PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Cohort profile: Stanford's Outcomes Research in Kids (STORK) - A prospective study of healthy pregnant women and their babies in Northern California.
AUTHORS	Ley, Catherine; Sanchez, Maria de Luz; Mathur, Ankur; Yang, Shufang; Sundaram, Vandana; Parsonnet, Julie

VERSION 1 - REVIEW

REVIEWER	Hanna Lagström University of Turku, Finland
REVIEW RETURNED	25-Jan-2016

GENERAL COMMENTS	The current study seeks to determine the effect of infectious diseases on weight, linear growth and immune system development during childhood. The data is based on ongoing prospective cohort of healthy pregnant women and their babies: The Stanford's Outcomes Research in Kids (STORK). In general, the paper is well written, but to date the authors are able to show only very little results. In addition to this, I highlight some major points: 1. End of introduction is mentioned "a randomized intervention of TC-containing household and personal cleaning products (HPCP)", but I can't find any description of intervention in method section (or anywhere else). 2. Cohort description when (year and month) the recruitment started and ended? Figure 2 should be figure 1, and the so called main findings are more description of the study population. How old the children are at the moment? How many father are in the study? 3. The response rate at recruitment is extremely low. Attempts to increase participation need to be documented and reasons for the low participation rate provided. If possible, description of the methods used to recruit participants; numbers invited and numbers who entered the study (give response proportion); differences between responders and non-responders at baseline (ideally a table of socio-demographic characteristics comparing responders to non-responders or responders to the general population from which the responders came). 4. How about possible loss to follow-up over time? How this affect to results (small sample size)? 5. How about ethics approval; when and where the research plan has been approved? Are both mother and father signed the informed consent etc?

REVIEWER	GV Krishnaveni Research scientist, Holdsworth Memorial Hospital, India
REVIEW RETURNED	02-Feb-2016

GENERAL COMMENTS	This manuscript a cohort of mother and baby pairs established to examine the role of infectious disease on offspring growth, obesity and immunity. Though small in size, the study involves a detailed assessment of the mother and the baby, including weakly surveys and annual blood sampling. The authors expect that the findings of the study will form an important addition to the literature in this important area of health. I have a few comments as listed below: General comment: 1. The study does not state clearly what are the public health and clinical implications of frequent assessments that it involves. As repeated assessments, for long time periods involve a lot of time and effort commitment from the participants this needs to be clearly justified. 2. Would the authors please make a clear distinction of the observational and the intervention part of this study? It moves frequently between these two designs and makes the reading difficult. 3. Why do the authors include strengths and limitations twice? Abstract 1. The abstract should indicate when baseline data collection started, when will recruitments end and what is the proposed sample size. 2. Gestational age at pregnancy assessments should be included here. 3. Line 25: It says that “information and samples are collected at follow-up visits. Please indicate what information was collected. 4. A number of biological samples are being collected. Please briefly mention what assessments will be done using them. This is important especially since invasive investigations are being carried out in babies as young as 4 months, and repeated annually. This information should also be given in the main text. 5. The methods section should describe the intervention trial. 6. It is not clear if the recruitment and baseline assessments are complete, which is a requirement for the cohort profile. 7. The authors may include Trial Registration details here. Strengths and limitations 1. The authors state that it is a unique cohort, but do not sufficiently justify their statement. Please mention what unique feature sets this apart from existing pregnancy and birth cohorts in the world. Cohort description 1. Please make statement as to why the sample was chosen from lower socio-economic and Hispanic dominant regions? Can you also make a statement on the representativeness of the cohort for this region? 2. The description of assessments and samples can be better organised. Eg. A section for mothers with all the various assessments during pregnancy, and another section headed as follow-up which includes assessments after delivery. At present it veers between mother and the baby in every paragraph and can be

	confusing. 3. Pages 8 and 9, under the heading samples: Please state at what time points these different samples are collected from the mother and the baby. It says the blood is being collected at baseline and annually for the mother. Similar information should be given for all samples in the mother and the baby. This information is available in the abstract, but it should be described in detail here. 4. I think the objectives presented in the statistical methods section should be given in the Introduction/ rationale section. Statistical methods should include the proposed analysis plan. 5. Considering the huge amount of data that this study generates, a description of data processing, cleaning and analysis should be given. Findings to date: 1. The details about the recruitment, loss to follow-up etc. are more suited for the previous section. This information should be moved there. 2. In this study, only ~10% of those approached, ~18% who met the screening criteria, were finally recruited. This not only resulted in a small cohort size as the authors acknowledge, but may have implications for potential bias. The authors should discuss this in detail in their limitations section. If available, please would the authors include a table comparing socio-demographic characteristics for women included in the cohort at baseline and the general population of the women of the same age in this area? Please would they also include a comparison between the women screened and both the 902 who were eligible and 158 who formed the cohort of mothers at baseline? A comparison of those eligible but refused and the recruited mothers will also be helpful to assess the implications of the study. These tables should cover education, occupation, income, in addition to age and any available measures of health. Strengths and limitations 1. This section needs streamlining, and repetitions and superfluous sentences may be removed. 2. Lines 45-46 state that the cohort includes families from diverse racial and ethnic groups across a wide socioeconomic spectrum. However the cohort description section states that they were recruited from lower socio-economic and Hispanic dominant regions. This needs some rephrasing. 3. Page 12, line 3: Please explain in detail what is meant by ‘extraordinary depth’ here. 4. The authors repeatedly state that their sample is selected from diverse racial and ethnic groups across a wide socioeconomic spectrum. However, this characteristic has not been sufficiently projected in the manuscript to justify this. Please add a paragraph that brings out this diversity. 5. One of the strengths stated is the repeated sampling of the infants. I note that about 4 blood samples will be collected in 3 years. The authors should again justify the rationale for this and how this frequent sampling at young age is going to add extra value to the cohort.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Hanna Lagström
Institution and Country: University of Turku, Finland
Please state any competing interests or state 'None declared': None declared
Please leave your comments for the authors below.

The current study seeks to determine the effect of infectious diseases on weight, linear growth and immune system development during childhood.

The data is based on ongoing prospective cohort of healthy pregnant women and their babies: The Stanford's Outcomes Research in Kids (STORK).

In general, the paper is well written, but to date the authors are able to show only very little results. In addition to this, I highlight some major points:

1. End of introduction is mentioned "a randomized intervention of TC-containing household and personal cleaning products (HPCP)", but I can't find any description of intervention in method section (or anywhere else).
• The randomized intervention is briefly mentioned under COHORT DESCRIPTION, Recruitment as the entire third paragraph. We had intentionally chosen to keep this description very short as the focus of the paper is the cohort and not the intervention. We provide numbers of participants assigned to each intervention arm under FINDINGS TO DATE, second paragraph. A brief discussion of the participation rate and the intervention's timeliness is presented under STRENGTHS AND LIMITATIONS, third paragraph.

2. Cohort description when (year and month) the recruitment started and ended? Figure 2 should be figure 1, and the so called main findings are more description of the study population. How old the children are at the moment? How many father are in the study?
• We have included recruitment start and end dates (7/2011-2/2015) under COHORT DESCRIPTION, participant disposition (a new section).
• We have retained our original order of the figures, as the schedule of assessments (Figure 1) explains the entire data collection process under COHORT DESCRIPTION, Recruitment and the breakdown of the actual sample (Figure 2) is presented later under COHORT DESCRIPTION, Participant disposition (new section).
• We have included a sentence as to the current age of babies under FINDINGS TO DATE, last paragraph, last sentence.
• We have included a sentence as to the number of fathers who have consented to provide a weight measurement (FINDINGS TO DATE, last paragraph, first sentence). We have also clarified that the mother provided demographic information regarding the father (COHORT DESCRIPTION, Data collection, Household questionnaire, first sentence) and Table 1A (see table footer).

3. The response rate at recruitment is extremely low. Attempts to increase participation need to be documented and reasons for the low participation rate provided. If possible, description of the methods used to recruit participants; numbers invited and numbers who entered the study (give response proportion); differences between responders and non-responders at baseline (ideally a table of socio-demographic characteristics comparing responders to non-responders or responders to the general population from which the responders came).
• We agree that the response rate at recruitment is low. We have modified Figure 2 to include row percentages in addition to the total counts so that response proportions are easily identified. Under COHORT DESCRIPTION, Participant disposition, we provide a detailed breakdown of numbers invited and numbers who entered the study, with available characteristics described (language

spoken and reason for non-participation). Unfortunately, for privacy reasons our screening form did not include additional socio-demographic characteristics or other information in order to compare further responders and non-responders.

4. How about possible loss to follow-up over time? How this affect to results (small sample size)?
• We anticipated a 20% loss to follow-up per year as our sample is drawn from a highly mobile population. Under FINDINGS TO DATE, last paragraph, we had shown a 76% follow-up rate for the first year. We discuss the issues of small sample under STREGTHS AND LIMITATIONS, paragraph 5.

5. How about ethics approval; when and where the research plan has been approved? Are both mother and father signed the informed consent etc?
• Ethics approval was obtained from IRBs at both Stanford University and the Santa Clara Valley Medical Center and is listed as such under FURTHER DETAILS. A description of consent is provided under COHORT DESCRIPTION, Recruitment, paragraph 2 for the mother and paragraph 4 for both father and baby.

Reviewer: 2
Reviewer Name: GV Krishnaveni
Institution and Country: Research scientist, Holdsworth Memorial Hospital, India
Please state any competing interests or state 'None declared':None declared
Please leave your comments for the authors below.

This manuscript a cohort of mother and baby pairs established to examine the role of infectious disease on offspring growth, obesity and immunity. Though small in size, the study involves a detailed assessment of the mother and the baby, including weakly surveys and annual blood sampling. The authors expect that the findings of the study will form an important addition to the literature in this important area of health.
I have a few comments as listed below:

General comment:
1. The study does not state clearly what are the public health and clinical implications of frequent assessments that it involves. As repeated assessments, for long time periods involve a lot of time and effort commitment from the participants this needs to be clearly justified.
• We agree that this study has involved a lot of time and effort from the participants. It is precisely for this reason that our overall recruitment rate was low, as a three-year commitment with four-monthly visits and sampling is a serious one that many potential participants chose to decline. However, ethics review from two IRBs approved the study and its schedule of assessments, and participants were given the opportunity to decline to provide samples at every visit.

2. Would the authors please make a clear distinction of the observational and the intervention part of this study? It moves frequently between these two designs and makes the reading difficult.
• We agree that including information on both the observational and interventional components of STORK can seem complicated. We have attempted to minimize the description of the intervention as this was not intended to be the focus of the paper, which is the cohort. However, because it was part of the consent, we felt it important to present. The intervention is described briefly in COHORT DESCRIPTION, paragraph 3; its sample size by arm is provided in FINDINGS TO DATE, paragraph 2; and its value is mentioned briefly in STRENGTHS AND LIMITATIONS, paragraph 3.

3. Why do the authors include strengths and limitations twice?
• Contents of the page entitled STRENGTHS AND LIMITATIONS OF THIS STUDY are to be included in a separate box (for a requirement of BMJ Open Cohort Profile).

Abstract

1. The abstract should indicate when baseline data collection started, when will recruitments end and what is the proposed sample size.

• We have modified the first sentence of Findings to date to include the dates over which maternal recruitment occurred. The actual sample size is included in this same sentence.

2. Gestational age at pregnancy assessments should be included here.

• Under Findings to date, first sentence, we included mean gestational age at enrollment.

3. Line 25: It says that "information and samples are collected at follow-up visits. Please indicate what information was collected.

• Due to the requirement for 300 words in the abstract, we have not expanded "information". At baseline we collect demographic characteristics of household members, household characteristics including presence, type and number of pets and type of vermin, the mother's use of cleaning products or chemicals at her work outside of the home and maternal bathing habits. Information ascertained at each subsequent four-monthly household visit includes updates to household members or the residence. Once the baby is born, questions include types of foods given to the baby in the prior seven days, number of visible teeth, co-sleeping and childcare arrangements, and any clinical diagnoses made by a health-care provider, including allergy information (this information is in the main text, COHORT PROFILE, Data collection, Household questionnaire).

4. A number of biological samples are being collected. Please briefly mention what assessments will be done using them. This is important especially since invasive investigations are being carried out in babies as young as 4 months, and repeated annually. This information should also be given in the main text.

• Here in the abstract, we indicate that the samples are being stored (see Findings to date) and that samples will be available for hypothesis testing (Future plans). This is also present in the main text. We explain that judicious testing is required. Indeed, we have not yet identified the best methods available for testing for a wide spectrum of infectious diseases and their associated immune system responses.

5. The methods section should describe the intervention trial.

• The intervention is described briefly in the section Purpose.

6. It is not clear if the recruitment and baseline assessments are complete, which is a requirement for the cohort profile.

• Recruitment is complete, as are baseline assessments for all enrolled participants.

• Under COLLABORATIONS in the main text we indicate that, due to wide interest in this cohort, we are seeking additional funding to expand it at a later time.

7. The authors may include Trial Registration details here.

• Due to the requirement for 300 words in the abstract, we have not included trial registration details (see main text, FURTHER DETAILS).

Strengths and limitations

1. The authors state that it is a unique cohort, but do not sufficiently justify their statement. Please mention what unique feature sets this apart from existing pregnancy and birth cohorts in the world.

• These bullet points are a requirement for the journal and will be placed in a box.

Cohort description

1. Please make statement as to why the sample was chosen from lower socio-economic and Hispanic

dominant regions? Can you also make a statement on the representativeness of the cohort for this region?
• We were very interested in exploring the hygiene hypothesis and as such wanted to examine a range of race/ethnicity. Additionally, the public clinics where we performed recruitment serve a high proportion of Hispanic women.
• Our sample is characteristic of women using the public clinics where recruitment was performed. We have included a sentence in the main text to this effect

2. The description of assessments and samples can be better organised. Eg. A section for mothers with all the various assessments during pregnancy, and another section headed as follow-up which includes assessments after delivery. At present it veers between mother and the baby in every paragraph and can be confusing.
• We agree that the description of assessments and samples may appear confusing (we have re-written this section several times!). When we wrote separate sections for the mother and the baby, there was so much repetition that we thought the reader would become frustrated by extremely similar paragraphs. So we collapsed mother and baby into the same paragraphs, using a chronological format. We trust that with careful reading, it is not too complex.

3. Pages 8 and 9, under the heading samples: Please state at what time points these different samples are collected from the mother and the baby. It says the blood is being collected at baseline and annually for the mother. Similar information should be given for all samples in the mother and the baby. This information is available in the abstract, but it should be described in detail here.
• Under COHORT DESCRIPTION, Samples, a sentence was included for each sampling of households (sentence 2), mothers (sentences 3 and 4) and babies (sentences 5-8).

4. I think the objectives presented in the statistical methods section should be given in the Introduction/ rationale section. Statistical methods should include the proposed analysis plan.
• Our introduction currently includes the overriding objectives of the cohort and the intervention. We followed instructions from the journal, which indicated that detailed statistical plans should not be reported.

5. Considering the huge amount of data that this study generates, a description of data processing, cleaning and analysis should be given.
• We provide details on how data are obtained (which data systems used), transferred and stored (see COHORT DESCRIPTION, Data collection). Additionally we provide information on our validation study. We have modified sentences to include data cleaning for household questionnaires and double data entry for chart review.

Findings to date:
1. The details about the recruitment, loss to follow-up etc. are more suited for the previous section. This information should be moved there.
• As per your recommendation, we have moved this information to the previous section as a new paragraph (see COHORT DESCRIPTION, Participant disposition).

2. In this study, only ~10% of those approached, ~18% who met the screening criteria, were finally recruited. This not only resulted in a small cohort size as the authors acknowledge, but may have implications for potential bias. The authors should discuss this in detail in their limitations section. If available, please would the authors include a table comparing socio-demographic characteristics for women included in the cohort at baseline and the general population of the women of the same age in this area? Please would they also include a comparison between the women screened and both the 902 who were eligible and 158 who formed the cohort of mothers at baseline? A comparison of those eligible but refused and the recruited mothers will also be helpful to assess the implications of the

study. These tables should cover education, occupation, income, in addition to age and any available measures of health.
• See paragraph as moved above (COHORT DESCRIPTION, Participant disposition). Unfortunately, for privacy reasons, we could not collect information on our non-responders other than language spoken and reason for non-participation. So we cannot identify how well our sample represents the group from which it is drawn.
• The following is what is currently in main text:
The remaining 902 (53.9%) women met screening criteria; of these, 124 (13.7%) declined further contact and 778 (86.3%) agreed to be contacted for eligibility screening. Of these women screened for eligibility, 364 (46.8%) were excluded, primarily due to gestational age greater than 36 weeks by the time they were contacted (14%) or loss to follow-up (80%). Of the 414 remaining eligible women, 256 (71.5%) declined participation – primarily because of the time commitment (31%), home visits (16%) and baby blood draws (12%) – and 158 (38.2%) were enrolled in the cohort
• We have also added the following to the limitations section:
A final limitation of this cohort is the low recruitment rate with only 18% of those meeting screening criteria enrolled. Given though the frequent assessments at the home, multiple sample collection and long length of follow-up, it is a testament to the amazing study staff that the retention rate has been excellent.
Strengths and limitations
1. This section needs streamlining, and repetitions and superfluous sentences may be removed.
• We believe that when the section “Strengths and limitations of this study” (after the abstract; will get turned into a box) is not taken into consideration, this section is not repetitive.

2. Lines 45-46 state that the cohort includes families from diverse racial and ethnic groups across a wide socioeconomic spectrum. However the cohort description section states that they were recruited from lower socio-economic and Hispanic dominant regions. This needs some rephrasing.
• In the US, few birth cohorts have focused on Hispanic and/or Spanish speaking families, or underserved families. The STORK cohort does so: 65% of mothers are Hispanic; 50% have at most a high-school education (30% have less than a high-school education) and 21% have post graduate education (17+ years of education) - so the range is wide. Our local population is variable and mixed. Under COHORT DESCRPTION, Recruitment, we say: “these clinics serve a high proportion of both Hispanic families and families of lower socioeconomic status (SES)…”.

3. Page 12, line 3: Please explain in detail what is meant by ‘extraordinary depth’ here.
• We believe that the amount of information and data collected in this cohort is unique. We have modified the sentence to this effect: “Because of this plethora of data, this cohort has extraordinary depth…”

4. The authors repeatedly state that their sample is selected from diverse racial and ethnic groups across a wide socioeconomic spectrum. However, this characteristic has not been sufficiently projected in the manuscript to justify this. Please add a paragraph that brings out this diversity.
• We have modified the sentence regarding variation in maternal education and crowding as a surrogate for SES (STRENGTHS AND LIMITATIONS, paragraph 5).

5. One of the strengths stated is the repeated sampling of the infants. I note that about 4 blood samples will be collected in 3 years. The authors should again justify the rationale for this and how this frequent sampling at young age is going to add extra value to the cohort.
• One of our key goals is to understand infection and the development of the immune system in babies over time. While many tests can be performed using urine, blood provides an important source of immune cells in particular. With ethics review and IRB approval, we currently obtain a blood sample by venipuncture at ages 12, 24 and 36 months.

VERSION 2 – REVIEW

REVIEWER	GV Krishnaveni CSI Holdsworth Memorial Hospital, Mysore, India
REVIEW RETURNED	20-Mar-2016

GENERAL COMMENTS	The authors have satisfactorily addressed my concerns. I have no further comments.