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Adiponectin as a Predictor of Metabolic Dysfunction-Associated Steatotic Liver Disease and Non-Alcoholic Fatty Liver Disease: A 17-Year Korean Cohort Study (*Diabetes Metab J* 2026;50:331-42)

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We sincerely appreciate the correspondents' interest in our recent publication, 'Adiponectin as a predictor of metabolic dysfunction-associated steatotic liver disease and non-alcoholic fatty liver disease: a 17-year Korean Cohort Study' [1], and their thoughtful methodological comments. We thank them for the opportunity to clarify these points and to provide additional analyses that address their concerns.

First, we appreciate the comment on outcome definition using administrative codes. As imaging or biomarker validation is not currently available in this dataset, we acknowledge that future studies incorporating radiologic or laboratory confirmation are warranted to further refine diagnostic specificity. Regarding alcohol, weekly gram-based intake could not be incorporated into the primary analyses because alcohol-quantity variables had substantial missingness (>10,000 participants). In response to the readers' concern, we conducted sensitivity analyses by estimating weekly alcohol intake from drinking frequency per week and average drinks per occasion and excluded participants exceeding sex-specific weekly thresholds (men ≥210 g/week; women ≥140 g/week). The graded associations between adiponectin quintile and outcomes remained consistent (Table 1), supporting the robustness of our findings.

Second, we appreciate the readers' detailed comments on measurement variability and longitudinal modeling. Adiponectin was measured using the validated AdipoMark enzyme-linked immunosorbent assay (ELISA), which has demonstrated acceptable intra- and inter-assay precision, recovery, and linearity in a prior validation study [2]. Therefore, substantial differential measurement error across assays is unlikely. Repeated adiponectin measurements were not available in the Korean Cancer Prevention Study-II (KCPS-II) cohort, precluding joint modeling or reliability-adjusted analyses. However, regression dilution bias from a single baseline measurement would generally attenuate the association toward the null rather than inflate it; thus, our estimates are likely conservative [3]. We agree that future longitudinal studies with repeated biomarker measurements will be valuable to further refine the temporal relationship between adiponectin and metabolic dysfunction-associated steatotic liver disease (MASLD) risk.

Third, we appreciate the concern regarding potential early-event bias (including immortal time–related issues) as well as the possibility of overadjustment and model instability. Because adiponectin was ascertained at baseline and follow-up started from the measurement date (time zero), the classical immortal time bias that arises when exposure is defined using post–time-zero information is unlikely in our design [4,5]. To

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Table 1. Association between adiponectin quintile and MASLD in landmark and sensitivity analyses

Adiponectin quintile (AQ)	HR (95% CI)
A. 1-year landmark analysis (model 3, $n=35,008$)[a]	
AQ 5	(Ref.) 1.00
AQ 4	1.39 (1.02–1.89)
AQ 3	1.65 (1.22–2.24)
AQ 2	2.05 (1.51–2.78)
AQ 1	2.52 (1.85–3.43)
B. Excluding above-threshold alcohol intake and events within 1 year ($n=19,783$), model 3[b]	
AQ 5	(Ref.) 1.00
AQ 4	1.49 (0.94–2.36)
AQ 3	1.59 (1.03–2.46)
AQ 2	1.68 (1.09–2.59)
AQ 1	1.87 (1.22–2.88)
C. Minimal adjustment ($n=19,783$)[c]	
AQ 5	(Ref.) 1.00
AQ 4	1.46 (0.97–2.20)
AQ 3	1.66 (1.12–2.44)
AQ 2	1.82 (1.24–2.69)
AQ 1	2.18 (1.48–3.21)

MASLD, metabolic dysfunction-associated steatotic liver disease; HR, hazard ratio; CI, confidence interval.
[a]In the main analysis, 18 MASLD events occurred within 1 year after baseline and were excluded from the 1-year landmark analysis; no deaths occurred within 1 year. Model 3 was adjusted for the covariates as defined in the original article, [b]Weekly alcohol intake (g/week) was estimated as drinking frequency×drinks per occasion, assuming 10 g ethanol per drink. Among 23,170 participants, we excluded 3,369 with above-threshold alcohol intake (men ≥210 g/week; women ≥140 g/week) and 18 who experienced the outcome within 1 year. Follow-up started at 1 year among those event-free at that point ($n=19,783$). Model 3 was adjusted for the covariates defined in the original article, [c]Same sample as B. Minimally adjusted for age, sex, body mass index, physical activity, and smoking status.

address early-event concerns, we conducted a 1-year landmark analysis (i.e., resetting time zero at 1 year and excluding events occurring within the first year; no deaths occurred within 1 year); the dose–response pattern across adiponectin quintiles remained consistent (Table 1). We also compared our prespecified fully adjusted model with a reduced/minimally adjusted model, demonstrating unchanged estimates (Table 1). In addition, in Table 1 of the original article, 'non-alcoholic fatty liver disease (NAFLD)$^{\text{-cardiometabolic}}$ ($n=531$)' denotes the number of incident events observed in the full cohort during follow-up. Accordingly, the events-per-parameter ratio is well above commonly cited thresholds and is inconsistent with an events-per-variable ratio <3 [6,7].

Fourth, our primary objective was to evaluate etiologic associations between baseline adiponectin and incident MASLD/NAFLD. Accordingly, we used cause-specific Cox models to estimate cause-specific hazard ratios, whereas Fine–Gray subdistribution models primarily target the cumulative incidence function (absolute risk) in the presence of competing events. For clarity, the curves in the supplementary data represent Kaplan-Meier–based cumulative event probability (1−S(t)), i.e., a graphical transformation of the survival function with death treated as censoring, presented descriptively rather than as a competing-risk cumulative incidence function. Regarding proportional hazards (PH), we did not present covariate-level PH diagnostics given our focus on etiologic association and space constraints; moreover, formal PH tests can have limited/variable power depending on sample size and event counts [8]. Importantly, our key sensitivity analyses (1-year landmark and reduced vs. fully adjusted models) yielded consistent estimates (Table 1), suggesting that major time-varying effects are unlikely to explain our findings.

Fifth, we acknowledge the discrepancies in the cohort description and person-time reporting identified by the readers. In the Results, the exclusion categories of 2,493 and 5,090 were inadvertently interchanged, and 615 participants with pre-existing liver disease were omitted from the description, although Fig. 1 correctly reflects the cohort derivation. In the published version of Table 1 (and Supplementary Table 1), person-time was mistakenly labeled as person-years; the correct unit is person-days. These errors do not affect the hazard ratio estimates. These corrections have been incorporated into the e-pub (online) article and the accompanying tables.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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