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Can dietary mineral deficiencies in a rural Malawi population be improved through the consumption of maize flour enriched using micronutrient fertilizers?

Submission date
20/02/2019

Recruitment status
No longer recruiting

Registration date
05/03/2019

Overall study status
Completed

Last Edited
25/01/2022

Condition category
Nutritional, Metabolic, Endocrine

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Selenium deficiency is widespread in Malawi. Deficiency of selenium leads to sub-optimal thyroid function and has a range of consequences including impaired cognitive development in children. Biofortification may be a cost-effective strategy to reduce selenium deficiency. Biofortification is the production of crops with greater concentrations of nutrients in their edible portions. One way to achieve this is through application of micronutrient-containing fertilizers during crop production, a process known as 'agronomic biofortification'. Biofortification has the potential to reach poorer, marginalised populations who rely heavily on the staple food maize with little dietary diversity.
Agronomic biofortification to address selenium deficiency is a promising technology, and widespread selenium deficiency in Finland was addressed through mandatory incorporation of selenium in fertilizers since the mid-1980s. However, there is currently insufficient evidence to know whether agronomic biofortification is an effective approach in the context of Malawi. The AHHA trial aims to test the efficacy of improving human selenium status through consumption of maize flour enriched with selenium through agronomic biofortification.

Who can participate
The trial is based in Wimbe Traditional Authority, Kasungu District, Central Region, Malawi. The area is characterised by predominantly subsistence farming alongside smallholder and estate tobacco production. Participants will be selected from a predefined study area with a recruitment target of 180 non-pregnant women of reproductive age and 180 school-aged children.

What does the study involve?
Households in the study area will be provided with maize flour for a period of 12 weeks. Participants will be randomly allocated to one of two arms to receive flour enriched with

selenium or control flour that is not biofortified with selenium. Blood samples will be drawn from participating individuals before and after flour distribution. Selenium status will be measured in the laboratory and individuals in the different trial arms will be compared.

What are the possible benefits and risks of participating?
Participants will receive free maize flour for the duration of the 12-week flour distribution period. Enough maize flour will be provided to meet household needs. This will allow households to save their own maize reserves or money that would have been spent on purchasing maize. There are minimal risks to participating. During formative research, participants raised the potential concern of negative social stigma through receiving free maize flour. This will be addressed through a comprehensive community sensitisation process.

Where is the study run from?
The study will be run in the community. The trial is led by researchers from the London School of Hygiene & Tropical Medicine (UK), the Lilongwe University of Agriculture and Natural Resources (Malawi), the College of Medicine, University of Malawi, and the University of Nottingham (UK).

When is the study starting and how long is it expected to run for?
Preparations for the study started in July 2018 with a period of formative research. The flour distribution period will run from mid-July to mid-October 2019 with baseline and end-line surveys conducted immediately before and after. Sample and data analysis will be completed by March 2020.

Who is funding the study?
The study forms part of the GeoNutrition project (www.geonutrition.com) which is a 42-month project funded by the Bill & Melinda Gates Foundation (OPP1181048).

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
2018-KEP-196

Study information

Scientific Title
Alleviating Hidden Hunger with Agronomy: a randomised, controlled trial in rural Malawi to test the efficacy of alleviating selenium deficiency through consumption of maize flour enriched with fertilizers

Acronym
AHHA

Study objectives
Current study hypothesis as of 21/06/2019:
The study team hypothesise that the selenium status of women of reproductive age and school-aged children in rural Malawi can be improved through consumption of maize flour that is enriched with selenium through agronomic biofortification, i.e. application of micronutrient-containing fertilizers.

Previous study hypothesis:
The study team hypothesise that the zinc or selenium status of women of reproductive age and school-aged children in rural Malawi can be improved through consumption of maize flour that is enriched with zinc or selenium through agronomic biofortification, i.e. application of micronutrient-containing fertilizers.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Approved 11/01/2019, London School of Hygiene & Tropical Medicine Interventions Research Ethics Committee (UK) (Keppel Street, London, WC1E 7HT; +44 (0) 20 7636 8636; Ethics@lshtm.ac.uk), ref: 16181
2. Approved 28/01/2019, College of Medicine Research Ethics Committee (Malawi) (3rd Floor, John Chiphangwi Learning Resource Centre, Private Bag 360, Chichiri, Blantyre 3, Malawi; +265 11 871 911; comrec@medcol.mw), ref P.11/18/2539

Study design
Two-arm double-blind randomised controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Community

Study type(s)
Prevention

Participant information sheet
Not available in web format, please use contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Deficiency of selenium

Interventions
Current interventions as of 21/06/2019:
The study area was defined by selecting two neighbouring Enumeration Areas with sufficient population to meet the target sample size, based on existing demographic information. All households in the study area will be enumerated. Households containing at least one non-pregnant woman of reproductive age (20-45 years) and one school-aged child (5-10 years) will be eligible for the trial and randomised into one of two arms: 'Selenium arm' or 'Control arm' in a 1:1 ratio. Randomisation will be conducted centrally after the baseline survey using simple randomisation. Grain will be processed into ‘Granmill’ maize flour prior to bagging and distribution. ‘Granmill’ flour is made from the whole grain after removing the bran. Households will receive maize flour in multiples of 5 kg bags sufficient to meet requirements of all household members for the 90-day flour distribution period, with distributions at two-week time points. Household requirements will be calculated based on estimated consumption of 330 g /capita/day for all household members over the age of 1 year (equivalent to 10 kg/capita /month).

Selenium arm
Households (n=90) will receive maize flour enriched with selenium through application of selenium-containing fertilizers during the production of the maize. The target selenium concentration in the selenium-biofortified maize flour is >0.2 ppm.

Control arm
Households (n=90) will receive maize flour grown with conventional application of plant macronutrients, thus not enriched with selenium. The expected range of selenium concentration in the control flour is 0.02-0.04 ppm.

Previous interventions:
The study area was defined by selecting three neighbouring Enumeration Areas with sufficient population to meet the target sample size, based on existing demographic information. All households in the study area will be enumerated. Households containing at least one non-pregnant woman of reproductive age (20-45 years) and one school-aged child (5-10 years) will be eligible for the trial and randomised into one of three arms: 'Zinc arm', 'Selenium arm' or 'Control

arm' in a 2:1:2 ratio. Randomisation will be conducted centrally after the baseline survey using simple block randomisation stratified by village. Grain will be processed into 'Granmill' maize flour prior to bagging and distribution. 'Granmill' flour is made from the whole grain after removing the bran. Households will receive maize flour in multiples of 5 kg bags sufficient to meet requirements of all household members for the 90-day flour distribution period, with distributions at two-week time points. Household requirements will be calculated based on estimated consumption of 330 g/capita/day for all household members over the age of 1 year (equivalent to 10 kg/capita/month).

Zinc arm
Households (n=120) will receive maize flour enriched with zinc through application of zinc-containing fertilizers and compost during the production of the maize. The target zinc concentration in the zinc-biofortified maize grain is >30 ppm.

Selenium arm
Households (n=60) will receive maize flour enriched with selenium through application of selenium-containing fertilizers during the production of the maize. The target selenium concentration in the selenium-biofortified maize flour is >0.2 ppm.

Control arm
Households (n=120) will receive maize flour grown with conventional application of plant macronutrients, thus not enriched with zinc or selenium. The expected range of concentrations in the control flour are 18-22 ppm for zinc and 0.02-0.04 ppm for selenium.

Intervention Type
Other

Primary outcome measure
Current primary outcome measure as of 21/06/2019:
Serum selenium concentration
Serum selenium concentration will be determined by Inductively-Coupled Plasma Mass Spectrometry (ICP-MS). The unit of measure is µg Se/L of serum. Serum Se concentrations will be compared against established thresholds for deficiency measured at baseline and 12-weeks.

Previous primary outcome measure:
1. Zinc arm: DNA fragmentation analysis
DNA fragmentation will be quantified using the Comet Assay method and Comet Assay IV Lite software (Perceptive Instruments, London, UK) will be used to measure tail moments. The unit of measure is mean (±SEM) comet tail moment, defined as the product of the tail length and the fraction of total DNA in the tail (Tail moment=tail length x % of DNA in the tail) measured at baseline and 12-weeks.
2. Selenium arm: Serum selenium concentration
Serum selenium concentration will be determined by Inductively-Coupled Plasma Mass Spectrometry (ICP-MS). The unit of measure is µg Se/L of serum. Serum Se concentrations will be compared against established thresholds for deficiency measured at baseline and 12-weeks.

Secondary outcome measures
Current secondary outcome measures as of 21/06/2019:
1. Haematology
Haemoglobin concentrations will be measured using HemoCue and compared against standard thresholds to indicate anaemia status. Inflammatory markers (α1-acid glycoprotein and C-

reactive protein) will be measured using a sandwich ELISA. Measured at baseline and 12-weeks.
2. Morbidity
Diarrhoea incidence, severity and duration, incidence of vomiting and incidence of fever will be recorded. Prevalence of pneumonia will be measured among school-aged children, i.e. number of days of coughing and fast or difficult breathing (due to a problem in the chest) in the two weeks prior to the baseline and end-line surveys.
3. Dietary selenium supplies
Dietary data will be collected among participating women of reproductive age using 4-pass interactive 24-hour recall at baseline and end-line surveys. Dietary data will be collected across all days of the week (population level) to account for any day of the week effect. Dietary data will be combined with relevant food composition data (including specific data for intervention maize flour) to determine the intakes of energy and nutrients (including selenium). The percentage of women at risk of inadequate intakes of selenium will be estimated using the Estimated Average Requirement cut-point method after adjustment for intra-subject variability. The percentage of energy from food groups, sub-groups and specific foods will be estimated to examine changes in diet patterns.

Previous secondary outcome measures:
1. Serum zinc concentration
Serum zinc concentration will be determined by Inductively-Coupled Plasma Mass Spectrometry (ICP-MS). The unit of measure is mg Zn/L of serum. Serum zinc concentrations will be compared against established thresholds for deficiency, adjusted for inflammation. Measured at baseline and 12-weeks.
2. Serum zinc: copper molar ratio
Serum zinc and copper concentrations will be determined by Inductively-Coupled Plasma Mass Spectrometry (ICP-MS). The molar zinc:copper ratio will be calculated and compared between trial arms. Measured at baseline and 12-weeks.
3. Fatty acid ratio
The molar ratio of linoleic acid:dihomo-γ-linolenic acid will be determined in erythrocytes through gas chromatography and compared between trial arms. Measured at baseline and 12-weeks.
4. Haematology
Haemoglobin concentrations will be measured using HemoCue and compared against standard thresholds to indicate anaemia status. Inflammatory markers (α1-acid glycoprotein and C-reactive protein) will be measured using a sandwich ELISA. Measured at baseline and 12-weeks.
5. Morbidity
Diarrhoea incidence, severity and duration will be recorded using a standard score card. Prevalence of pneumonia will be measured among school-aged children, i.e. number of days of coughing and fast or difficult breathing (due to a problem in the chest) in the two weeks prior to the baseline and end-line surveys.
6. Dietary Zn supplies
Dietary data will be collected among a subset of at least 60 participating women of reproductive age using 4-pass interactive 24-hour recall at baseline and end-line surveys. Dietary data will be collected across all days of the week (population level) to account for any day of the week effect. Dietary data will be combined with relevant food composition data (including specific data for intervention maize flour) to determine the intakes of energy and nutrients (including zinc and selenium). The percentage of women at risk of inadequate intakes of zinc and selenium will be estimated using the Estimated Average Requirement cut-point method after adjustment for intra-subject variability; and assuming low bioavailability for Zn. The percentage of energy from food groups, sub-groups and specific foods will be estimated to examine changes in diet patterns.

Overall study start date
01/07/2018

Completion date
01/02/2020

Eligibility

Key inclusion criteria
Current inclusion criteria as of 21/06/2019:
Household level:
1. Participating households should have at least one non-pregnant woman of reproductive age (WRA; 20-45 years) and at least one school-aged child (SAC; 5-10 years) in residence during July-October
2. Household typically prepares and consumes meals at home
3. Household head provides permission to receive and consume assigned flour in place of their own flour for 12-week flour distribution period
Individual level:
1. One WRA and one SAC will be randomly selected to participate from each eligible household. Pregnancy status will be self-reported
2. Participant is planning to be in residence during July-October
3. Participant WRA is willing and able to provide consent, and caretaker of participant SAC is willing and able to provide assent

Previous inclusion criteria:
1. Participating households should have at least one non-pregnant woman of reproductive age (WRA; 20-45 years) and at least one school-aged child (SAC; 5-10 years). Pregnancy status will be self-reported. One WRA and one SAC will be randomly selected to participate from each eligible household
2. Household typically prepares and consumes meals at home
3. Household are willing and able to receive and consume assigned flour in place of their own flour for 12-week flour distribution period
4. Individual participants are willing and able to give informed consent (for WRA) or assent (for SAC)

Participant type(s)
Healthy volunteer

Age group
Mixed

Sex
Both

Target number of participants
180 women of reproductive age and 180 school aged children

Total final enrolment
360

Key exclusion criteria
Does not meet inclusion criteria

Date of first enrolment
26/06/2019

Date of final enrolment
06/07/2019

Locations

Countries of recruitment
Malawi

Study participating centre
Lilongwe University of Agriculture and Natural Resources
Bunda Campus
Lilongwe
Malawi
PO Box 219

Sponsor information

Organisation
London School of Hygiene & Tropical Medicine

Sponsor details
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Sponsor type
University/education

Website
http://www.lshtm.ac.uk

ROR
https://ror.org/00a0jsq62

Funder(s)

Funder type
Charity

Funder Name
Bill and Melinda Gates Foundation

Alternative Name(s)
Bill & Melinda Gates Foundation, Gates Foundation, BMGF, B&MGF, GF

Funding Body Type
Government organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United States of America

Results and Publications

Publication and dissemination plan
Results will be written up as academic research papers for submission to peer-reviewed journals. Papers will be published open-access. Findings will also be discussed in face-to-face meetings with policy and practitioner stakeholders in Malawi, and will be presented at relevant conferences including the 2020 National Research Dissemination Meeting in Malawi.

Raw data will be shared through the LSHTM Data Compass repository with appropriate protections in place to ensure participant anonymity.

Results of the trial will be presented to the study communities through village-level meetings. The vital contribution of the communities and the trial participants will be highlighted. Results will also be presented to local extension workers and District-level offices, to show how their support enabled the generation of evidence to inform policy decisions.

Intention to publish date
01/10/2021

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be stored in a publically available repository

IPD sharing plan summary
Stored in repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Other publications	Participants' experiences	03/12/2021	30/12/2021	Yes	No
Protocol article		30/12/2019	30/12/2021	Yes	No
Results article		06/01/2022	25/01/2022	Yes	No