PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Cohort profile: FOETALforNCD - Foetal exposure and Epidemiological Transition: the role of Anaemia in early Life for Non-Communicable Diseases in later life. - A prospective preconception study in rural Tanzania
AUTHORS	Hjort, Line; Møller, Sofie; Minja, Daniel; Msemo, Omari; Nielsen, Birgitte; Christensen, Dirk L.; Theander, Thor; Nielsen, Karsten; Larsen, Lise; Grunnet, Louise; Groop, Leif; Prasad, Rashmi; Lusingu, John; Schmiegelow, Christentze; Bygbjerg, Ib

VERSION 1 - REVIEW

REVIEWER	Ketil Størdal Norwegian Institute of Public Health
REVIEW RETURNED	06-Jul-2018

GENERAL COMMENTS	The manuscript consists of a study profile of an ongoing pregnancy cohort study in North-Eastern Tanzania. The overall aim is to identify risk factors of non-communicable diseases (NCDs) in a low-income area during rapid transition, with a particular focus on maternal anemia during pregnancy. The study is ambitious and relatively large-scale, given the settings. The manuscript is well written. At this stage, only baseline data are provided, though still the content is of interest and expected to serve as a reference paper for future publications. As a minor comment, the title uses FETAL whereas later in the manuscript FOETAL is used as acronym. There are two major weaknesses of the study: 1. A much lower prevalence of severe anemia than expected in the planning phase and 2. Lack of description of how NCDs are going to be captured and defined during follow-up. The first weakness is well covered, and during recruitment additional efforts were initiated to increase the number of anemic mothers, deviating from the intended plan of including only before pregnancy by later also including early pregnancies. However, there are inconsistencies in the definitions used for anemia grading: The initial power calculations defined “moderate/severe anemia” as <8.0 g/dL (lower part, page 6). Probably due to the lower prevalence of this grade of anemia, the authors without explanation change the definition of “moderate/severe” to <9.0 g/dL. Table 3 reports the numbers <11.0 g/dL and <9.0 g/dL. It would be fair to include also the numbers meeting the protocolled definition, and to comment this change in the text. The association between pregnancy hemoglobin and birth weight may be non-linear, and the reference #5 even states the U-shaped relation in the title. Thus, the causal language in line 6 should be

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	modified to a more careful phrasing, as it is done in the middle of this page with differentiation for the differences seen by trimester. The main hypothesis – that maternal anemia mediated through restricted fetal growth may increase NCD risk – is intriguing however debatable: The study has the potential by careful interpretation and statistical modeling to explore factors in addition to anemia affecting fetal and placental growth and risk of later NCD. Other macro- and micronutrients besides iron (i.e. iodine, vitamin B12) could be as important, and it would be of interest to know whether the mothers did take any supplements during pregnancy. The title and overall aim of the study is NCDs, however the description of NCDs as the final endpoint is vaguely mentioned (p 12). I would expect that the Figure 2 should contain more information regarding later follow-up. Tanzanian children are followed by monthly weighing; do the researchers aim to use data from the health clinics (growth charts)? Are there any existing plans to screen for obesity, hypertension, markers of atherosclerosis or type 2 diabetes later in life? Though this is certainly a challenging task, later data collection deserves some more explanation. From the manuscript including Table 1 and Figure 2, it may seem like the current plan is to use fetal and placental growth and epigenetic markers as the final end point. This would be proxy markers for future NCDs, and should be discussed as a weakness of the study.

REVIEWER	Michael Osei Mireku University of Lincoln, Lincoln, UK
REVIEW RETURNED	03-Aug-2018

GENERAL COMMENTS	The manuscript by Hjort and colleagues reports of a cohort profile which aims to evaluate anaemia-induced alterations of foetal and placental development and susceptibility to NCDs, taking into consideration the contribution of malaria. Overall, this manuscript presents results that would be of interest to the community of scientists and clinicians concerned with this problem. However, there are a few issues in this manuscript. Major: Although the FETALforNCD study aims to understand the consequences of perinatal anaemia (at preconception, during pregnancy and early postnatal stages) on birth outcomes and the risk of non-communicable diseases in later life, the authors did not discuss these essential ongoing debate: (i) The potential role of high Hb concentration on birth and childhood outcomes: During pregnancy, a small decline in Hb concentration (i.e. high Hb concentration) has been reported to be associated with adverse birth outcomes and child development (Jwa et al., 2015. Changes in maternal hemoglobin during pregnancy and birth outcomes. BMC Pregnancy and Childbirth; Stephansson et al., 2000. Maternal Hemoglobin Concentration During Pregnancy and Risk of Stillbirth. The American Journal of Clinical Nutrition; Mireku et al., 2015. Prenatal Hemoglobin Levels and Early Cognitive and Motor Functions of One-Year-Old Children. Pediatrics)

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	(ii) Prenatal iron deficiency not necessarily associated with neonatal iron deficiency and adverse birth outcomes: Just like the previous examples, several papers have shown that prenatal iron deficiency/ iron supplementation is not associated with adverse birth outcomes i.e. (Angulo-Barroso et al., doi: 10.1542/peds.2015-3547 etc) It would be good to discuss how this was or will be considered in the design or analysis of the FETALforNCD study. Minor: Abstract: 1. Line 56-59: Consider rephrasing the sentence. The list includes measures, processes and samples collected and not only measures. 2. Line 61-62: Indicate that this is the prevalence of anaemia at preconception. Introduction: Line 180: With regards to your control group for the omics study, it will be important to state later in your results section or tables, the number of women with no anaemia and malaria throughout pregnancy. Methods: Line 216 – 234: It is unclear which of the outcomes were used to determine the required sample size for this study. Knowing this will explain to the readers which analysis (in relation to the specific outcome of interest) will be sufficiently powered. Strengths and limitations: 1. The sentence on line 388-390 is unclear. Please consider rephrasing sentence. 2. Line 402-406: I would prefer you compare you study and its future findings to that conducted in other LMICs. The causes of anaemia in LMICs is multifactorial and not only do to iron deficiency so your study findings may not be easily generalizable to the population of pregnant women in Denmark for example. 3. It would be important to discuss how the previous major debates in this area (of research mentioned at the beginning of my comments) affects your study and how they have or will be accounted for. I suggest slight revision of the grammar, tense and punctuation in the manuscript - there are a few errors and although they may appear minor they disrupt the flow of the manuscript. E.g. (i) Line 238: “The following” instead of “Following” (ii) Line 318: After giving oral information comma (iii) Line 333: analysis instead of “analyse” (iv) Line 365 missing a full stop

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VERSION 1 – AUTHOR RESPONSE

Reviewer comments

Reviewer: 1

Reviewer Name: Ketil Størdal

Institution and Country: Norwegian Institute of Public Health

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below:

The manuscript consists of a study profile of an ongoing pregnancy cohort study in North-Eastern Tanzania. The overall aim is to identify risk factors of non-communicable diseases (NCDs) in a low-income area during rapid transition, with a particular focus on maternal anemia during pregnancy. The study is ambitious and relatively large-scale, given the settings.

The manuscript is well written. At this stage, only baseline data are provided, though still the content is of interest and expected to serve as a reference paper for future publications. As a minor comment, the title uses FETAL whereas later in the manuscript FOETAL is used as acronym.

Author answer:

We kindly thank the reviewer for these encouraging comments.

We have corrected the spelling of "fetal" so it's the same throughout.

There are two major weaknesses of the study: 1. A much lower prevalence of severe anemia than expected in the planning phase and 2. Lack of description of how NCDs are going to be captured and defined during follow-up.

The first weakness is well covered, and during recruitment additional efforts were initiated to increase the number of anemic mothers, deviating from the intended plan of including only before pregnancy by later also including early pregnancies. However, there are inconsistencies in the definitions used for anemia grading: The initial power calculations defined "moderate/severe anemia" as <8.0 g/dL (lower part, page 6). Probably due to the lower prevalence of this grade of anemia, the authors without explanation change the definition of "moderate/severe" to <9.0 g/dL. Table 3 reports the numbers <11.0 g/dL and <9.0 g/dL. It would be fair to include also the numbers meeting the protocolled definition, and to comment this change in the text.

Author answer:

Thank you for pointing out the inconsistencies regarding the moderate to severe anemia definitions. We have corrected the text throughout the manuscript to clearly state our definitions of anemia: severe anemia <8.0 g/dl and moderate to severe <9.0 g/dl. To be true to the initial power calculations, as the reviewer also comment, we have included the results of the severe anemia<8.0 g/dl in table 3, as well as in the abstract and results section as shown below:

Line 62-65:

"During pregnancy, in total 359 (66.7%) women had anemia of which 85 (15.8%) women had moderate to severe anemia (Hb≤9g/dl), and 33 (6.1%) women had severe anemia (Hb≤8g/dl). In total, 185 (34.4%) women were diagnosed with malaria during pregnancy."

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Line 377-378:

During pregnancy, 359 (66.7%) women had anemia (Hb<11g/dl) of which 85 (15.8%) women had moderate to severe anemia (Hb≤9g/dl), and 33 (6.3%) had severe anemia (Hb≤8g/dl).

The association between pregnancy hemoglobin and birth weight may be non-linear, and the reference #5 even states the U-shaped relation in the title. Thus, the causal language in line 6 should be modified to a more careful phrasing, as it is done in the middle of this page with differentiation for the differences seen by trimester.

Author answer:

We thank the reviewer for this comment, and we acknowledge that the association between pregnancy hemoglobin and birth weight may not be linear. We agree that the phrasing in line 126 is too strong and have modified it as shown below.

Line 126:

“Anemia in pregnancy may decrease birthweight….”

The main hypothesis – that maternal anemia mediated through restricted fetal growth may increase NCD risk – is intriguing however debatable: The study has the potential by careful interpretation and statistical modeling to explore factors in addition to anemia affecting fetal and placental growth and risk of later NCD. Other macro- and micronutrients besides iron (i.e. iodine, vitamin B12) could be as important, and it would be of interest to know whether the mothers did take any supplements during pregnancy.

Author answer:

We fully agree that other both macro- and micro nutrients besides iron could be as important. All women were offered daily iron and folic acid supplementation from recognition of pregnancy If a woman was diagnosed with anemia, she was treated with increased supplementation with either 2-3 combination tablets of iron-folic acid per day or with Hemovit® multivitamin syrup (200 mg Ferrous sulfate, 0.5 mg B6, 50 µg B12, 1.5 mg Folic acid and 2.33 mg zinc sulphate per 5mL in a dose of 10 ml 2-3 times daily depending on severity. Supplement intake was documented.

Line 262-268:

“All women were offered daily iron and folic acid supplementation from the time pregnancy was recognized and until delivery (combination tablet of 200mg ferrous sulfate (~43mg elemental iron) and 400µg folate per day (Ferrolic–LF®, Laboratory and Allied LTD, Mombasa, Kenya)). If anemia was diagnosed, it was treated with increased supplementation with either 2-3 combination tablets of iron-folic acid per day or with Hemovit® multivitamin syrup (200mg Ferrous sulfate, 0.5mg B6, 50µg B12, 1.5mg Folic acid and 2.33mg zinc sulphate per 5mL (Shelys Pharmaceuticals, Dar es Salaam, Tanzania)) in dose of 10ml 2-3 times daily depending on severity.”

The title and overall aim of the study is NCDs, however the description of NCDs as the final endpoint is vaguely mentioned (p 12). I would expect that the Figure 2 should contain more information regarding later follow-up. Tanzanian children are followed by monthly weighing; do the researchers aim to use data from the health clinics (growth charts)? Are there any existing plans to screen for obesity, hypertension, markers of atherosclerosis or type 2 diabetes later in life? Though this is certainly a challenging task, later data collection deserves some more explanation.

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Author answer:

Thank you for this comment. We fully agree that it would be of high importance and interest to conduct further follow-up studies of the children of this cohort, however, follow-up of the newborns after the 1 month's neonatal visit was beyond the funding of the current study. Yet, the baseline of data has now been established to be able to conduct such later studies, which we most definitely will do if potential funding is acquired. This have been mentioned in the manuscript as shown below:

Line 419-425:

"It will be of high importance to follow-up the children of this cohort to further investigate the outcome of the development programming with focus on risk markers of NCDs, e.g. hypertension, metabolic profile and obesity. Longitudinal studies, commencing prior to conception and with continuous follow-up, are indeed required to unravel the potentially complex interplay between maternal health and offspring epigenetic profile to understand how epigenetic mechanisms may contribute to disease risk."

From the manuscript including Table 1 and Figure 2, it may seem like the current plan is to use fetal and placental growth and epigenetic markers as the final end point. This would be proxy markers for future NCDs, and should be discussed as a weakness of the study.

Author answer:

We acknowledge that the fetal and placental markers are only proxies for later development of NCDs, and that offspring follow-up is of highest importance. We have included a discussion of this in the manuscript as shown below:

Line 417-422:

"The aims of this study include use of fetal and placental growth markers and epigenetic changes as end points in analyses of the effect of anemia on fetal health. However, we acknowledge that these measurements are only proxy markers for future NCDs. It will be of high importance to follow-up the children of this cohort to further investigate the outcome of the development programming with focus on risk markers of NCDs, e.g. hypertension, metabolic profile and obesity."

Reviewer: 2

Reviewer Name: Michael Osei Mireku

Institution and Country: University of Lincoln, Lincoln, UK

Please state any competing interests or state 'None declared': None

Please leave your comments for the authors below:

The manuscript by Hjort and colleagues reports of a cohort profile which aims to evaluate anaemia-induced alterations of foetal and placental development and susceptibility to NCDs, taking into consideration the contribution of malaria. Overall, this manuscript presents results that would be of interest to the community of scientists and clinicians concerned with this problem. However, there are a few issues in this manuscript.

Author answer:

We kindly thank the reviewer for the positive response.

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Major:

Although the FETALforNCD study aims to understand the consequences of perinatal anaemia (at preconception, during pregnancy and early postnatal stages) on birth outcomes and the risk of non-communicable diseases in later life, the authors did not discuss these essential ongoing debate:

(i) The potential role of high Hb concentration on birth and childhood outcomes: During pregnancy, a small decline in Hb concentration (i.e. high Hb concentration) has been reported to be associated with adverse birth outcomes and child development (Jwa et al., 2015. Changes in maternal hemoglobin during pregnancy and birth outcomes. BMC Pregnancy and Childbirth; Stephansson et al., 2000. Maternal Hemoglobin Concentration During Pregnancy and Risk of Stillbirth. The American Journal of Clinical Nutrition; Mireku et al., 2015. Prenatal Hemoglobin Levels and Early Cognitive and Motor Functions of One-Year-Old Children. Pediatrics)

Author answer:

Thank you for this comment, and we agree that the role of high HB concentration is an interesting and potential role also to consider. We have now included a section describing this in the introduction as well as how we will account for this in the analyses, as shown below.

Line 140-144:

“Of note, it is also debated whether high Hb concentration in pregnancy has a positive or negative effect on birth and childhood outcomes(17), i.e. it has been shown that high Hb concentrations (≥14.6g/dl) were associated with an increased risk of stillbirths in a Swedish case-control study(18), and furthermore that reduction in Hb concentration from early pregnancy to delivery was associated with increased birthweight (18).”

Line 431-433:

“In addition, with this study design, we will be able to account for the effects of moderate to severe anemia vs. mild anemia, vs. no anemia as well as high Hb concentrations.”

(ii) Prenatal iron deficiency not necessarily associated with neonatal iron deficiency and adverse birth outcomes: Just like the previous examples, several papers have shown that prenatal iron deficiency/ iron supplementation is not associated with adverse birth outcomes i.e. (Angulo-Barroso et al., doi: 10.1542/peds.2015-3547 etc)

It would be good to discuss how this was or will be considered in the design or analysis of the FETALforNCD study.

Author answer:

This is an interesting point, and it is indeed important to include the iron- and Hb dynamics in the analyses. We have repeated measurements of these markers as well as measures of iron deficiency before conception. We will hence be able to include these considerations in the analyses. These analyses will hopefully add to the current knowledge of how maternal iron deficiency and anemia – as well as the timing of maternal iron deficiency - may or may not lead to neonatal iron deficiency and adverse birth outcomes. We have now included a section in the discussion, to describe why and how this will be considered in the subsequent analyses, as shown below:

Line 436-443:

“Although several studies report that prenatal anemia is associated with adverse birth outcomes(5,10), prenatal iron deficiency is not necessarily associated with neonatal iron deficiency, as shown in a recent randomized control study by Angulu-Barosso et al.(44). To account for the

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dynamics of iron deficiency during the pregnancy, we have obtained repeated measurements of iron and Hb concentrations preconception and throughout pregnancy. Therefore, we will be able to include the iron- and Hb dynamics in the subsequent analyses, which will improve the understanding of how maternal iron deficiency may or may not lead to fetal iron deficiency and adverse birth outcomes."

Minor:

Abstract:

1. Line 56-59: Consider rephrasing the sentence. The list includes measures, processes and samples collected and not only measures.

Author answer:

Thank you for this suggestion, we have now rephrased the sentence to the following:

Line 56:

"Data collection included: maternal blood, screening for NCDs and malaria……"

2. Line 61-62: Indicate that this is the prevalence of anaemia at preconception.

Author answer:

Thank you for pointing this out, we have now rephrased the sentence to the following:

Line 61-61:

"In total, 458 (36.7%) women had anemia (Hb<12g/dl) and 34 (3.6%) women were diagnosed HIV positive at preconception."

Introduction:

Line 180: With regards to your control group for the omics study, it will be important to state later in your results section or tables, the number of women with no anaemia and malaria throughout pregnancy.

Author answer:

Thank you for this comment. We agree that it would be useful to include the number of women with neither anemia nor malaria during pregnancy. These numbers have now been included in table 1 and in the results section as shown below:

Line 380-381:

"In total, 147 (27.3%) women were non-anemic and never had malaria throughout pregnancy (Table 3)."

Methods:

Line 216 – 234: It is unclear which of the outcomes were used to determine the required sample size for this study. Knowing this will explain to the readers which analysis (in relation to the specific outcome of interest) will be sufficiently powered.

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Author answer:

The power calculation was based on severe anemia (≤8g/dl) in second trimester as exposure, and Z-score for birthweight as the outcome. We have rephrased the sentence to make the explanation of the sample size calculation clearer, as shown below:

Line 229-232:

“Sample size calculation was originally based on the observed effect of severe anemia (Hb≤8g/dl) in the 2nd trimester on z-score of birthweight (-0.31) in the STOPPAM study(30) conducted in the same area, with a significance level of 0.05, power of 0.80, and an assumption of 15% lost to follow-up.”

Strengths and limitations:

1. The sentence on line 388-390 is unclear. Please consider rephrasing sentence.

Author answer:

Thank you for pointing this out, we have now rephrased the sentence to the following:

Line 400-407:

“The uniqueness of this study lies in the establishment of a population that is followed continuously before and during pregnancy with an accurate estimation of GA using early ultrasound, and includes detailed, high-quality data of fetal weight and placental blood flow monitoring, stringent screening for development of hypertension or diabetes, and a substantial biobank of plasma, serum, cord blood and placenta, including stereology and epigenetic markers, which to our knowledge not have been collectively studied before in a rural African setting.”

2. Line 402-406: I would prefer you compare you study and its future findings to that conducted in other LMICs. The causes of anaemia in LMICs is multifactorial and not only do to iron deficiency so your study findings may not be easily generalizable to the population of pregnant women in Denmark for

example.

Author answer:

We acknowledge that it is important to recognize that anemia in LMICs compared to a country as i.e. Denmark may have quite different causes, and not necessarily iron deficiency alone, and that these causes may give rise to different outcomes. We have included this in the discussion section as shown below:

Line 429-435:

“Yet, the higher number of mild anemia cases might relate more to areas of the world where mild pregnancy anemia prevails, so our subsequent analyses may reveal if even slight decrease of Hb may have adverse effects. In addition, with this study design, we will be able to account for the effects of moderate to severe anemia vs. mild anemia, vs. no anemia as well as high Hb concentrations. Still it’s important to recognize that causes for anemia may highly wary from LMICs to more westernized countries, i.e. Denmark, and therefore the consequences of anemia may also be different.”

3. It would be important to discuss how the previous major debates in this area (of research mentioned at the beginning of my comments) affects your study and how they have or will be accounted for.

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Author answer:

Thank you for this comment, which we fully agree upon. Please see our author response to your previous comment regarding this issue.

I suggest slight revision of the grammar, tense and punctuation in the manuscript - there are a few errors and although they may appear minor they disrupt the flow of the manuscript. E.g.

(i) Line 238: “The following” instead of “Following”

(ii) Line 318: After giving oral information comma

(iii) Line 333: analysis instead of “analyse”

(iv) Line 365 missing a full stop

Author answer:

Thank you for pointing this out. We have now revised the manuscript with careful focus on grammar and have corrected it to the best of our abilities, including the above kindly mentioned suggestions from the reviewer.

VERSION 2 – REVIEW

REVIEWER	Ketil Størdal Norwegian Institute of Public Health
REVIEW RETURNED	09-Oct-2018

GENERAL COMMENTS	Thanks for allowing to again revise the current manuscript. The authors have well clarified the issues from the previous version. A few minor remaining comments: I note that the authors have made a distinction of preconception and pregnancy cut-offs for anemia of <12 and 11 g/dL, respectively. The definitions now appear clear. I suggest to clarify and rephrase line 406-407: “…high income countries are having high prevalence of anemia in pregnancy.” Besides, references should be given to underpin the statement. As iron is actively transported across the placenta, fetal iron metabolism is likely as relevant as the maternal for fetal growth and later NCD risks. The added statement in line 440-441: “…repeated measurements of iron and Hb concentrations preconception and throughout pregnancy.” may be improved by adding here iron markers and Hb in cord blood as well as during pregnancy.

REVIEWER	Michael Osei Mireku University of Lincoln, Lincoln, UK
REVIEW RETURNED	22-Sep-2018

GENERAL COMMENTS	All my comments have been addressed by the authors.

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VERSION 2 – AUTHOR RESPONSE

Reviewers' Comments to Author:

Reviewer: 1

Reviewer Name: Ketil Størdal

Institution: Norwegian Institute of Public Health

Please state any competing interests or state 'None declared': None declared

Thanks for allowing to again revise the current manuscript. The authors have well clarified the issues from the previous version. A few minor remaining comments:

I note that the authors have made a distinction of preconception and pregnancy cut-offs for anemia of <12 and 11 g/dL, respectively. The definitions now appear clear.

I suggest to clarify and rephrase line 406-407: "…high income countries are having high prevalence of anemia in pregnancy." Besides, references should be given to underpin the statement.

Author answer:

We kindly thank the reviewer for this comment. We have now rephrased the sentence, as well as added a reference:

Line 406-407:

"Anemia before, during and after pregnancy is much more prevalent in LMICs, compared to high income countries (HICs) which mainly have high prevalence of anemia during pregnancy(4)."

As iron is actively transported across the placenta, fetal iron metabolism is likely as relevant as the maternal for fetal growth and later NCD risks. The added statement in line 440-441: "…repeated measurements of iron and Hb concentrations preconception and throughout pregnancy." may be improved by adding here iron markers and Hb in cord blood as well as during pregnancy.

Author answer:

Thank you for this comment. We agree that it would be very valuable to also measure iron markers in cord blood, but this was not part of the initial planned analyses. We do however have serum and plasma stored at -80 degrees, enabling us to do this in the future. HB was measured in cord blood.We have now rephrased the sentence, to include this knowledge:

Line 437-440:

"To account for the dynamics of iron deficiency during the pregnancy, we have obtained repeated measurements of iron and Hb concentrations preconception and throughout pregnancy. Cord blood serum and plasma is also stored and available for future measurements of iron markers."

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Correction: *FOETAL for NCD—FOetal Exposure and Epidemiological Transitions: the role of Anaemia in early Life for Non-Communicable Diseases in later life: a prospective preconception study in rural Tanzania*

Hjort L, Lykke Møller S, Minja D, *et al*. FOETAL for NCD—FOetal Exposure and Epidemiological Transitions: the role of Anaemia in early Life for Non-Communicable diseases in later life: a prospective preconception study in rural Tanzania. *BMJ Open* 2019;9:e024861. doi: 10.1136/bmjopen-2018-024861

This article was previously published with missing information.
Christentze Schmiegelow and Ib C Bygbjerg contributed equally to the paper.

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