A reply to "Lung cancer outcomes: Are BMI and race clinically relevant?"

Liu G, Brenner H, Chen C, Christiani D, Field JK, Hung R, Jie Z, Le Marchand L, Ryan B, Schabath MB, Schwartz AG, Shete S, Shiraishi K, Tardon A, Teare MD, Yang P, Zhang Z-F, Xu W

Dear Editor,

We have read the recent letter from Braillon and appreciate his interest in our work. We would like to reply to a few specific comments that he raised. While we certainly agree that meta-analyses should be pre-registered, pooled analyses based on individual-level data are not considered systematic reviews and thus, PRISMA or Cochrane would not be appropriate sources to pre-register such an analysis. Further, while we are highly supportive of open science platforms, it is not routine to pre-register observational analyses.

The International Lung Cancer Consortium (ILCCO) has a standardized formal review process for all proposal requests of data access for analysis that any set of investigators (both internal and external to ILCCO) can submit. The review is performed with oversight by a Steering Committee. Therefore, while we agree that unplanned subgroup analyses should only be hypothesis generating, our BMI-survival analyses [1,2] were pre-planned, reviewed and approved by the ILCCO Steering Committee prior to the initiation of all analyses. Lung cancer risk and survival are well known to vary by ethnicity, sex, and smoking status [3,4], and most recently in relation to differing proportions of patients with *EGFR* and other mutations [5,6]. Therefore, the present manuscript's hypotheses were based on *a priori* research questions and were not cherry-picked after the main analysis. We would bring to Dr. Braillon's attention that once analysis of consortium investigator-initiated projects are completed, lead investigators are responsible for publishing the specified analysis, including those with null findings [7,8]. Finally, the present article adhered to the STROBE guidelines for observational studies.

Acknowledging that all observational studies have intrinsic limitations, we would like to draw attention to the immense work performed over the years by ILCCO to create a consortium, which brings strength, rigor, and statistical power to our approach in asking and answering important research questions. The present analysis [2] is based on a disease cohort design where risk factors are collected at time of diagnosis, and outcomes obtained during systematic follow-up. In particular, our main purpose was to estimate (i.e., *quantify*) the modifying effect of these pre-specified variables on the relationship between BMI and survival, and not simply test or generate hypotheses. Though we are sure that his oversight was unintentional, it is important to remind Dr. Braillon that the biological relevance, implications and potential limitations of our findings were thoroughly addressed in our manuscript [2]. Braillon mentioned an additional point regarding the lack of information on the quality and receipt of care among study participants. We recognize the relevance of these variables, and most investigators in the field understand and accept the difficulty to quantify these factors even in the best of circumstances (e.g., controlled clinical trials). While approximately 45% of participants were former smokers at the time of diagnosis, smoking cessation data after diagnosis was not available for most participating sites.

We appreciate Braillon's suggestion to compute population attributable fractions. However, we feel strongly that, in this specific case, it would lead to an over-interpretation of the data. Our 16 pooled studies come from three continents, each with its own population structure, study design, demographic characteristics and health care system. As such, relationships such as absolute risk reduction would be significantly heterogeneous across the study populations and cannot be readily summarized based on our combined estimations.

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