Commentary

Risk factors for non-alcoholic fatty liver disease delineate the battlegrounds in optimizing disease prevention

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Multiple environmental factors impact non-alcoholic fatty liver disease (NAFLD). While the association with dietary habits and physical activity is broadly characterized (1), the contribution of socioeconomic disparities to these risk factors remains elusive to date (2). A cross-sectional study of the National Health and Nutrition Examination Surveys (NHANES) (3) recently examined a cohort representative of the adult U.S. population for combined effects of socio-demographic and lifestyle patterns on NAFLD risk behavior. Physical activity, a high-quality diet and higher education, but not income level, were found to reduce the risk of NALFD, irrespective of ethnicity or gender. As NAFLD is estimated to affect up to a quarter of the global population and particularly become more prevalent in industrialized countries (4), proper characterization of associated population-based risk factors is crucial in optimizing public health and educatory preventive and treatment directives. The study demonstrates that promotion of a high-quality diet, irrespective of individual ingredients, and physical activity above a threshold of 600 metabolic equivalents of task (MET) min/week, may be key to preventing metabolic syndrome/NAFLD, yet implementation of such strategy remains challenging, especially in the lower socioeconomic sectors that would most benefit from it.

Indeed, a large proportion of the subjects enrolled in NAFLD lifestyle intervention programs does not achieve or sustain targets such as weight loss or improved physical activity (4). In addition, sectors at risk of NAFLD, especially those of lower socioeconomic status, exert lower adherence to lifestyle interventions (5). Acknowledging the increase in social inequality as a driver of NAFLD-promoting lifestyle is essential in designing inclusive and effective NAFLD preventive and therapeutic measures. Moreover, such understanding may enable the re-focusing of NALFD trials towards the most vulnerable cohorts, rather than to those featuring the best compliance. For example, advanced 'personalized' dietary interventions are suggested to be potentially superior to current, one-size-fits-all guidelines in preventing hyperglycemia and possibly other features of the metabolic syndrome such as NALFD (6,7). However, these approaches and associated clinical trials may be inaccessible to the under-privileged who would benefit most from such measures preventing or ameliorating NAFLD and its complications. Integration of population-based risks, such as the ones depicted in Vilar-Gomez *et al.* (3), may enable to redirect efforts and funds, including the more sophisticated data-driven personalized nutritional interventions, towards those who most need rather than those who can more easily afford them.

A limitation of the study by Vilar-Gomez *et al.* (3) includes an assessment of dietary habits utilizing the healthy eating index (HEI-2015). Designed to estimate adherence to American food intake guidelines, this tool does not

necessarily reflect the consumption of single components, such as those depicted in food frequency questionnaires. Examples of candidate food groups requiring further assessment as possible contributors to NALFD include red and processed meat as well as fructose and sweetened beverages (8). The tradeoff advantage of HEI-2015 lies in assessing diet in its entirety, irrespective of possible confounders such as subjects' cultural eating habits. Combining the two dietary assessment modalities would provide a holistic approach towards mitigation of dietary NALFD risks across society.

Collectively, the findings by Vilar-Gomez *et al.* (3). elegantly demonstrate that diet and physical activity directly influence the risk of NAFLD, while socioeconomic status and education strongly impact the ability to modify these risk factors. These important conclusions become even more alarming in light of the ongoing Covid-19 pandemic and the associated reduction in physical activity and weight gain, which further challenge NAFLD mitigation strategies among the socioeconomically under-privileged (9). Identifying populations at-risk prone to feature limited adherence to lifestyle-related preventive measures may enable to better integrate primary prevention across diverse sectors of society, while reducing the risk of NALFD and associated cardiometabolic disease.

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