Author’s response to reviews

Title: NASCITA Italian birth cohort study: a study protocol

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Author’s response to reviews:

Dear Editor,

we have revised our protocol based on the reviewers’ comments and are providing, below, our point by point replies to the comments.

The authors, again, confirm that this protocol has not been, and will not be published elsewhere and all authors have agreed to the contents in its submitted form. The authors have no conflicts of interest to declare. No related publications, with or without results, have been published or submitted to any journal.

Kind regards,

Chiara Pandolfini

Reviewer reports:
Muneera Rasheed (Reviewer 1): The study can be a major contribution to understand ECD in the Italian context leveraging the existing mechanism. The paper can be strengthened further if the following information can be requested.

Recruitment:

The selection of the geographical sites. While the final recruitment of doctors depends on their consent, there can be other means of making the data as systematic as possible like using a systematic random sampling technique. Similar approach can be followed for recruitment of the families. The sampling strategy has not been defined for the families.

REPLY: No random sampling was applied in the selection of doctors. Under the recruitment section (page 9) we state that the recruitment involves a purposive (non-random) sampling approach. The method applied involves convenience sampling – volunteer pediatricians who agree to participate – and we cite two related publications.

Concerning the recruitment of the doctors, since the project is an independent initiative set up by the Mario Negri Institute, a non-profit organization, and it is not run by a National Agency, and also given the limited funding, the participation of the pediatricians had to be on a voluntary basis and with no financial contribution. In this context we decided to begin selection based on the National Association of Pediatricians (ACP) with whom we had previous, validated collaborations. In order to have as large a sample as possible we therefore used the already existing network to begin the first identification of the locally representative pediatricians, who were then asked to identify additional pediatricians, not necessarily belonging to the ACP, in their areas for participation. We have added the details concerning the ACP to the text as well in order to better clarify the selection.

The newborns, on the other hand, as stated on page 15 second paragraph, are assigned to the pediatrician by the LHU based on places that have been freed up, so no further selection bias should occur in the newborn population.

How will parents receive information? Who will provide the information?

REPLY: Different tools will be used to update the participating families, mainly through the website. The data will be periodically analyzed and findings will be reported to lay people and the scientific community. Ad-hoc information material will be created and will be disseminated to families through newsletters and the website. This was stated in the Strengths and limitations section on page 15, and has been moved in part to the Materials produced section on page 13. The coordinating center will provide the information, but the pediatricians will also be able to provide the families with information deriving from the cohort during their visits.

Data Collection
What measures will be used?

Are we expecting the paediatricians to complete the forms? Were the forms tested for the time taken? Will it be feasible?

REPLY: The measures used depend on the data collected. The authors have attempted to be as precise as possible in describing the data collected by creating Table 1. The measurements collected are based on the child's age and are part of the routine measurements taken by pediatricians in Italy as part of the programmed health visits, which are similar to the well-child care visits in other countries. Anthropometric evaluations, for example, will involve the routine measurements such as height, weight, and head circumference for age. The demographic and health status of parents, for example, will involve questions concerning household size and composition, and parental chronic diseases and allergies. Measures of the children's physical and cognitive development will involve mainly the Neonatal Behavioral Assessment Scale (NBAS), while analysis of the children’s vaccination status will entail parental notification to the pediatrician. We have added these examples to the Data collection section on page 10, and have made the analysis plan more detailed.

Case report forms were discussed with a group of family pediatricians and tested by them in a pilot phase. The time needed to fill the forms was recorded by each participant and difficulties or doubts were reported to the coordinating center. The participants in the pilot phase assured the coordinating team that the data collection was feasible. We have added this specification to the text on page 9, under the Recruitment section.

Sample Size

How was the sample size calculated?

REPLY: Table 2 reports the national prevalence of health characteristics and the expected number of cases for different enrolling scenarios in order to obtain a minimum number of participants that would permit all these characteristics to be sufficiently represented.

With an expected minimum of 5000 newborns, representing about 1% of the newborns in Italy, we will have enough power to study common child exposures and outcomes. As documented by the PiccoliPiù cohort (Farchi et al. BMC Pediatrics 2014, 14:36) with 2700 newborns, we are even more confident of having enough power to be able to test the relationships between dependent variables and outcome measures. We have added a phrase stating this in the text under Study population size (page 11).

Analysis Plan

The analysis plan is not an analysis plan at the moment. What are the independent variables? What are the dependent variables? What are the confounders?
What are the main outcomes? What statistical methods will be used?

REPLY: We have changed the text in the analysis plan (page 12) to make the planned evaluations more clear and to better define the outcome measures and exposure factors. More specifically, we have added a list of the main independent and dependent variables that will be tested and have reordered and rephrased the list of research questions to make it more similar to that of the PiccoliPiù cohort’s published protocol, given that it is a similar cohort with general aims. Moreover, as stated in the reply to Reviewer 2’s request (Under Analysis plan), we have also modified the aims section (page 6) so that it is more clear and so that the analysis plan could reflect it more clearly. We have also added a paragraph detailing the statistical methods that will be used.

Reviewer 2 (Reviewer 2): PEER REVIEWER ASSESSMENTS:

OBJECTIVE - Full research articles: is there a clear objective that addresses a testable research question(s) (brief or other article types: is there a clear objective)?

No - there are minor issues

DESIGN - Is the current approach (including controls and analysis protocols) appropriate for the objective?

No - there are minor issues

EXECUTION - Are the experiments and analyses performed with technical rigor to allow confidence in the results?

N/A - no experiments or analyses

STATISTICS - Is the use of statistics in the manuscript appropriate?

N/A - there are no statistics in this study

INTERPRETATION - Is the current interpretation/discussion of the results reasonable and not overstated?

Yes - the author’s interpretation is reasonable
OVERALL MANUSCRIPT POTENTIAL - Is the current version of this work technically sound? If not, can revisions be made to make the work technically sound?

Probably - with minor revisions

PEER REVIEWER COMMENTS:

GENERAL COMMENTS:

* What is your overall impression of the study?

As said in the protocol, this is large and ambitious birth cohort proposing to check many associations of child development. The protocol proposes to investigate various differences or inequalities in child outcomes in Italy. The authors need to take care on their aims and analysis plan

* What have the authors have done well?

The authors have proposed a large important birth cohort study representative of Italy

In what ways does it not meet best practice?

Even though it is in early stage, the authors need to be clear on objectives, corresponding outcome and exposures variables, inclusion criteria, and analysis plan. Some comments regarding these are included below.

REQUESTED REVISIONS:

Abstract

Background: Has NASCITA study been already going on? The present article seems the protocol to conduct the study but the authors claim it was already created.

REPLY: NASCITA began enrollment in April 2019, one month after the original submission of this protocol for publication. When the protocol was written the first phases of the cohort were already underway, such as creation and testing of the eCRF, identification of the pediatricians, etc. Participant enrollment and, consequently, data collection, had not yet begun.

We will leave it up to the Editor to decide if it would be preferable to modify the phrases to reflect the fact that recruitment is already underway.

Methods: If the study is ongoing, why the expected number of newborns, because it sounds like newborns have been already enrolled in the study.
REPLY: We stated an expected number of newborns because enrollment had not yet begun and, in any case, because it will continue for a period of one year for each pediatrician.

Background:

Even though the study is large and ambitious with broad views, I think that, for particular investigation, it should focus on specific areas. Investigators need to have clear aim.

REPLY: The study will collect basic data that are part of those routinely collected by the family pediatricians, but will also focus on specific areas such as nutrition, environment, and nurturing care, for which specific questions were added. We have structured the cohort in a way that will permit us to expand, in a second phase, data collection and analysis based on the research interests and willingness of the pediatricians. We have modified the phrases already specified under Data collection, on page 10, in order to better explain this concept.

Hypothesis and significance:

Hypothesis/aims should not be just set as there are differences among geographic areas but how these differences impact upon the outcome (child development) or in which condition the differences will be high or low.

Aims:

There are aims, additional aims and more specific aims. Having said broad views and main purpose of the study, I suggest investigators to have specific aims for the investigation.

At one hand, it seems like the outcome measures are physical, cognitive, and psychological development of child; but again authors have indicated to measure 'nurturing care' (health, nutrition, safety and security, responsive care giving and early learning. So, what are the actual outcome measures and exposure factors? How they will be assessed?

REPLY: Concerning the specific aims, we have rephrased the text and made the aims more distinct and clear (Aims section, page 6). In this regard, we have also modified the analysis plan (page 12) to make the relevant, planned evaluations more clear and to better define the outcome measures and exposure factors, also detailing the types of analyses that will be carried out.

Methods:

Overall, the subtopics in this section are scattered such that the coherent steps or methods of a cohort study are hard to follow. So, there is better way to organise and present this section more logically.
REPLY: We have changed the order of the subsections (Inclusion/exclusion criteria and Organization framework) so that they are more clear.

Setting

How a cluster is defined? How the 22 clusters will be selected? What these clusters need to represent? From which areas of Italy?

REPLY: The clusters are representative of the country based on geographic and socio-economic characteristics and administrative divisions, and we calculated them using the national Statistics Institute (ISTAT) definitions for each town/city (ISTAT – Main geographic statistics on cities. https://www.istat.it/it/archivio/156224). We have added the fact that the calculation for the clusters was based on the ISTAT definitions, as well as the relevant reference, to the text. This is stated on page 8, first paragraph.

Recruitment:

Is there a pool of paediatricians in the selected clusters so that you need to sample? Otherwise there are, I suppose, paediatricians assigned in the clusters or health units.

REPLY: Based on the ISTAT data, the towns/cities were grouped into clusters, and each city has a defined number of pediatricians that form the national pediatric healthcare coverage. As in the response to reviewer 1, no random sampling was applied in the selection of doctors. Concerning the recruitment of the doctors, since the project is an independent initiative set up by the Mario Negri Institute, a non-profit organization, and it is not run by a National Agency, and also given the limited funding, the participation of the pediatricians had to be on a voluntary basis and with no financial contribution. In this context we decided to begin selection based on the National Association of Pediatricians (ACP) with whom we had previous, validated collaborations. In order to have as large a sample as possible we therefore used the already existing network to begin the first identification of the locally representative pediatricians, who were then asked to identify additional pediatricians, not necessarily belonging to the ACP, in their areas for participation. We have added this information to the text as well in order to better clarify the selection.

Inclusion and exclusion criteria

There can be inborn defects in some newborns which will affect on development. How will such defects accounted for or excluded in the enrolment?

REPLY: All newborns have been included. The presence of congenital malformations and genetic defects is covered by the data collection and such cases will follow the same follow ups as the entire population. The analyses will account for these variables.
Analysis plan:

There are so many associations to be tested but I do not see them to match to the specific aims perfectly. The specific aims and analysis plan to answer these aims should match. Another issue, what happens to 'lost to follow up data'.

REPLY: The aims of the study are many and general. We have reordered and rephrased the specific aims listed on page 6 and modified the analysis plan (page 12) accordingly, reordering and expanding the examples of research questions that will be tested, and listing the main independent and dependent variables that will be tested. We have changed the editing in the list of research questions to make it more similar to that of the PiccoliPiù cohort’s published protocol, given that it is a similar cohort with general aims.

Concerning the ‘lost to follow up data’, we will calculate this percentage and confront it with that of other similar studies. We hypothesize that, given the fact that the data collection is based on routine visit by the pediatrician, attrition in NASCITA will be irrelevant in at least the first two years. Analyses to estimate bias due to loss to follow-up will be performed, comparing the baseline population with the follow-up populations. Considering the previous experience of other Italian cohorts, NINFEA (https://www.progettoninfea.it/attachments/70) and Piccoli Più (https://www.piccolipiu.it/files/piccolipiu_protocol_BMC_pediatrics_2014.pdf), we estimate a 20% loss to follow up after the first two years, maintaining a sample size of 4000 children.

With the parents’ consent, data on children withdrawing after 12 months of age will be considered in the analysis for the relevant time period of participation (e.g. rate of exclusive breastfeeding, reading out loud, SIDS prevention, etc.). Data will be deleted upon parents’ request.

We have added these details to the text under Study population size (page 11) and the Strengths and limitations of this study section (page 17).

ADDITIONAL REQUESTS/SUGGESTIONS:

See above my comments.