Reviewer's report

Title: Common variants in LEPR, IL6, AMD1, and NAMPT do not associate with risk of juvenile and childhood obesity in Danes: a case-control study

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Reviewer: Jose Fernandez

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This study was designed as a replication of recent findings evaluating four obesity-associated gene variants in the IL6, LEPR, NAMPT and AMD1 genes. The study combines data from two existing cohorts used to categorized obesity into normal weight vs overweight/obese. The genetic methodology of the study seems appropriately applied and well thought, and the study delivers an overall message of how important is to replicate obesity-related findings in other populations, as the results may or may not be the same as expected.

There are two aspects of the study that concern this reviewer. First, according to the letter of submission, the study seems to be a resubmission; however, it is not clear how the authors addressed the concerns of previous reviewers as the letter of response does not provide an item by item explanation. Second, and perhaps more important, is the phenotypic classification used in the study. The authors combined overweight and obesity into one category, taking the risk of confounding their results and missing a potential association. Physiologically, obesity as a disease may activate predisposing genes that may not be expressed during the overweight stage, which serves as a precursor stage in obesity development. Another aspect is the homogeneity, or generalizability, or the classification itself when taking into account that they used an obesity prevalence dependent on a historical definition of 40 years ago (the GOYA study). It is recommended to perform some preliminary analysis with obese individuals (eliminating the overweight), and within study populations to evaluate if there are differences in the results. A reader will benefit from some description of these exploratory analyses in the discussion.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests