analyses to examine mechanisms that underlie observed relationships between independent and dependent variables via a third, hypothetical mediator variable.
2. Organisational network analyses of nodes (families, sites, countries, social determinants, environmental and geographical factors, health, and biomarkers) and the relationships that connect them. Visual network representations provide new understandings and convey the results to our partners.

Regularly engaged partners are the communities, scientists, health practitioners, regional/national ministries of health, and multilaterals.

We aim to identify factors that predict optimal maternal and child health trajectories, especially factors that may be modifiable.

Our analytical approach will include:

Exploratory analyses

- Univariable analyses comparing individual variables with outcomes.
- Multivariable analyses to assess the independent contribution of putative aetiological pathways to healthy and compromised health trajectories. We have developed
multivariable models for discovery science [71] and clinical [72-75] variables that have informed the design of a mobile health platform used in >20,000 African and South Asian pregnancies [76-82].

- Agnostic analyses of samples using a multi-omics approach to define pathways to maternal and childhood outcomes, using state-of-the-art bioinformatics [83].

**Causal models**

- Hypothesis-driven laboratory-based analyses to define pathways to maternal and childhood outcomes. Causal inference is a framework for attributing causality to variables such as exposures and treatments and has been applied to pregnancy and birth cohort studies [83-85] (145-147). Usually the exposure is perceived to be modifiable through some intervention, and the model requires an *a priori* understanding of underlying relationships.

- Assessment of confounders that predict both exposure and outcome; in this context the social determinants of health are good examples of confounders [86-88] (148-150). The WHO has identified 10 social determinants of health [89] (151); all of which are being assessed within the PRECISE-DYAD continuum.

- Mediation analyses to examine observed relationships between independent and dependent variables via a third, hypothetical mediator variable; an approach established in pregnancy studies [90-92] (152-154), including our analysis of the pre-eclampsia-postpartum haemorrhage relationship (155).

**Organisational network analysis**

- We will assess the ability of organisational network analyses of nodes (families, sites, countries, social determinants, environmental and geographical factors, health, and biomarkers) and the relationships that connect them to visualise the complexity of our dataset [93] (156). Visual networks provide new understandings, could convey results to our partners, have been used in health services and policy research [94] (157) and can track infectious disease outbreaks [95] (158) to facilitate the identification of points where early interventions would benefit target groups.

**Sample size and general statistical approaches**

We should achieve 80% follow-up for 2-3 years [66-69] (161-164), resulting in a cohort of ≈4800 women and ≈4500 children (≈6% stillbirths/infant deaths); ≈960 (20%) will follow-up a placental disorder.

*Primary maternal outcome:* WHODAS (continuous variable), comparing women who experienced a placental disorder with those who did not; ≥75% of PRECISE-DYAD women with uncomplicated pregnancies will experience good health [68, 69] (163-164) (165;166). We can identify a 4%
absolute difference in the proportion of women with ‘maternal health’ (two-sided $\alpha=0.05$; $\beta=0.2$) in women with ($n=947$) and without placental complications ($n=947$).

Primary child outcome: age-adjusted Z-score for weight-for-length/height (18), compared between those born of placental disease-complicated pregnancies with those not. $\approx 70\%$ of children will have normal Z-scores [96, 97] (165;166) (167;168). We can identify a 4% absolute difference in the proportion of children with ‘adequate growth’ (two-sided $\alpha=0.05$; $\beta=0.2$) in women with ($n=1052$) and without placental complications ($n=1052$).

For dichotomous predictors, we can detect differences as small as 5%, irrespective of the proportion with the predictor in the control population, and for continuous predictors, we can detect effect sizes as small as 0.1.

Non-parametric analytical methods will be used, with $p<0.05$ for statistical significance for primary outcomes of each analysis and $p<0.01$ for all other comparisons.

Our primary foci are pathways to maternal and infant cardiometabolic, respiratory, mental, and, for children, physical and neurodevelopmental health, to avoid multimorbidities.

Ethics

For PRECISE, we have Ethics Committee approvals from King's College London, the London School of Hygiene and Tropical Medicine (for both London and The Gambia), the University of British Columbia, the Aga Khan University, Centro de Investigação em Saúde de Manhiça (Mozambique), the University of Oxford, and Midlands State University (Zimbabwe). In addition, national approvals have been received in the Gambia, Kenya, Mozambique and Zimbabwe.

PRECISE-DYAD is an observational programme of work. In these settings, there is an absence of clinical pathways to respond to identified clinical conditions, even a condition as common as diabetes. As a consortium it is our considered opinion that it is unethical to make real-time diagnoses for which there are no available clinical responses. However, secondary batch testing of samples will delineate the burden of certain conditions and act as advocacy tools for future funding prioritisation, both within the health systems and research.

The biological samples collected through the PRECISE-DYAD study will be owned and permanently stored by the country from which they were collected. Our default position is that all laboratory science will occur in-country, as part of our research enterprise strengthening mandate. In instances where the samples are required for research purposes, and the equipment required for this research is unavailable in the country in which they were collected, these samples, with ethical approval and required MTAs, will be transported to the country where the necessary equipment to conduct the research can be found. Again, our default position will be to access laboratories within sub-Saharan Africa, as part of our remit to strengthen in-continent research capacity; this is a model already adopted by H3Africa, the human biorepository.
consortium created by the African Union. The consent forms that will be signed by women who have agreed to be in the PRECISE-DYAD cohorts, describe this in the following way: I agree to the use of the biological samples in future studies approved by the PRECISE Network Data and Sample Access Committee. This may involve the transfer of the samples to other research collaborators/institutions or commercial companies in other countries.

PRECISE-DYAD will be overseen by a Project Executive Group of the PI, site PIs and Co-PIs (1 per country), and theme leads and the PRECISE Programme Manager/representative. Strategic oversight will be provided by the independent Technical Advisory Group.

**Mental health ethical considerations**

All members of the research team will receive training in maternal mental health and how to administer the mental health measures by a mental health specialist. Research staff and service providers participating in the project will receive mental health training to enable them to identify distress in participants and provide basic psychological treatments using the World Health Organization’s mhGAP Intervention Guide. Every attempt will be made to reduce any distress to participants. If a participant does show any signs of distress during a data collection session, the session will be discontinued immediately. Participants who screen positive on the mental health assessment measures used will receive care as described below. If any participant seems to be fatigued, they will be invited to suspend the session and continue at a later time. Women who disclose or are suspected victims of violence by research team will be given advice on how they can report or receive support if wanted. The details of all suspected mental health and victims of violence will be entered into the study adverse event electronic database by the researcher. This database will be used to follow-up those referred and encourage attendance at initial appointments.

PRECISE-DYAD will work with local referral and care pathways for mental health problems within each site. Where mental health services are weak or non-existent, basic mental health care will be provided by trained service providers under the supervision of a mental health specialist working within the study.

**Timeline**

Below is a general project timeline. Each country has developed its own internal Gantt chart. Specific re-consenting and ethics approvals will be sought for PRECISE-DYAD and ethics approval will be obtained in The Gambia, Kenya, UK, and Canada.

Table 9. Timeline of PRECISE-DYAD activity

<table>
<thead>
<tr>
<th>Task</th>
<th>Months 1-6</th>
<th>Months 7-28</th>
<th>Months 29-36</th>
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<tbody>
<tr>
<td>Modify existing PRECISE contracts and budgets</td>
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<tr>
<td>Updated ethics &amp; re-consenting</td>
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<tr>
<td>Add PRECISE-DYAD fields to PRECISE database</td>
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<td>SOPs, biorepository policies, &amp; publication policy updates</td>
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<td>Active clinical phase</td>
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<td>Refine specific hypotheses</td>
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<td>Design dummy tables</td>
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<tr>
<td>Statistical plans &amp; code</td>
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<tr>
<td>Funding to undertake ‘omics and other science &amp; maintain PRECISE-DYAD cohort</td>
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<tr>
<td>Design &amp; fund ‘omics science &amp; intervention studies</td>
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<tr>
<td>Presentations &amp; publications</td>
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Research Themes

1. Social Determinants of Health (Working Group: Graham, Makanga, Barratt, Filippi, Sandall, Blencowe, Vidler, von Dadelszen, Diallo, Naanyu, Martinez-Alvarez, Temmerman, Gladstone, Jah, Pickerill)
   
a. Environmental and Geographic Sciences (air quality, health geography, water, sanitation & hygiene) (Leads: Barratt, Graham, Makanga)

   In more-developed countries there is an increasing body of evidence linking air quality with adverse pregnancy outcomes, such as placental complications and low birth weight, and childhood health trajectories. In much of Africa, women are exposed to considerable levels of air pollution due to indoor fires and cooking stoves and this is compounded by poor outdoor air quality, especially in the growing African cities.

   The aim of this component is to characterise mother and child exposure to WASH, indoor and outdoor air pollution for linkage to maternal and infant health trajectory data

   Objectives:

   • Carry out field assessment of indoor (residential) and outdoor (ambient) air quality via measurement campaigns during the dry and rainy seasons, utilising portable particulate matter monitors at the health centre and a random sampling of homes at each study site. The subset will be selected as representative of the full cohort, based on fuel use informed by the cohort questionnaire.
   • Carry out WASH assessment once per study site at the same homes, including state of hygiene determinants, surface swabs and water samples.
   • Combine air quality and WASH results to create empirical personal environmental exposure models.
   • Compare exposure assessments with pre-existing PRECISE questionnaire responses and existing databases to extend the random sample assessments to the full cohort.

b. Access, barriers and systems of care (Leads: Sandall, Filippi, Vidler, Blencowe, Martinez-Alvarez)

   Mothers and newborns need access to safe, efficient and high-quality health services along the maternal and neonatal health continuum of care, spanning the pregnancy, birth and postnatal periods. This is particularly important for mothers and babies with placental disorders. Quality care can only be provided within functional health systems, which need to have efficient and equitable financing, adequately-trained and motivated human resources, effective governance and accountability structures, functioning referral pathways, sufficient physical resources and well-functioning information systems [98].

   It is essential to understand the role of the quality of the care provided in the PRECISE facilities to help interpret the strength of the relationships between the biomedical exposures documented by PRECISE and placental disorders. Within functional health systems, quality of
care dimensions include both the provision and the experience of care [99]. Although the data cannot paint an exhaustive picture of care provision, and some are likely to be missing or of variable quality, we believe it is possible to construct a quality of care conceptual framework for the analysis of relevant data.


This group will focus on identifying genetic, and proteomic signatures of women destined to develop placental disorders and their severe consequences on child and women’s health. This research will be based on the agnostic metabolomic, proteomic, genomic, epigenomic, and metagenomic screening of samples from women and children following complicated and uncomplicated pregnancies.

PRECISE-DYAD also gives opportunities to test hypotheses relating to nutrition-related molecular mechanisms impacting on child health. We have a particular interest in exploring the potential for embryonic, fetal and placental epigenetic changes to mediate inter-generational links between maternal pre- and post-conception nutrition, and infant and child development.

3. **Epidemiology & Co-exposures** (Working Group: Temmerman, Barratt, von Dadelszen, Magee, Chappell, Moore, D’Alessandro, Roca, Filippi, Salisbury, Khalil, Singer, Bone, Cundiff, Lawn, Blencowe, Erhart, Jah, Koech, Abubakar, Gladstone, Diallo, Volvert, Mistry, Edmond, MacDermott, Lawn)

a. **Diet/nutrition** (Lead: Moore)

Undernutrition during the early years of life has a harmful and irreversible impact on child development. Poor maternal nutrition (both pre- and post-partum) and/or sub-optimal caregiving practices because of maternal ill health, may impact of infant and young child feeding practices and on childhood growth and development. The extensive clinical and socio-demographic data available through PRECISE will enable a detailed study of factors impacting childhood growth and development in Kenya and The Gambia. Further, detailed records on infant feeding and household food security will support other planned analyses within PRECISE-DYAD.

With reference to childhood nutritional status and growth, the following specific hypotheses have been identified:

1. Significant morbidity following placental disease impacts on a mother’s ability to care and nurture her child, resulting in greater risk of childhood malnutrition and developmental delays.
2. Maternal undernutrition, as a consequence of placental disease, impacts on a mother’s ability to care and nurture her child, resulting in greater risk of childhood malnutrition and developmental delays.

3. Infant/childhood undernutrition, especially micronutrient deficiencies, significantly interact with household environmental exposures (air and water quality): children exposed to both micronutrient deficiencies and adverse environments will be at greatest risk of ill health.

Infant and young child feeding practices and household food security will be assessed by questionnaire, administered at each contact point. A questionnaire adapted from the Chain network (https://chainnetwork.org/) will be used.

Maternal and infant micronutrient status will be assessed on blood samples collected at these visits.

b. **Cardiology** (Lead: Khalil, Erhart)

Women who experienced a pregnancy which was complicated by a placental disease, such as preeclampsia or fetal growth restriction, are at increased risk of cardiovascular mortality and morbidity later in life. In fact, these women are more likely to have subclinical cardiovascular dysfunction even prior to pregnancy. Pregnancy represents a window of opportunity to identify those women at future risk, where early intervention is likely to reduce their chances of cardiovascular disease later in life. Many of the known risk factors for cardiovascular disorders are also risk factors for placental dysfunction. Our research team has pioneered the use of non-invasive techniques to assess maternal cardiovascular function in pregnancy.

**Research question**

Following placental disease, what is the effect on the maternal cardiovascular health?

**Hypothesis**

Following placental disease there is no effect on the maternal cardiovascular health

**Objectives**

*Primary Objective*

- To investigate the maternal cardiovascular parameters following a pregnancy complicated by placental disease

*Secondary Objectives*

- To investigate the maternal cardiac output (CO), stroke volume (SV), heart rate (HR) and systemic vascular resistance (SVR) following a pregnancy complicated by placental disease
• To study the maternal arterial stiffness, pulse wave velocity (PWV), augmentation index (AIx) and central systolic blood pressure (SBP Ao) following a pregnancy complicated by placental disease
• To determine the risk factors for impaired cardiovascular health among women who had a pregnancy complicated by placental disease
• To establish whether a pregnancy complicated by placental disease is associated with impaired maternal cardiovascular health in the absence of the known epidemiological risk factors (e.g. maternal age, obesity, etc)

c. **Maternal Mental Health** (Lead: Salisbury)

Within PRECISE-DYAD we will test the following hypotheses:

• That maternal mental disorders will modify pathways to placental disorders and secondary outcomes.

• That pregnancy complications and the style of their management contribute to the burden of mental disorders assessed at the end of the puerperium.

**Assessment measures**

The hypotheses will be tested using the following measures:

*World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0)*

The WHODAS 2.0 is a generic assessment instrument assessing health and disability. It is used across all diseases, including mental, neurological and substance use disorders [100]. It is simple to administer and applicable across cultures and can be used in all adult populations. WHODAS 2.0 covers six domains (cognition, mobility, self-care, getting along, life activities, and participation). It assesses difficulties people have due to their illness across these domains during the last 30 days. Difficulties are scored as none, mild, moderate, severe, or extreme.

*Patient Health Questionnaire (PHQ-9)*

The PHQ-9 [101] is a nine-item diagnostic instrument for depression. It scores each of the nine DSM-IV criteria as "0" (not at all) to "3" (nearly every day). A PHQ-9 score ≥10 had a sensitivity of 88% and a specificity of 88% for major depression.

*Generalised Anxiety Disorder (GAD-7)*

The GAD-7 is a seven-item screening tool for generalised anxiety disorder [102]. It scores seven items using the criteria “not at all” (0) to “nearly every day” (3). A total score is used to determine mild (5), moderate (10) or severe (15) anxiety. A GAD-7 score ≥10 had a sensitivity of 89% and a specificity of 82% for generalised anxiety disorder.

*PCL-C: Post-traumatic Stress Disorder Checklist (civilian)*

The PCL-C is a 17-item screening tool for post-traumatic stress disorder (PTSD) based on DSM-IV criteria [103]. Each item is rated from 1 (“not at all”) to 5 (“extremely) to indicate the impact of
a symptoms over the previous month. A total score is used to determine PTSD. A score of ≥50 denotes probable PTSD. A PCL-C score of ≥50 had a sensitivity of 78% and specificity of 83%.

Within each site, where measures have not yet been adapted and validated, the International Test Commission Guidelines for Translating and Adapting Tests [104] will be followed and validity assessed.

Data collection procedures

A trained member of the research team in each site will deliver the assessment measures through interviews with women during DYAD visits 1 (6 weeks to 6 months post-partum) and 2 (12 months post-partum). During DYAD visit 1 women will complete the PHQ-9, and GAD-7. During DYAD visit 2 women will complete the PHQ-9, GAD-7, and PCL-C. The mental health measures will take up to 25 minutes to complete in each visit.

d. Neurodevelopment (Leads: Gladstone, Abubakar)

Researchers have estimated that up to 250 million children are not reaching their developmental potential globally. Much of this has been estimated linked to issues such as stunting and poverty but we know that there are many other factors which play a role in the poor developmental outcomes of mothers and their infants, but to what extent, this is unclear – and through which mechanisms – also unclear. We know that a number of perinatal factors can have an impact on child development and the likelihood of childhood disability, but the mechanisms for this are also not entirely clear. Studies have demonstrated that premature birth, infections in pregnancy (HIV exposure, malaria in pregnancy and infection with Group B strep for example) and hypoxic ischaemic encephalopathy are linked to neurodevelopmental delay but the mechanisms for this are far from clear. How complications in pregnancy (pregnancy induced hypertension, fetal growth restriction, placental insufficiency) may precede this or be related is not clear and has not been well studied – particularly in low- and middle-income settings and in Africa, where many of the risk factors for these disorders are more common. We still do not know how complicated pregnancies may precede or affect neurodevelopmental delay and disorders and we do not know how the aetiologies relate to maternal and infant outcomes and how these inter-relate over time.

The reasons for the lack of research relate to the difficulties in identifying well-phenotyped cohorts of women from very early in the gestational period and being able to follow these cohorts’ until the children are born and the infants grow and develop during childhood. Furthermore, undertaking neurodevelopmental assessments on large cohorts of children in field settings – particularly assessments of disability – has not been easy due to previous lack of tools, capacity and experience. The DYAD study when linked to the previous PRECISE network, enables this, by having already identified a cohort of women in two sites in Africa with deeply phenotyped maternal fetal dyads and by having created a consortium of researchers who have the capacity to conduct neurodevelopmental assessments as required for this study.
The aim of the DYAD study (in relation to neurodevelopmental outcomes of children) is to understand what the pathways and mechanisms to neurodevelopmental delay and disability in infants and children up to 3 years of life following normal vs complicated (those mothers with pregnancy induced hypertension, fetal growth restriction and preterm birth) pregnancies.

The objectives of the study (in relation to neurodevelopmental outcomes) are to understand:

1. What is the **measurable impact** of complicated pregnancies on physical, mental and neurodevelopmental health trajectories (specifically moderate to severe neurodevelopmental, visual or hearing disabilities) of children at 2-3 years of age? More specifically, what is the relationship between A and B

2. What are the biological mechanisms which underpin the relationship between intrauterine and early postnatal exposures and neurodevelopmental outcomes? What is the relationship between biological mechanisms and A and B?

3. Are neurodevelopmental outcomes and moderate to severe disability modified by environmental exposures (e.g. air and water) and co-exposures (nutrition, lifestyle, and quality of care (SES, maternal education, maternal depression, family care indicators, adversity measures in the home) in pregnancy and perinatal period?

4. **Advocacy** (Working Group: Temmerman, von Dadelszen, Jah)

Our team has experience working in the WHO, leading the FIGO Safe Motherhood and Newborn Health Committee and the relevant maternal, fetal, newborn and under-5 mortality and health Lancet series. We will embed advocacy and engagement with governments, multilaterals and NGOs. Critical partners will be those that ultimately fund the implementation of the PRECISE evidence-based interventions. They will be encouraged to share project ‘ownership’ from the design phase onwards. This thematic working group will include two stakeholders from each country, one embedded at the interface between maternity care and ministry of health and the other from either the Ministry of Higher Education, Ministry of Science or the national research funding body.
References

37. Riise, H.K., et al., Incident Coronary Heart Disease After Preeclampsia: Role of Reduced Fetal Growth, Preterm Delivery, and Parity. J Am Heart Assoc, 2017. 6(3).


