

Author's response to reviews

Title: OBAYA: Obesity and adverse health outcomes in young adults, feasibility of a population-based multiethnic cohort study using electronic medical records

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Author's response to reviews: see over

Christopher J.L. Murray
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April 13, 2012

Dear Drs. Murray and Lopez:

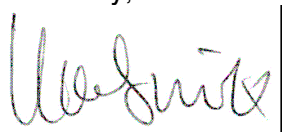
Attached is the revised manuscript titled "*OBAYA: Obesity and adverse health outcomes in young adults, a population-based multiethnic cohort study*" written by Corinna Koebnick, Ning Smith, Karl Huang, Mayra P. Martinez, Heather A. Clancy, Andrew E. Williams, and Lawrence H. Kushi.

We felt that the reviewer's comments were very helpful and revised the manuscript accordingly. Please find our point-by-point responses listed on the following pages. All changes have been highlighted in the manuscript. We hope this version meets with your approval.

Among other concerns, we addressed the main reviewer concern regarding retention bias. Almost every epidemiologic study is subject to bias but particularly in highly mobile populations such as young adults. Therefore, understanding the population and the potential bias due to migration is crucial. The potential of bias exists in all epidemiologic studies due to low and selective responses to recruitment attempts, survey fatigue, migration of subjects and other factors. However, the control of this bias can be addressed through careful study design and interpretation of the data. As part of the study design, the potential existence of such bias has to be acknowledged, appropriate measures to assess such bias have to be made, and potential effects of such bias for direction and magnitude have to be estimated. Therefore, these potential biases are extremely important to understand and we feel that our manuscript contributes important knowledge to the understanding of potential bias.

Thank you for considering our manuscript and for the opportunity for a revision. Please contact me regarding the reviews for this paper at 626-564-3693 or Corinna.Koebnick@kp.org.

Sincerely,



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Reviewer 1:**Major problems:**

The association between obesity and cancer among young adults is an interesting area that is currently understudied. The manuscript described some baseline information for the cohort study. However, there were lots of uncertainties of the further follow-up. Based on the data, 31.6% of participants were lost to follow-up during 2007 and 2009. To investigate cancer risk and associated risk factors, the follow-up period may be longer than 5 years even though it is not stated in the manuscript. I am not sure what the retention rates will be after 5 years. It is difficult to draw conclusion from this cohort study if the retention rate is <50% because the participants who were lost to follow-up were not quite comparable to the participants who stayed in the study (Table 4).

Answer: The follow-up of the cohort will increase with years. Future retention rates cannot be predicted from 3-year results as individuals leave and reenter the health plan.

Therefore, the assumption that the 5 year retention will be <50% cannot be made. The political situation (e.g. Affordable Care Act) is quite unpredictable and losses to follow-up may drop dramatically in this age group.

Almost every epidemiologic study is subject to bias but particularly in highly mobile populations such as young adults. Therefore, understanding the population and the potential bias due to migration is crucial. This information can be used to inform later analysis and to better understand potential limitations in the interpretation of the results. With this study, we try to be open and honest about potential bias to better understand estimated risks. We included a paragraph in the introduction about the importance to understand demographics and the potential bias due to migration as follows: "Managed care systems are a unique system to study associations between rare outcomes in young adults due to its large population and the potential for long passive follow-up periods. However, lack of generalizability due to healthy worker bias (i.e. insured versus uninsured individuals) and the potential loss of subjects in epidemiologic studies using members of managed care systems are of concern because it can be a major source of bias. Study subjects may lose their health insurance coverage or migrate out of the coverage area but also may re-enroll based on their employment status or other financial decisions and life events. If subjects who leave the health plan are systematically different from those who remain in the health plan in terms of exposure and the association with health outcomes, the estimates of association between exposure and outcome may be systematically biased. The potential of bias exists in all epidemiologic studies due to low and selective responses to recruitment attempts, survey fatigue, migration of subjects and other factors. However, the control of this bias can be addressed through careful study design and interpretation of the data. As part of the study design, the potential existence of such bias has to be acknowledged, appropriate measures to assess such bias have to be made, and potential effects of such bias for direction and magnitude have to be estimated. Therefore, these potential biases are extremely important to understand."

Minor problems:

1. Line 29, need a reference for the definition of severe obesity besides Flegal's article (e.g. National Heart, Lung, and Blood Institute Clinical Guidelines).

Answer: The NHLBI clinical guidelines are based on CDC growth charts and usually refers to CDC publications regarding thresholds for childhood obesity. There is currently no consensus on how to define severe obesity in children. The use of the 99th percentile of the CDC growth charts as stated by some groups is not in accordance with current CDC recommendations because percentiles above the 97th percentile are based on very low sample sizes. Therefore, we decided to reference the latest CDC suggestion to use 1.2 x 95th percentile (Flegal et al).

2. Line 36 & 141, it would be better to replace "body size" with "weight status".

Answer: We replaced body size with weight status as recommended.

3. Line 102-103, I don't quite understand "replacing waist-to-hip ratio by a BMI #35 kg/m²". Does it make sense to replace all the ratios with BMI #35 kg/m²?

Answer: Waist-to-hip ratio is not available in most electronic medical records because waist and hip circumferences are generally not measured during routine health care and BMI is used as a proxy instead. However, we deleted the confusing paragraph as these data are not relevant to the data presented here.

4. Line 124, based on table 2, the young adult cohort should have lower proportion of minorities.

Answer: The KP cohort has a higher proportion of individuals classified as Hispanic, Black, Asian (64.7%) than the California Census (51.1%). However, a large proportion of the Census population stated to be of other race. We have rephrased this sentence in the results and are now referring to the Hispanics, Blacks, and Asian appear in a higher proportion and individuals of other race appear in a lower proportion. This is due to a shortcoming in the Census data where a large proportion could not identify themselves with the given choices and self-classified themselves as others (see Risch et al, Genome Biol, 2002 discussing self-classification versus genetic classification of race and shortcomings of US Census surveys).

5. Line 133, based on table 4, those who were lost to follow-up should be more likely to be minorities.

Answer: A large proportion of those lost to follow-up are of unknown race/ethnicity. Comparing retained individuals to those lost, a lower proportion of minorities (Hispanics, Blacks, Asians and individuals of other race) leave the health plan.

6. Line 173, since the participants who were lost to follow-up were not quite comparable to the participants who stayed in the study, we cannot conclude that "our data do not suggest major bias.

Answer: The only major difference between participants who stayed in the study and those who were lost to follow up, was the proportion of individuals with unknown race/ethnicity. In the first enrollment years, race assessment was inconsistent. The longer one stays in the health plan, the more medical encounters they have, the higher were the chances to have race/ethnicity assessed. This has changed in 2009 where a consistent race assessment was introduced as mandatory field for the clerk at check-in. Therefore, individuals retained have a higher change that their race is known. We added this information into the discussion.

7. Line 190. "Not" was missed after "have".

Answer: We added the word "older" before adults. The associations between obesity and cancer have been reported in many studies. However, these were mainly comprised of older adults. They have not been reported in young adults or studies failed to find any association or the association was reversed. Because all studies in young adults were based on small sample sizes, the association between obesity and cancer has yet to be established.

8. The demographic information of the young adult cohort presented in table 1 and table 2 were inconsistent.

Answer: Demographic information appeared to be inconsistent regarding to race/ethnicity because individuals with unknown race were omitted in table 2 and the racial distribution of those with known race is shown. This is indicated in the footnote and was necessary to make data comparable to Census data.

Reviewer 2

This paper posed importance issues with minority research in the U.S. which lack of data considering health disparities. However, this study needs to be specified how they get permission from each individuals who agree to participated in the study. It seems that they use individual's medical records to conduct the data but did not describe details of informed consent and its process. Also I am not sure whether Kaiser Permanente IRB would be sufficient for this study.

Answer: FDA regulations define the Institutional Review Board as an appropriately constituted group that has been formally designated to review and monitor biomedical and social science research involving human subjects. In accordance with FDA regulations, the KPSC IRB has the authority to approve, require modifications in (to secure approval), or disapprove research. To balance individual privacy with public interest, the IRB also has the authority to grant a waiver for the requirement of individual informed consents in large epidemiologic studies with minimal risk involved – as long as HIPPA rules are followed.

Minor comment – please do not use KP in the abstract.

Answer: We replaced KP by managed care organization to omit KP from the abstract.

This study would need longer follow-up period to evaluate feasibility of this study setting. Please discuss this within study limitation.

Answer: We added some paragraphs in the discussion limitation as follows; “In addition to the aforementioned limitations, the cohort currently has a relatively short follow-up that enables us to draw conclusions on for short- and medium term outcomes. Analyses have to be designed carefully to account for systematic differences beyond demographic factors such as body weight and obesity-related conditions to investigate long-term health risks such as cancer risk.”

Reviewer 3:

1 – The length of the study is not clear. With 30% of loss to follow up, it would be a threat to the validity of the results even after 2-3 of 3-year period.

Answer: The length of the study is indefinite. However, as described above, future retention rates cannot be predicted accurately because of ongoing changes in health policy such as the Affordable Care Act; the interpretability of our results is limited to medium term retention. However, we speculate that the expansion of health care to a larger population as planned in the Affordable Care Act would increase retention rates in this age group known for high rates of uninsured individuals. Individuals also disenroll and re-enroll continuously.

2 - What cancers are going to be measured? What will be your definition of the new cases? First ever? Issue of recurrence?

3 – With current rates of incidence of the cancers, the risk factor distributions, and desired associations; how much is the power to find the relationships? Is this sample size adequate? A table of objectives and the estimated power would be very helpful. It also answers the question on the length of follow up or sample size adequacy.

Answer: The primary cancers in young adults with a potential link to obesity are breast, thyroid, and testicular cancer. As the data will be available for collaborations, recurrence of cancers or cancer survival will depend on outside investigators interested in this topic. Definitions usually follow SEER coding instructions of cancer registries. Enough cases for breast cancer to enable subgroup analysis will be in 2013, thyroid and testicular cancer in 2015. However, this was not included in the present study because the data shown here focuses on demographics and the understanding of potential bias by underrepresenting certain groups or by migration bias to account for the potential effects in future analysis and the design of nested case-control studies. We changed title and introduction to clarify that the current study is not exclusively investigating cancer but also other obesity-related outcomes.

4 – With current rates of retention, how much would be the size of possible loss to follow up bias? What is the plan to find lost participants by record linkage? How successful would it be?

Answer: The long-term follow-up cannot be estimated based on 3-year retention rates. We added information and modified existing information in the limitation section of the discussion to clarify that members are continuously enrolling and disenrolling. Therefore, it cannot be assumed that a 3-year trend will continue in a monotonous fashion. Several sections – as listed in response to reviewer comments above – have been added: limitation of interpretation to short-term outcomes, limitation due to factors unknown and not included in the current analysis, limitations of estimating future retention as a result of health policy changes such as Affordable Care Act – which may significantly decrease attrition in this age group.

Lost participants can be found through three mechanisms: internal linkage between KP regions (limited to those who stay with KP), linkage with state death files (restricted to death cases), linkage with state cancer registries (limited to those who remain in the state and limited to cancer diagnosis).

5 – What are the baseline characteristics of the participants by chronic diseases and cancers? Is it different by the retention status?

Answer: Currently, we do not have retention rates by disease status. We added the following information: “Future retention rates cannot be predicted accurately because of ongoing changes in health policy such as the Affordable Care Act; the interpretability of our results is limited to medium term retention. However, we speculate that the expansion of health care to a larger population as planned in the Affordable Care Act would increase retention rates in this age group known for high rates of uninsured individuals.”

We also added BMI class by retention status into table 3 showing only minor differences between both groups. Normal weight individuals are slightly more likely to leave the health plan – however, they might re-enroll later.

6 - What are your exclusion and inclusion criteria based on the current situation.

Answer: As described, the only inclusion requirement was the availability of a valid BMI. Inclusion and exclusion criteria for future analyses may vary by outcome of interest.

7 – What is the protocol for intermittent evaluation of the risk factors? Is it active or passive? It needs more clarification.

Answer: The cohort follow-up will be passive follow-up by extraction of data from electronic medical records.