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Reply to Mantovani: “Causality between non-alcoholic fatty liver disease and risk of cardiovascular disease and type 2 diabetes”

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Abbreviations

NAFLD: Non-alcoholic fatty liver disease

CVD: Cardiovascular disease

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CONFLICTS OF INTEREST

KK: speaker for Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Servier and Merck Sharp & Dohme. Grants in support of investigator and investigator initiated trials from Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Pfizer, Boehringer Ingelheim and Merck Sharp & Dohme. Funds for research, honoraria for speaking at meetings and advisory boards for Lilly, Sanofi-Aventis, Merck Sharp & Dohme and Novo Nordisk.

MJD: Consultant, advisory board member and speaker for Novo Nordisk, Sanofi–Aventis, Lilly, Merck Sharp & Dohme, Boehringer Ingelheim, AstraZeneca and Janssen; speaker for Mitsubishi Tanabe Pharma Corporation. Grants in support of investigator and investigator initiated trials from Novo Nordisk, Sanofi–Aventis and Lilly.

We thank Mantovani for the interest and appreciation in our meta-analysis.¹ In a comment letter,² three points were raised, all concerning the association between non–alcoholic fatty liver disease (NAFLD) and risk of incident cardiovascular disease (CVD).

In our analysis, the overall hazard ratio for CVD comparing participants with NAFLD vs those without was 1.48 [95% confidence interval: 0.96, 2.29], which suggests a possible association yet not “statistically significant”, if accepting a p-value threshold for significance at 0.05. In the attempt to avoid a p-value-based interpretation of the results,³ we stated that “there is evidence but uncertainty”; moreover, the observed absence of evidence, rather than the evidence of absence, did not exclude the possibility that there could be a true difference.⁴ As a corollary, the absence of a strong evidence of a causal relationship does not indicate the absence of a causal relationship. We believe that further studies are required for CVD, likely because the association between NAFLD and CVD, even if true (causal), could be of smaller magnitude compared to that between NAFLD and type 2 diabetes.

Not all studies reported in previous meta-analyses have been included in our investigation, for reasons related to population, exposure, or outcome definition and ascertainment. To assure a larger generalisability, when possible we extracted data from studies including general populations (i.e., from observational cohorts of general population or population-based routine data) rather than studies reporting data only for specific populations (for example, cohorts defined by the presence of a specific condition); most of the studies, however, were excluded as they relied on overlapping populations, which were nevertheless included in previous meta-analyses: this decision may result in biased overall and confidence interval estimates. Similar to a previous study in the same cohort,⁵ the paper quoted in the letter reports the relationship between NAFLD and CVD in a cohort of patients all with diabetes:⁶ its inclusion in our analysis results in a virtually identical overall hazard ratio:⁷ 1.50, 95% confidence interval 1.01, 2.23.

As regards the remaining two comments, we completely agree on the importance of presenting stratified analysis by type of CVD events, an analysis which was not possible due to the limited number of nonoverlapping studies with available stratified data. Similarly, nothing more can be added to the observation that the results of the on-going randomised controlled trials could potentially complement current evidence about the nature and the strength of the relationship between NAFLD, type 2 diabetes and CVD.

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