Author’s response to reviews

Title: Understanding the impact of five major determinants of health (genetics, biology, behavior, psychology, society/environment) on type 2 diabetes in U.S. Hispanic/Latino families: Mil Familias - A cohort study

Authors:

Jessikah Morales (nglantz@sansum.org;jmorales@sansum.org;rod.everhart@syneoshealth.com;nglantz@sansum.org)
Namino Glantz (nglantz@sansum.org)
Arianna Larez (alarez@sansum.org)
Wendy Bevier (wbevier@sansum.org)
Mary Conneely (mconneely@sansum.org)
Ludi Fan (ludi.fan@lilly.com)
Beverly Reed (reed_beverly_l@lilly.com)
Carlos Alatorre (alatorre_carlos@lilly.com)
Rosirene Paczkowski (paczkowski_rosirene@lilly.com)
Tamim Ahmed (tahmed@sbaactuaries.com)
Andrew Mackenzie (amackenzie@sbaactuaries.com)
Ian Duncan (iduncan@sbaactuaries.com)
David Kerr (dkerr@sansun.org)

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NOTE: Page and line references below refer to the file named Mil Families CE Protocol_Revised_Clean_2019.10.21 in Track Changes mode with All Markup visible.
Responses to Reviewer 1.

Comment 1. It will be helpful if the authors can provide information on how the families will be identified? For example, will it be a combination of advertisements, referrals, targeted recruitment events? Thank you and the approach will be a multi-faceted. We have added text describing these in the “Participants” section in the Methods (pages 9-10, lines 161-166).

Comment 2. Will there be an evaluation of the Especialista competency in conducting the data collection? Some comments will be important to understand that the collected data will be of consistent quality. Additionally, if there is a way to score the Especialista competency, then recording those will be important in the post data analysis. We agree with the reviewer that this is very important and have added a section on quality control of the data collection in the Methods section. In addition, the research team meet with the Especialistas on a weekly basis for de-briefing (page 13, lines 231-232).

Responses to Reviewer 2.

Major comments

Comment 1 (Overall): Though involving a relative large number of families in this cohort study is a strength, quality control to ensure standardization of protocol implementation including patient selection, enrollment, and data collection become critically important. This paper should include a description on quality assurance in this study. Thank you and we have added a description of quality control which describes our approaches to standardization of implementation of the protocol and data collection (pages 20-21, lines 411-422).

Comment 2 (Overall): Description of outcomes needs to be clarified in a concise way. This paper should include a description on the primary and major secondary outcomes and their definitions in the methods section. As suggested by the reviewer, we have added these to the Methods section including a link to our published list of secondary end-points listed on clinicaltrials.gov (pages 8-9, lines 125-146).

Comment 3 (Overall): Prognostic outcomes are important in long-term cohort studies assessing the influence of determinants and other risk factors associations. Particularly, will the “hard outcomes” or events be collected during the study period (namely, death, diabetes major vascular complications, and micro vascular complications), and how will the events be collected and adjudicated? How about events not captured in the study hospitals? Or through self-report? In addition to the listed variables covering the 5 major determinants of health, we also plan to collect, prospectively, clinical information and this has been added to the Methods section (pages 8-9, lines 125-146).
Comment 4: The study actually began in about February 2019 according to clinicaltrials.gov registry information, and it is nearly half year ago. The recruitment should have started already. Consider disclosing the timeline/progress status of the study. In agreement with the reviewer, we have added the February 2019 start date at the beginning of the Methods section (page 7, line 108). We have also ensured that the text is consistently written in present tense. These revisions begin on p. 3, line 43, and continue throughout the manuscript.

Comment 5: Please provide a brief description on the pilot study that involved over 100 adult Latino individuals including the study design, results, and findings. We do have a short description of the Operational Pilot in the Methods section (page 8, lines 120-123) but have not included further detail as we have a complete description of this submitted for publication.

Comment 6: Please specify how will the bio samples (e.g. blood samples, urine samples) be processed and stored in the study center. As requested, a section describing this has been added to the Methods section (page 16, lines 309-318).

Comment 7: I wonder if you expect a bit too much from the patients and families population? The study aims to collect data annually on over 100 different variables during each visit and expects patients to monitor certain things (blood pressure etc). Are there any data on how long the encounter will be for each patient according to pilot study results? Most people that will enroll in the study will likely have little experience in long-term research participation and there is some research indicating that participants could be overwhelmed by the things they are asked to do. As a result, they might give up early on. Have you considered this? A streamlined study design will be much easier for the study implementation and ensure data quality. Although the burden on the participants may seem onerous, during the Operational Pilot we achieved more than 85% of total data capture and participant retention (page 21, lines 419-422). We believe that this is a direct consequence of the trusting and sustained relationship between each participant and their Especialista. In our experience, participants find value in the one-on-one in-person contact with Especialistas knowledgeable about type 2 diabetes as well as related education, research, and care resources and opportunities. They also enjoy wearing the activity monitoring devices and receiving the results of their health assessments, laboratory tests and wearable device data. Additionally, this study is community-based to avoid any possible barriers to transportation, trust, and time before they arise. Therefore, in addition to the primary site (SDRI), some activities occur at public community centers and partner sites. Another key to retention is SDRI’s ability to accommodate participant visits outside of regular working hours, i.e. early mornings, evenings, and weekends. In sum, given the operational pilot success based on these customized strategies, we do not plan to streamline the protocol.

Comment 7: Methods (statistical analysis): Please specify the statistical analysis methods and plans in the protocol (or add in appendix). The current descriptions are unclear and too vague. We have added a description of the statistical methods and justification for the sample size as requested by the reviewer (pages 19-20, lines 387-410).
Comment 8: Please acknowledge potential limitations of the study in the discussion. A section acknowledging the limitations of the study has been added to the Discussion (page 22-23, line 423 and lines 445-452).

Minor comments

Comment 1: Abstract: Please spell out an acronym the first time it is used (e.g. “US” in the abstract). As requested, acronyms have been added where needed, including but not limited to US in the first line of the Background section of the abstract. This begins on page 3, line 33 and continues through the manuscript. A list of abbreviations appears on pages 23-24, lines 463-470.

Comment 2: Introduction: The author explained that genetics, biological factors and society/environment influences are important factors in determining diabetes risks. How about the other two determinants (i.e. behavior and phycology influence)? In addition, the associations between many of the above risk factors and outcomes have been well studied in previous studies actually; please add statements about why the study needs to be done now and what are the gaps in existing data and evidence. As requested we have added a statement in the introduction highlighting the uniqueness of this study with the focus on the 5 major determinants of human health within a defined underserved U.S. population (pages 5-6, lines 87-91).

Comment 3: Introduction (Line 85-89): Definitions of the study population (“Hispanic/Latino” and “Latinos” identification) should be explained under the methods section. Thank you for this help suggestion and we have moved the relevant text from the introduction (page 6, lines 91-96) to the beginning of the methods section (page 7, lines 99-103).

Comment 4: Methods (Participants): Will there be logs of people who are not eligible or declined from the study? If so please add in the paper, otherwise please state the reason. We agree with the reviewer that a screening log is recommended but the reality is that, given our experience in the Operational Pilot, this population, and the fact that some individuals may be undocumented, they often decline to provide personal details if they are not interested in participating and therefore we are not including a log.

Comment 5: Methods (Participants): The current definitions for family representative and family members are unclear. I would suggest separate definitions for two populations, for example, clarify the inclusion and exclusion criteria for family representative first, and then explain the identification (or eligibility criteria) for family members. We have rearranged the text in the Methods section to explain the definitions and divided the inclusion criteria as suggested by the reviewer (pages 10-11, lines 172-203).
Comment 6: Methods (Activity Monitoring): Why do you choose the cutoff value of 13 years old for wearable monitors? The study require the participants to wear the devices for up to a week, however, how will the study monitor the adherence of the wearable devices? How will the data be transferred to the study center (e.g. by Bluetooth?). According to Fitbit’s Terms of Service (Fitbit, Inc., San Francisco, CA, effective September 18, 2018) “Persons under the age of 13, or any higher minimum age in the jurisdiction where that person resides, are not permitted to access or use the Fitbit Service” in the absence of parenteral consent. For this study we wish to avoid introducing potential conflicts within the families. We have added a definition for Adherence to the test as requested together with a description of the handling of the wearable data (page 17, lines 339-342). In our experience with the Operational Pilot, the participants enjoyed using the wearable devices and adherence was very high.

Comment 7: Methods (Activity Monitoring): The wearable monitor is a kind of the intervention on participants’ physical activity in this observational cohort study although the concern will be alleviated since the device is only used for a week and up to twice within 12 months. We agree with the reviewer that the very short duration of the use is unlikely to be a major influencing factor and have therefore not introduced a control.

Comment 8: Methods (Statistical analysis): The author stated that given the size of the cohort, a power calculation is not required. However, sample size calculation needs to be performed previous to the study and it would be better if the authors could provide a formal sample size calculation. We have added content as suggested (see above, Major Comment 7 and page 20, lines 393-410).

Comment 9: Methods (Figure 1): It is unclear that whether the HPA encounter, laboratory encounter and questionnaires encounter are conducted at the same visit, or are there any interval requirements between these encounters. The author should clarify this in the methods text and figure. The legend to Figure 1 has been extended to describe the encounter visits (page 31, lines 633-634).

Comment 10: Discussion (Line 335-337): Please add reference for the cited literatures. The relevant references have been cited (37-40) (page 22, line 430) and we have added two additional references added (41 and 42) (page 22, line 434 and page 23, line 449, respectively).