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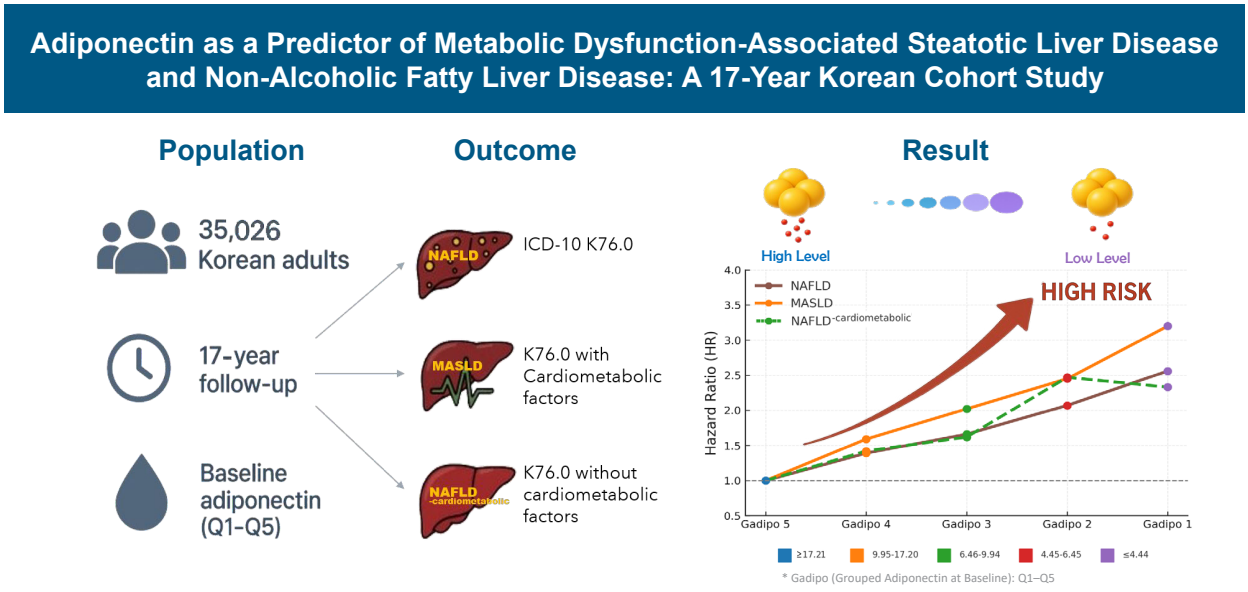


## Highlights

- **Lower adiponectin levels showed a dose-dependent increase in MASLD and NAFLD risk.**
- **NAFLD$^{\text{-cardiometabolic}}$ also showed increased risk in lower adiponectin groups.**
- **Abdominal obesity with a BMI <23 kg/m$^2$ independently predicted NAFLD.**
- **MASLD identifies metabolic liver disease more effectively than previous classifications.**
- **Adiponectin emerged as a robust indicator of metabolic liver disease risk.**

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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

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**Background:** This study aimed to investigate the association between adiponectin levels and the incidence of metabolic dysfunction-associated steatotic liver disease (MASLD) and nonalcoholic fatty liver disease (NAFLD), and to explore the predictive value of adiponectin in the onset of these conditions.
**Methods:** A 17-year follow-up of 35,026 individuals from the Korean Cancer Prevention Study-II biobank cohort (2004–2021) was conducted. Adiponectin levels were categorized into quintiles. Outcomes were defined as: NAFLD (10th revision of the International Classification of Diseases [ICD-10] K76.0); MASLD (K76.0 with cardiometabolic factors); NAFLD$^{\text{-cardiometabolic}}$ (K76.0 without cardiometabolic factors); and non-steatotic liver disease. The cause-specific Cox model accounted for death as a competing risk, with interaction terms for non-proportional hazards.
**Results:** Our findings indicated a heightened risk of MASLD in individuals in low adiponectin groups. Hazard ratios (HRs) for different adiponectin levels, using Gadipo 5 (≥17.21 μg/mL) as the reference, were: Gadipo 1, HR 3.20 (95% confidence interval [CI], 2.08 to 4.92); Gadipo 2, HR 2.45 (95% CI, 1.59 to 3.76); Gadipo 3, HR 2.02 (95% CI, 1.32 to 3.11); and Gadipo 4, HR 1.59 (95% CI, 1.02 to 2.46). These associations remained consistent across outcomes and models. Sex stratification revealed a stronger association among females. Furthermore, lower adiponectin levels were associated with increased MASLD and NAFLD risk. Similar associations were also observed in individuals with NAFLD$^{\text{-cardiometabolic}}$, indicating consistency across subtypes.
**Conclusion:** Different adiponectin levels revealed distinct risks. This study emphasizes adiponectin's potential as a predictive indicator of MASLD and NAFLD, stressing the need for further investigation across diverse demographic groups.

**Keywords:** Adiponectin; Fatty liver; Liver diseases; Metabolic syndrome; Non-alcoholic fatty liver disease

## INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a significant contributor to liver disease globally, affecting an estimated 25% of the world's population [1]. The prevalence of NAFLD in Asian countries is approximately 27.4%, which is comparable to that observed in Western countries [1,2]. In Korea, the prevalence of NAFLD in the general population is approximately 27%, while it is diagnosed via ultrasound in 16.1% of cases (21.6% in males and 11.2% in females) [3]. NAFLD is a chronic disease characterized by aberrant accumulation of fat in the liver. It is correlated with metabolic disorders, including obesity, diabetes, and hyperlipidemia, and increases the likelihood of developing cirrhosis and other complications associated with type 2 diabetes mellitus (T2DM) [4,5]. Furthermore, there has been a concurrent increase in the prevalence of NAFLD, obesity, T2DM,

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and metabolic syndrome [6]. NAFLD not only increases the risk of liver-related complications and mortality, but also affects numerous extrahepatic organs, including the cardiovascular system. Identification of the illness as a multisystem disorder has become more evident [7]. Over the next decade, NAFLD has become the leading cause of liver cirrhosis, requiring liver transplantation [8]. Recently, the concept of metabolic dysfunction-associated steatotic liver disease (MASLD) was introduced, providing a broader framework that includes NAFLD under the umbrella of metabolic dysfunction-related liver diseases. MASLD emphasizes the role of metabolic dysfunction in liver disease and helps better understand and categorize these conditions. MASLD is defined as the presence of hepatic steatosis in conjunction with at least one cardiometabolic risk factor, such as obesity, T2DM, or hypertension [9]. The emergence of MASLD is driven by the need to address limitations of the NAFLD terminology, which often excluded patients with significant metabolic risks who consumed moderate amounts of alcohol and used potentially stigmatizing language like 'nonalcoholic' and 'fatty.' This change aims to create a more inclusive and precise classification that better reflects the underlying metabolic issues and reduces the stigma associated with the disease [10].

A consistent increase in the number of patients with NAFLD has received medical attention in Korea. NAFLD-related hospital visits have increased by more than 40% over the course of 5 years, from 283,038 patients in 2017 to 405,950 in 2021, according to data from the National Health Insurance Service (NHIS) [11]. The increase in NAFLD outbreaks can be primarily ascribed to the westernization of dietary practices, which are characterized by excessive caloric consumption and lack of physical activity. Thus, the significance of research in this field is underscored by the remarkably high importance of managing NAFLD.

Adiponectin is a unique hormone abundantly secreted in adipose tissue and is reported to increase insulin sensitivity, contribute to metabolic activation, and alleviate hepatic inflammation and fibrosis [5]. According to prior studies [12], a reduction in adiponectin levels is linked to processes such as fibrosis, inflammation, and intrahepatic fat accumulation, which are all considered to be involved in the development and progression of NAFLD. Adiponectin levels are reduced in obese individuals as well as in those with coronary heart disease or diabetes [13-15]. Moreover, low levels of adiponectin promote insulin resistance, increase intrahepatic lipid accumulation, and inflammation in the liver and tend to be linked to metabolic diseases such as obesity, T2DM, and metabolic syndrome. Adiponectin has been used to predict the degree of fatty liver disease and severity of NAFLD because adiponectin levels are associated with insulin resistance and inflammation, which are associated with the onset and progression of NAFLD [5]. Thus, these results support the hypothesis that adiponectin may affect the progression and development of NAFLD, and suggest that adiponectin depletion may be associated with NAFLD severity.

Low levels of adiponectin in the blood are a common finding among patients with NAFLD [16], and are known to be related to the development and progression of NAFLD [13,17]. Adiponectin is a biomarker that reflects insulin resistance and has been proposed as an indicator of NAFLD [18,19]; however, prospective studies are lacking.

Additionally, we examined instances of lean obesity in the present study. As per prior research, about 10% to 20% of individuals with NAFLD fall into the category of 'Lean NAFLD,' without being overweight or obese (body mass index [BMI] $<25$ kg/m$^2$ or, for Asians, BMI $<23$ kg/m$^2$) [20]. This condition is a significant contributor to cryptogenic liver disease [21], and lean individuals with NAFLD exhibit a heightened risk of impaired glucose tolerance, hypertension, metabolic syndrome, and cardiovascular mortality [22]. Essentially, while lean individuals with NAFLD share similar risks of complications as those who are visibly obese, their condition goes unrecognized owing to the absence of apparent obesity, thus posing a notable severity in terms of disease awareness [22,23].

This study aimed to investigate the prospective risk of NAFLD, MASLD, and NAFLD, excluding cardiometabolic syndrome (NAFLD$^{\text{-cardiometabolic}}$) incidence due to adiponectin levels, and explore whether adiponectin could be utilized as a potential targeted indicator for the prediction or prevention of NAFLD in a 17-year follow-up in the Korean Cancer Prevention Study-II (KCPS-II) cohort. In addition, this study sought to confirm the appropriateness of the newly proposed MASLD definition by including various metabolic conditions and lean obesity.

## METHODS

### Participants

The KCPS-II Biobank cohort consists of individuals who visited comprehensive health checkup facilities in 15 locations within the Seoul and Gyeonggi regions, as well as three addi-

tional regions in South Korea, between 2004 and 2013. A detailed description of the Biobank cohort design and methods of participant selection has been previously published [24,25]. This study was approved by the Institutional Review Board of Yonsei University (IRB No. 4-2011-0277). Written informed consent was obtained from all participants in accordance with the Declaration of Helsinki. This study focused on 43,270 individuals with variable adiponectin levels.

**Data and blood collection**

All participants completed a structured questionnaire interview to gather data on smoking (never, former, current), alcohol consumption (non-drinker, regular), and exercise habits (active or not). Height and weight were measured with participants in lightweight clothing and barefoot, and BMI was calculated as weight (kg)/height ($m^2$). The BMI categories adhered to the World Health Organization Asian-Pacific classification: individuals weighing less than 18.5 kg/$m^2$ were classified as 'underweight,' those weighing between 18.5 and 22.9 kg/$m^2$ were considered 'normal,' and those weighing more than this range were categorized as 'overweight' (23≤ BMI ≤25 kg/$m^2$) or 'obese' (BMI >25 kg/$m^2$) [26]. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured using automated or mercury sphygmomanometers after a 15-minute rest.

Serum samples, collected after 12-hour fasting and stored at –70°C, were analyzed for fasting blood sugar (FBS), total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) using a COBAS INTEGRA 800 (Roche Diagnostics, Mannheim, Germany) and Hitachi-7600 analyzer (Hitachi, Tokyo, Japan). Adiponectin levels were measured using an enzyme immunoassay method with a self-developed kit (Adipomark, Mesdia Co., Seoul, Korea) [27,28].

**Follow-up and outcomes**

Our study participants were followed-up from the day adiponectin levels were measured until December 31, 2021. The mean follow-up periods were 7.7 years for the NAFLD group, 7.4 years for the MASLD group, 8.5 years for the NAFLD$^{\text{-cardiometabolic}}$ group, and 14.6 years for the non-steatotic liver disease (SLD) group.

Adiponectin levels were categorized into quintiles within the KCPS-II Biobank cohort. Participants were then divided into four groups based on outcomes: (1) 'NAFLD,' classified under 10th revision of the International Classification of Diseases (ICD-10) code K76.0 without considering potential cardiometabolic risks; (2) 'MASLD,' classified under ICD-10 code K76.0 with at least one cardiometabolic factor; (3) 'NAFLD$^{\text{-cardiometabolic}}$,' defined as individuals classified under K76.0 with no cardiometabolic factors; and (4) 'non-SLD,' individuals without SLD.

Additionally, 'Lean NAFLD' was defined as individuals diagnosed with NAFLD (ICD-10 code K76.0) who also met the criteria for lean obesity, characterized by a BMI <23 kg/$m^2$ and abdominal obesity (waist circumference ≥90 cm for males and ≥80 cm for females, based on Asian-specific guidelines). The definitions of cardiometabolic factors follow those from previous studies [10], and the adiponectin levels were categorized into five groups: Gadipo 1 (≤4.44 μg/mL), Gadipo 2 (4.45–6.45 μg/mL), Gadipo 3 (6.46–9.94 μg/mL), Gadipo 4 (9.95–17.20 μg/mL), and Gadipo 5 (≥17.21 μg/mL).

**Statistical analysis**

The mean and standard deviation were used to represent data that conformed to the normal distribution. In contrast, the median and interquartile range (IQR) were used to represent data that did not conform to a normal distribution. The Student's *t*-test was frequently employed to examine data that followed a normal distribution. Conversely, non-normally distributed data were analyzed using the Mann-Whitney *U* test. In accordance with the suitability of the data for analysis, categorical data were expressed as numbers and percentages, and either Fisher's exact test or chi-square test was used. With the study outcome being the time-to-event for liver disease, survival analysis was conducted. A cause-specific Cox proportional hazards (PH) model, accounting for death as a competing risk, was used to evaluate the association between adiponectin levels (Gadipo 1–5) and the incidence of all outcomes (MASLD, NAFLD, NAFLD$^{\text{-cardiometabolic}}$). Interaction terms with time were incorporated to address variables that violated the PH assumption, which was assessed using log(–log(survival)) plots and Schoenfeld residuals. Three models were applied to estimate hazard ratios (HRs) for different adiponectin levels, with the highest adiponectin level (≥17.21 μg/mL) serving as the reference. Model 1 was an unadjusted crude model. Model 2 was adjusted for age and sex. Model 3 was further adjusted for BMI, FBS, TC, alanine aminotransferase (ALT), alkaline phosphatase (ALP), SBP, DBP, TG, LDL-C, HDL-C, gamma-glutamyltransferase (GGT), insulin, aspartate aminotransferase (AST), exercise, current smoking status, and former smoking status, while maintaining adiponectin level stratification. All analyses were performed using SAS version 9.4 (SAS Insti-

tute Inc., Cary, NC, USA).

## RESULTS

Of the 43,270 individuals with adiponectin data, 5,090 were excluded due to liver disease at the time of measurement, and 2,493 were excluded for being diagnosed with NAFLD within 1 year prior. Additionally, 46 participants with a BMI <16 kg/m² or ≥100 kg/m² were excluded, as were 615 patients with pre-existing conditions. The final cohort comprised 35,026 Korean participants (22,359 males and 12,667 females), as shown in Fig. 1. Baseline characteristics stratified by sex are presented in Supplementary Table 1.

Throughout the 17-year follow-up period (2004–2021), NAFLD was identified in 2,318 of 35,026 individuals (1,631 males and 687 females). The non-SLD group exhibited the following characteristics: the average age was 41.8±9.8 years. Compared with the SLD group, the non-SLD group had lower BMI, waist circumference, SBP, DBP, FBS, TC, AST, ALT, TG, LDL-C, and insulin levels, except for the NAFLD$^{\text{-cardiometabolic}}$ group. Adiponectin and HDL-C levels were significantly higher in the non-SLD group. The mean ages were 44.0±9.7 years in the NAFLD group, 44.5±9.7 years in the MASLD group, and 42.1±9.5 years in the NAFLD$^{\text{-cardiometabolic}}$ group. The median BMI values were 25.5 kg/m² (IQR, 23.5 to 27.3) for the MASLD group, 24.6 kg/m² (IQR, 22.7 to 26.6) for the NAFLD group, and 22.5 kg/m² (IQR, 20.7 to 23.7) for the NAFLD$^{\text{-cardiometabolic}}$ group. The median waist circumference values were 86.0 cm (IQR, 81.0 to 91.0) for the MASLD group, 84.0 cm (IQR, 78.0 to 90.0) for the NAFLD group, and 77.0 cm (IQR, 71.0 to 81.5) for the NAFLD$^{\text{-cardiometabolic}}$ group (Table 1).

Using Gadipo 5 (≥17.21 μg/mL) as the reference group, the

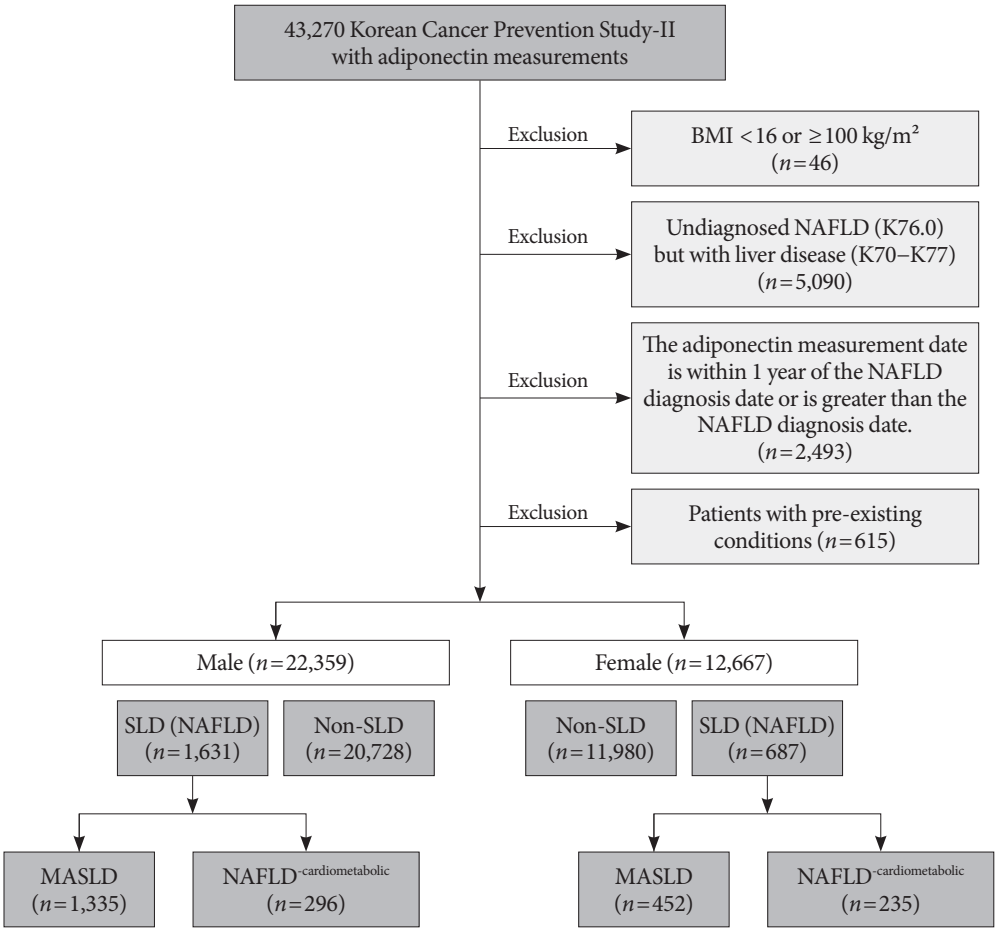


**Fig. 1.** Study flowchart. BMI, body mass index; NAFLD, nonalcoholic fatty liver disease; SLD, steatotic liver disease; MASLD, metabolic dysfunction-associated steatotic liver disease.

**Table 1.** Baseline characteristics of study participants in Korean Cancer Prevention Study-II

| Characteristic | SLD groups | | | | | | Non-SLD group | |
|---|---|---|---|---|---|---|---|---|
| | Person-day | NAFLD (*n*=2,318) | Person-day | MASLD (*n*=1,787) | Person-day | NAFLD$^{\text{-cardiometabolic}}$ (*n*=531) | Person-day | Non-SLD (*n*=32,708) |
| Age, yr | 7.66±4.14[a] | 43.98±9.69 (21–80) | 7.42±4.09[a] | 44.53±9.69 (21–80) | 8.50±4.17[a] | 42.14±9.46 (23–71) | 14.56±1.15[a] | 41.82±9.76 (20–86) |
| <30 | 323,099 | 106 (4.57) | 201,138 | 64 (3.58) | 121,961 | 42 (7.91) | 13,380,897 | 2,527 (7.73) |
| 30–40 | 1,989,480 | 719 (31.02) | 1,403,010 | 529 (29.60) | 586,470 | 190 (35.78) | 66,576,694 | 12,506 (38.24) |
| 40–50 | 2,405,442 | 852 (36.76) | 1,824,223 | 672 (37.60) | 581,219 | 180 (33.90) | 58,752,029 | 10,986 (33.59) |
| 50–60 | 1,365,515 | 480 (20.71) | 1,070,109 | 383 (21.43) | 295,406 | 97 (18.27) | 25,886,788 | 4,887 (14.94) |
| 60–70 | 368,430 | 144 (6.21) | 310,776 | 124 (6.94) | 57,654 | 20 (3.77) | 7,940,173 | 1,532 (4.68) |
| >70 | 32,267 | 17 (0.73) | 28,484 | 15 (0.84) | 3,783 | 2 (0.38) | 1,315,223 | 270 (0.83) |
| Sex | | | | | | | | |
| Male | 4,407,476 | 1,631 (70.36) | 3,528,277 | 1,335 (74.71) | 879,199 | 296 (55.74) | 109,655,050 | 20,728 (63.37) |
| Female | 2,076,757 | 687 (29.64) | 1,309,463 | 452 (25.29) | 767,294 | 235 (44.26) | 64,196,754 | 11,980 (36.63) |
| BMI, kg/m$^2$ | | 24.60 (22.69–26.64) | | 25.49 (23.53–27.31) | | 22.45 (20.72–23.65) | | 23.37 (21.35–25.35) |
| Under weight (<18.5) | 99,759 | 31 (1.34) | 21,997 | 6 (0.34) | 77,762 | 25 (4.71) | 6,708,790 | 1,267 (3.87) |
| Normal weight (18.5–22.9) | 1,878,604 | 628 (27.09) | 978,308 | 334 (18.69) | 900,296 | 294 (55.37) | 71,855,924 | 13,499 (41.27) |
| Over weight (23–25) | 1,829,630 | 636 (27.44) | 1,161,195 | 424 (23.73) | 668,435 | 212 (39.92) | 44,941,143 | 8,460 (25.87) |
| Obese (>25) | 2,676,240 | 1,023 (44.13) | 2,676,240 | 1,023 (57.25) | - | 0 | 50,345,947 | 9,482 (28.99) |
| Waist, cm | | 84.00 (78.00–90.00) | | 86.00 (81.00–91.00) | | 77.00 (71.00–81.50) | | 80.00 (73.00–86.00) |
| SBP, mm Hg | | 120.00 (110.00–130.00) | | 122.00 (115.00–131.00) | | 111.00 (104.00–121.00) | | 120.00 (110.00–129.00) |
| DBP, mm Hg | | 77.00 (70.00–81.00) | | 79.00 (70.00–84.00) | | 70.00 (65.00–79.00) | | 74.00 (69.00–80.00) |
| FBS, mg/dL | | 90.00 (83.00–97.00) | | 91.00 (84.00–100.00) | | 86.00 (80.00–91.00) | | 87.00 (81.00–95.00) |
| TC, mg/dL | | 192.00 (171.00–215.00) | | 195.00 (173.00–219.00) | | 182.00 (166.00–199.00) | | 186.00 (165.00–207.00) |
| ALT, U/L | | 25.00 (17.00–38.00) | | 28.00 (19.00–42.00) | | 18.00 (14.00–25.00) | | 19.00 (14.00–27.00) |
| AST, U/L | | 23.00 (19.00–29.00) | | 24.00 (19.00–30.00) | | 20.00 (18.00–24.00) | | 20.00 (17.00–24.00) |
| TG, mg/dL | | 132.00 (92.00–193.00) | | 154.00 (108.00–220.00) | | 86.00 (67.00–109.00) | | 109.00 (75.00–161.00) |
| LDL-C, mg/dL | | 114.40 (96.00–136.40) | | 115.80 (97.60–140.80) | | 110.80 (92.70–128.00) | | 110.00 (91.00–130.60) |
| HDL-C, mg/dL | | 49.00 (44.00–55.00) | | 47.00 (41.60–52.00) | | 55.00 (51.00–63.00) | | 51.00 (46.00–56.00) |

(*Continued to the next page*)

**Table 1.** Continued

| Characteristic | SLD groups | | | | | | Non-SLD group | |
|---|---|---|---|---|---|---|---|---|
| | Person-day | NAFLD (*n*=2,318) | Person-day | MASLD (*n*=1,787) | Person-day | NAFLD$^{\text{-cardiometabolic}}$ (*n*=531) | Person-day | Non-SLD (*n*=32,708) |
| Adiponectin, μg/mL | | 5.75 (3.92–8.38) | | 5.36 (3.67–7.67) | | 7.10 (5.11–10.86) | | 6.72 (4.48–10.02) |
| ≤4.44 | 1,950,253 | 760 (32.79) | 1,654,586 | 665 (37.21) | 295,667 | 95 (17.89) | 42,728,930 | 8,033 (24.56) |
| 4.45–6.45 | 1,781,125 | 639 (27.57) | 1,368,283 | 498 (27.87) | 412,842 | 141 (26.55) | 43,031,685 | 8,105 (24.78) |
| 6.46–9.94 | 1,552,820 | 520 (22.43) | 1,117,070 | 384 (21.49) | 435,750 | 136 (25.61) | 43,622,520 | 8,220 (25.13) |
| 9.95–17.20 | 988,112 | 330 (14.24) | 598,695 | 205 (11.47) | 389,417 | 125 (23.54) | 35,508,263 | 6,669 (20.39) |
| ≥17.21 | 211,923 | 69 (2.98) | 99,106 | 35 (1.96) | 112,817 | 34 (6.40) | 8,960,406 | 1,681 (5.14) |
| Insulin, μIU/mL | | 4.27 (2.86–6.39) | | 4.82 (3.25–6.97) | | 2.94 (2.14–4.18) | | 3.70 (2.50–5.34) |
| ALP, U/L | | 124.00 (69.00–162.00) | | 128.00 (71.00–164.00) | | 112.00 (68.00–152.00) | | 126.00 (75.00–160.00) |
| Exercise | | | | | | | | |
| No | 3,743,333 | 1,352 (63.24) | 2,778,862 | 1,033 (62.80) | 964,471 | 319 (64.71) | 95,629,977 | 18,077 (61.19) |
| Yes | 2,208,516 | 786 (36.76) | 1,637,332 | 612 (37.20) | 571,184 | 174 (35.29) | 61,149,262 | 11,463 (38.81) |
| GCCI | | | | | | | | |
| 0 | 387 | 1 (0.04) | 387 | 1 (0.06) | - | 0 | 26,853,498 | 5,053 (15.45) |
| 1 | 590,414 | 200 (8.63) | 402,186 | 140 (7.83) | 188,228 | 60 (11.30) | 49,217,210 | 9,236 (28.24) |
| ≥2 | 5,893,432 | 2,117 (91.33) | 4,435,167 | 1,646 (92.11) | 1,458,265 | 471 (88.70) | 97,781,096 | 18,419 (56.31) |
| eGFR, mL/min/1.73 $m^2$ | | 86.76 (77.87–97.08) | | 86.05 (76.79–96.40) | | 88.41 (81.23–98.71) | | 88.41 (79.19–98.54) |
| DM | | | | | | | | |
| No | 4,874,273 | 1,694 (73.08) | 3,227,780 | 1,163 (65.08) | 1,646,493 | 531 (100.00) | 148,168,146 | 27,873 (85.22) |
| Yes | 1,609,960 | 624 (26.92) | 1,609,960 | 624 (34.92) | - | 0 | 25,683,658 | 4,843 (14.78) |
| GGT, U/L | | 32.00 (19.00–56.00) | | 36.00 (22.00–61.00) | | 21.00 (15.00–33.00) | | 23.00 (16.00–38.00) |

Values are presented as mean±standard deviation (range), number (%), or median (interquartile range).
SLD, steatotic liver disease; MASLD, metabolic dysfunction-associated steatotic liver disease; NAFLD, nonalcoholic fatty liver disease; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBS, fasting blood sugar; TC, total cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; ALP, alkaline phosphatase; GCCI, grouped count of comorbid condition; eGFR, estimated glomerular filtration rate; DM, diabetes mellitus; GGT, gamma-glutamyltransferase.
[a]Mean follow-up duration (years) from baseline to event or censoring, presented as mean±standard deviation.

**Table 2.** Hazard ratios for MASLD, NAFLD, and NAFLD$^{\text{-cardiometabolic}}$ by adiponectin levels across different models

| Outcomes | Adiponectin level, μg/mL | | | | |
|---|---|---|---|---|---|
| | ≥17.21 | 9.95–17.20 | 6.46–9.94 | 4.45–6.45 | ≤4.44 |
| NAFLD | | | | | |
| Model 1 | Ref. | 1.20 (0.93–1.56) | 1.53 (1.19–1.97) | 1.90 (1.48–2.43) | 2.27 (1.77–2.90) |
| Model 2 | Ref. | 1.20 (0.92–1.55) | 1.48 (1.14–1.90) | 1.78 (1.38–2.29) | 2.08 (1.62–2.69) |
| Model 3[a] | Ref. | 1.39 (1.02–1.90) | 1.66 (1.23–2.26) | 2.07 (1.52–2.80) | 2.56 (1.88–3.49) |
| MASLD | | | | | |
| Model 1 | Ref. | 1.47 (1.03–2.10) | 2.22 (1.57–3.14) | 2.90 (2.06–4.09) | 3.88 (2.76–5.45) |
| Model 2 | Ref. | 1.43 (1.00–2.05) | 2.04 (1.44–2.89) | 2.54 (1.80–3.60) | 3.30 (2.33–4.67) |
| Model 3[a] | Ref. | 1.59 (1.02–2.46) | 2.02 (1.32–3.11) | 2.45 (1.59–3.76) | 3.20 (2.08–4.92) |
| NAFLD$^{\text{-cardiometabolic}}$ | | | | | |
| Model 1 | Ref. | 0.93 (0.64–1.36) | 0.83 (0.57–1.20) | 0.87 (0.60–1.26) | 0.59 (0.40–0.87) |
| Model 2 | Ref. | 0.98 (0.67–1.43) | 0.91 (0.62–1.34) | 0.99 (0.67–1.46) | 0.69 (0.46–1.03) |
| Model 3[a] | Ref. | 1.42 (0.91–2.20) | 1.62 (1.04–2.54) | 2.47 (1.57–3.88) | 2.33 (1.44–3.77) |

Values are presented as hazard ratio (95% confidence interval). Model 1: crude model; Model 2: further adjusted for age, sex; Model 3: further adjusted for body mass index, fasting blood sugar (FBS), aspartate aminotransferase, alanine aminotransferase (ALT), alkaline phosphatase, systolic blood pressure, diastolic blood pressure, total cholesterol, triglyceride, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol (HDL-C), gamma-glutamyltransferase (GGT), insulin, exercise, and smoking status.
MASLD, metabolic dysfunction-associated steatotic liver disease; NAFLD, nonalcoholic fatty liver disease.
[a]For MASLD, NAFLD, and NAFLD$^{\text{-cardiometabolic}}$, because certain variables did not meet the Cox proportional hazards assumption (ALT for MASLD; FBS, HDL-C, ALT, and GGT for NAFLD; and GGT for NAFLD$^{\text{-cardiometabolic}}$), we introduced interaction terms involving these variables over time to account for non-proportional hazards in our analysis.

risk increased with decreasing adiponectin levels. For MASLD, a clear linear relationship was observed, where lower adiponectin levels corresponded to higher risks across all the models. Specifically, the HR in model 3 was 1.59 (95% confidence interval [CI], 1.02 to 2.46) for Gadipo 4 (9.95–17.20 μg/mL), 2.02 (95% CI, 1.32 to 3.11) for Gadipo 3 (6.46–9.94 μg/mL), 2.45 (95% CI, 1.59 to 3.76) for Gadipo 2 (4.45–6.45 μg/mL), and 3.20 (95% CI, 2.08 to 4.92) for Gadipo 1 (≤4.44 μg/mL). For NAFLD, all models showed a similar trend, where lower adiponectin groups indicated higher risk. In model 3, the HR was 1.39 (95% CI, 1.02 to 1.90) for Gadipo 4, 1.66 (95% CI, 1.23 to 2.26) for Gadipo 3, 2.07 (95% CI, 1.52 to 2.80) for Gadipo 2, and 2.56 (95% CI, 1.88 to 3.49) for Gadipo 1. For NAFLD$^{\text{-cardiometabolic}}$, although a clear linear trend was less pronounced than in MASLD and NAFLD, lower adiponectin groups still corresponded to higher risks. In model 3, the HR was 1.42 (95% CI, 0.91 to 2.20) for Gadipo 4, 1.62 (95% CI, 1.04 to 2.54) for Gadipo 3, 2.47 (95% CI, 1.57 to 3.88) for Gadipo 2, and 2.33 (95% CI, 1.44 to 3.77) for Gadipo 1, as shown in Table 2, Fig. 2.

## DISCUSSION

In this prospective cohort study of the general population, individuals in low adiponectin groups and lean obesity showed a higher risk of developing NAFLD over 17 years. The scope of our study included a wide range of parameters, such as basic demographic information, potential risk or protective factors, and confounding variables, including clinical data, such as FBS, AST, and ALT. All possible confounding variables were accounted for to ensure the robustness of our findings [29].

Our findings of increased NAFLD risk among individuals in lower adiponectin groups align with earlier research, indicating a consistent association between low adiponectin and NAFLD prevalence, regardless of obesity status [17]. In addition, individuals in the NAFLD group tended to belong to lower adiponectin groups, with serum levels differing from those observed in healthy individuals [30]. Lower adiponectin groups were associated with a higher risk of MASLD, NAFLD, and NAFLD$^{\text{-cardiometabolic}}$, with a clear linear relationship observed across all models for MASLD and NAFLD. These findings reinforce the role of adiponectin as a key biomarker in

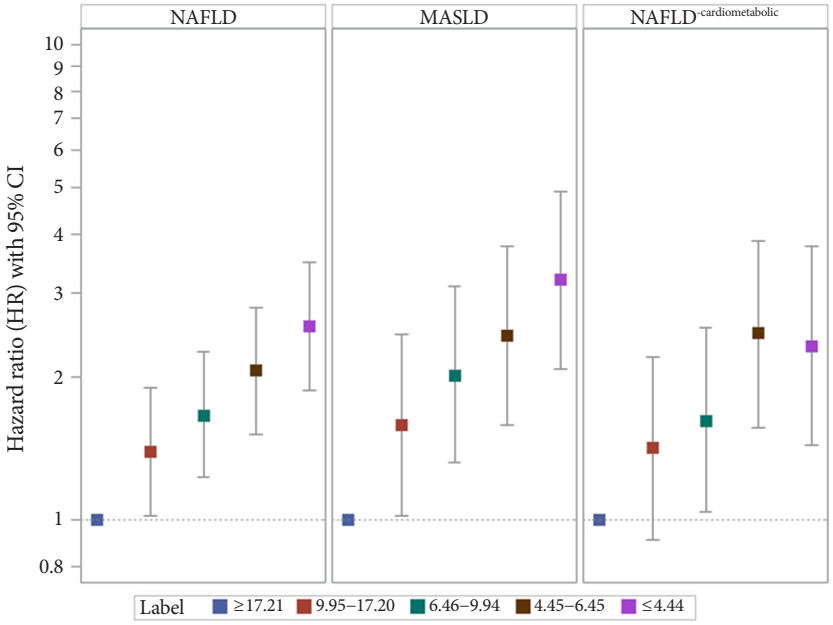


**Fig. 2.** Risk of metabolic dysfunction-associated steatotic liver disease (MASLD), nonalcoholic fatty liver disease (NAFLD), and NAFLD$^{\text{-cardiometabolic}}$ incidence by adiponectin levels across models. The hazard ratio (HR) of developing MASLD, NAFLD, and NAFLD$^{\text{-cardiometabolic}}$ in various groups, in comparison to the reference group with adiponectin levels exceeding 17.20 μg/mL. This figure is based on the results from model 3. Adiponectin levels are categorized as follows: Gadipo 1: ≤4.44 μg/mL, Gadipo 2: 4.45–6.45 μg/mL, Gadipo 3: 6.46–9.94 μg/mL, and Gadipo 4: 9.95–17.20 μg/mL. CI, confidence interval.

predicting liver disease, particularly in the presence of other metabolic factors. Following sex stratification, the strength of these associations was significantly greater in females (Supplementary Tables 2 and 3). Therefore, our analysis aligns with and reinforces the patterns observed in previous studies. Moreover, whereas previous research has primarily employed cross-sectional methodologies, the present study adopted a prospective design to investigate both the correlation and incidence of the condition.

To the best of our knowledge, this is the first prospective study to examine this association. Nevertheless, ongoing debate remains regarding the definition and measurement of lean obesity. Recent meta-analyses have acknowledged the limitations of using BMI alone to assess metabolic health, highlighting the importance of incorporating waist circumference as an indicator of abdominal obesity [31]. Individuals identified under this definition of lean NAFLD demonstrate higher fibrosis scores, cardiovascular morbidity, and overall mortality rates [20]. Although recent studies have reported similar findings across diverse ethnic groups, previous associations have primarily focused on lean NAFLD in Asian populations [31]. In our study, lean obesity was defined using both BMI and abdominal obesity criteria. Even after adjusting for adiponectin levels and other covariates, lean obesity remained a significant predictor of NAFLD development. In a supplementary analysis stratified by lean obesity status, individuals with lean obesity had a 1.49-fold higher risk of developing NAFLD (95% CI, 1.00 to 2.23) compared to those without lean obesity. This association remained statistically significant after controlling for adiponectin levels and other model variables (Supplementary Table 4).

The comprehensive analysis demonstrated a clear association between lower adiponectin groups and increased risks in the SLD subtypes (MASLD, NAFLD, and NAFLD$^{\text{-cardiometabolic}}$). Notably, individuals in lower adiponectin groups consistently exhibited higher risks across all subtypes. These findings suggest that the association between adiponectin levels and liver disease risk may be modified by additional metabolic factors.

This finding highlights the complex interplay between body composition and metabolic health, suggesting that lean obesity is an independent and important factor to consider in the context of NAFLD, regardless of adiponectin levels.

Collectively, these results emphasize the varying impact of adiponectin levels on liver disease risk. They underscore the

need for a nuanced understanding of how adiponectin interacts with other risk factors, including body composition, in the development of metabolic disorders. Unlike previous studies [32,33] that compared lean and non-lean NAFLD patients, our study is the first to assess lean obesity as an independent risk factor for NAFLD.

Adiponectin is known for its anti-inflammatory properties and its ability to enhance insulin sensitivity. This suggests that lean obesity, although not classified as traditional obesity, can still lead to metabolic dysfunction. Furthermore, while lean obesity shares some metabolic features with classical obesity, such as altered energy metabolism, it also exhibits distinct characteristics, particularly regarding vascular health. Adiponectin also exerts anti-inflammatory effects and improves insulin sensitivity [16].

To evaluate the therapeutic or preventive potential of adiponectin in NAFLD, it is essential to determine whether adiponectin plays a causal role in disease development. However, few human studies have specifically examined the mechanisms or pathways through which adiponectin may exert causal effects in NAFLD. Further investigation is required to evaluate the therapeutic potential of these pathways. Although ongoing research continues to explore the adiponectin-NAFLD relationship [34-38], the present study provides important insights into their long-term association. In particular, the cumulative incidence curve based on adiponectin levels demonstrated a linear increase in NAFLD risk over time, with the highest incidence observed in the lowest adiponectin group. For both MASLD and NAFLD, individuals in Gadipo groups 1 and 2 exhibited higher cumulative incidence, showing a clear linear trend across the groups. These findings suggest that adiponectin groups may serve as useful predictors for future risk of NAFLD and MASLD. However, longer-term follow-up studies are needed to assess the risk of liver cirrhosis and mortality (Supplementary Figs. 1 and 2; sex-stratified curves in Supplementary Fig. 2). Furthermore, an additional analysis was conducted to explore the relationship between adiponectin group and cardiovascular disease (CVD) risk based on liver disease status. The results revealed distinct patterns: in the non-MASLD group, lower adiponectin groups were associated with higher CVD risk, consistent with the expected inverse relationship. However, in the MASLD group, this linear trend was disrupted; higher adiponectin groups showed increased CVD risk, suggesting a paradoxical pattern (Supplementary Fig. 3). This phenomenon is consistent with previous studies reporting that elevated adiponectin levels may not always confer protective effects and may even reflect adverse outcomes under certain pathological conditions, such as advanced liver disease or amyloid-beta pathology [39-41]. Our findings support this possibility, although the underlying mechanisms—such as impaired adiponectin clearance, compensatory upregulation, or altered adiponectin signaling—remain speculative. Further research is warranted to clarify the role of adiponectin in cardiovascular outcomes within the context of metabolic liver disease.

The major strengths of this study include a large sample size, which enhances statistical power, and a long-term follow-up period, enabling a comprehensive assessment of disease progression. In addition, the study adjusted for a wide range of covariates to minimize confounding when evaluating risk factors. Furthermore, disease diagnoses were independently ascertained using nationwide health records, ensuring objective classification and minimizing recall bias.

This study has several limitations. First, although the study elucidates the temporal relationship between adiponectin levels and the incidence of MASLD and NAFLD, it provides only limited evidence of causality. Further research is needed to determine whether adiponectin can serve as a causal target for therapeutic intervention. Second, the KCPS-II data were derived from individuals who underwent biennial health examinations, introducing potential selection bias, as participants may have been more health-conscious or maintained healthier lifestyles [42]. This demographic specificity should be considered when interpreting the findings. Finally, we used data from the Korean NHIS, which includes hospital admissions, outpatient visits, and death records. However, because NAFLD is often asymptomatic in its early stages, some cases may have gone undetected among individuals who did not seek medical care. This potential misclassification could have led to an underestimation of the association between adiponectin levels and NAFLD risk. Nonetheless, the use of nationwide health insurance data covering over 95% of the Korean population minimizes the likelihood of significant attrition bias.

This study uniquely examined both adiponectin levels and lean obesity in individuals with NAFLD, providing a distinct contribution to current understanding. Moreover, this large-scale cohort study provides prospective and comprehensive insights into the long-term risk of NAFLD.

In conclusion, this prospective cohort study identified a clear association between lower adiponectin groups and the incidence of NAFLD and MASLD. The stratification of adiponec-

tin levels revealed distinct risk patterns, highlighting its potential as a predictive biomarker. Further research is warranted to evaluate the utility of adiponectin across diverse populations and to clarify its role in liver cirrhosis and mortality.

## SUPPLEMENTARY MATERIALS

Supplementary materials related to this article can be found online at https://doi.org/10.4093/dmj.2025.0007.

## CONFLICTS OF INTEREST

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

## AUTHOR CONTRIBUTIONS

Conception or design: Y.S.Y., H.K.
Acquisition, analysis, or interpretation of data: Y.S.Y., H.S.Z., S.K.
Drafting the work or revising: all authors.
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**Supplementary Table 1.** Baseline characteristics of study participants in Korean Cancer Prevention Study-II by sex

| Characteristic | Person-day | Male (*n*=22,359) | Person-day | Female (*n*=12,667) | *P* value |
|---|---|---|---|---|---|
| Age, yr | 13.98±2.46[a] | 42.27±9.37 (20–86) | 14.33±1.99[a] | 41.42±10.40 (20–78) | <0.0001 |
| <30 | 6,151,862 | 1,193 (5.34) | 7,552,134 | 1,440 (11.37) | <0.0001 |
| 30–40 | 43,875,242 | 8,546 (38.22) | 24,690,932 | 4,679 (36.94) | |
| 40–50 | 40,880,319 | 7,973 (35.66) | 20,277,152 | 3,865 (30.51) | |
| 50–60 | 17,605,455 | 3,490 (15.61) | 9,646,848 | 1,877 (14.82) | |
| 60–70 | 4,700,052 | 971 (4.34) | 3,608,551 | 705 (5.57) | |
| >70 | 849,596 | 186 (0.83) | 497,894 | 101 (0.80) | |
| SLD | | | | | |
| No SLD | | 20,728 (92.71) | | 11,980 (94.58) | <0.0001 |
| MASLD | | 1,335 (5.97) | | 452 (3.57) | |
| NAFLD$^{\text{-cardiometabolic}}$ | | 296 (1.32) | | 235 (1.86) | |
| BMI, kg/m$^2$ | | 24.18 (22.43–25.97) | | 21.83 (20.08–23.94) | <0.0001 |
| Under weight (<18.5) | 1,500,785 | 292 (1.31) | 5,307,764 | 1,006 (7.94) | <0.0001 |
| Normal weight (18.5–22.9) | 35,907,937 | 6,954 (31.10) | 37,826,591 | 7,173 (56.63) | |
| Over weight (23–25) | 34,221,745 | 6,676 (29.86) | 12,549,028 | 2,420 (19.10) | |
| Obese (>25) | 42,432,059 | 8,437 (37.73) | 10,590,128 | 2,068 (16.33) | |
| Waist, cm | | 84.00 (79.00–89.00) | | 73.00 (68.00–79.00) | <0.0001 |
| SBP, mm Hg | | 120.00 (110.00–130.00) | | 110.00 (101.00–120.00) | <0.0001 |
| DBP, mm Hg | | 79.00 (70.00–81.00) | | 70.00 (63.00–78.00) | <0.0001 |
| FBS, mg/dL | | 89.00 (82.00–97.00) | | 86.00 (79.00–92.00) | <0.0001 |
| TC, mg/dL | | 190.00 (168.00–212.00) | | 180.00 (160.00–200.00) | <0.0001 |
| ALT, U/L | | 23.00 (17.00–32.00) | | 14.00 (11.00–19.00) | <0.0001 |
| AST, U/L | | 22.00 (19.00–26.00) | | 18.00 (16.00–21.00) | <0.0001 |
| TG, mg/dL | | 130.00 (92.00–188.00) | | 82.00 (61.00–116.00) | <0.0001 |
| LDL-C, mg/dL | | 113.00 (94.00–133.20) | | 105.40 (87.40–126.00) | <0.0001 |
| HDL-C, mg/dL | | 48.00 (44.00–53.00) | | 56.00 (50.00–63.00) | <0.0001 |
| Adiponectin, μg/mL | | 5.64 (3.92–8.06) | | 9.23 (6.25–13.18) | <0.0001 |
| ≤4.44 | 37,416,729 | 7,386 (33.03) | 7,262,454 | 1,407 (11.11) | <0.0001 |
| 4.45–6.45 | 33,430,245 | 6,548 (29.29) | 11,382,565 | 2,196 (17.34) | |
| 6.46–9.94 | 27,310,368 | 5,326 (23.82) | 17,864,972 | 3,414 (26.95) | |
| 9.95–17.20 | 14,230,448 | 2,770 (12.39) | 22,265,927 | 4,229 (33.39) | |
| ≥17.21 | 1,674,736 | 329 (1.47) | 7,497,593 | 1,421 (11.22) | |
| Insulin | | 3.86 (2.58–5.60) | | 3.54 (2.42–5.08) | <0.0001 |
| ALP, U/L | | 139.00 (82.00–170.00) | | 108.00 (66.00–138.00) | <0.0001 |
| Exercise | | | | | |
| No | 69,591,068 | 13,699 (67.50) | 29,782,242 | 5,730 (50.33) | <0.0001 |
| Yes | 33,677,394 | 6,595 (32.50) | 29,680,384 | 5,654 (49.67) | |
| GCCI | | | | | |
| 0 | 17,870,369 | 3,374 (15.09) | 8,983,516 | 1,680 (13.26) | <0.0001 |
| 1 | 32,350,473 | 6,162 (27.56) | 17,457,151 | 3,274 (25.85) | |
| ≥2 | 63,841,684 | 12,823 (57.35) | 39,832,844 | 7,713 (60.89) | |
| eGFR, mL/min/1.73 m$^2$ | | 86.51 (77.86–96.40) | | 92.22 (82.26–103.18) | <0.0001 |
| DM | | | | | |
| No | 94,539,597 | 18,436 (82.45) | 58,502,822 | 11,131 (87.87) | <0.0001 |
| Yes | 19,522,929 | 3,923 (17.55) | 7,770,689 | 1,536 (12.13) | |
| GGT, U/L | | 31.00 (22.00–49.00) | | 15.00 (12.00–20.00) | <0.0001 |

Values are presented as mean±standard deviation (range), number (%), or median (interquartile range).
SLD, steatotic liver disease; MASLD, metabolic dysfunction-associated steatotic liver disease; NAFLD, nonalcoholic fatty liver disease; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBS, fasting blood sugar; TC, total cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; ALP, alkaline phosphatase; GCCI, grouped count of comorbid condition; eGFR, estimated glomerular filtration rate; DM, diabetes mellitus; GGT, gamma-glutamyltransferase.
[a]Mean follow-up duration (years) from baseline to event or censoring, presented as mean±standard deviation.

**Supplementary Table 2.** Hazard ratios for MASLD, NAFLD, and NAFLD$^{\text{-cardiometabolic}}$ by adiponectin levels across different models in males

| Analysis | Adiponectin level, μg/mL | | | | |
|---|---|---|---|---|---|
| | ≥17.21 | 9.95–17.20 | 6.46–9.94 | 4.45–6.45 | ≤4.44 |
| NAFLD | | | | | |
| Model 1 | Ref. | 1.16 (0.69–1.94) | 1.28 (0.77–2.11) | 1.49 (0.91–2.46) | 1.80 (1.10–2.96) |
| Model 2 | Ref. | 1.19 (0.71–1.98) | 1.32 (0.80–2.18) | 1.54 (0.93–2.53) | 1.85 (1.13–3.03) |
| Model 3[a] | Ref. | 1.16 (0.61–2.22) | 1.29 (0.68–2.42) | 1.51 (0.80–2.83) | 1.91 (1.02–3.59) |
| MASLD | | | | | |
| Model 1 | Ref. | 1.15 (0.62–2.14) | 1.44 (0.79–2.64) | 1.73 (0.95–3.15) | 2.36 (1.30–4.28) |
| Model 2 | Ref. | 1.18 (0.64–2.20) | 1.50 (0.82–2.74) | 1.79 (0.98–3.27) | 2.43 (1.34–4.42) |
| Model 3[a] | Ref. | 1.27 (0.56–2.92) | 1.43 (0.64–3.24) | 1.64 (0.73–3.68) | 2.26 (1.01–5.07) |
| NAFLD$^{\text{-cardiometabolic}}$ | | | | | |
| Model 1 | Ref. | 1.21 (0.48–3.02) | 0.94 (0.38–2.33) | 1.01 (0.41–2.48) | 0.60 (0.24–1.48) |
| Model 2 | Ref. | 1.21 (0.48–3.03) | 0.94 (0.38–2.33) | 1.01 (0.41–2.48) | 0.60 (0.24–1.48) |
| Model 3[a] | Ref. | 1.62 (0.57–4.57) | 1.83 (0.66–5.11) | 2.84 (1.02–7.90) | 2.42 (0.85–6.86) |

Values are presented as hazard ratio (95% confidence interval). Model 1: crude model; Model 2: further adjusted for age, sex; Model 3: further adjusted for body mass index, fasting blood sugar (FBS), aspartate aminotransferase, alanine aminotransferase (ALT), alkaline phosphatase, systolic blood pressure, diastolic blood pressure, total cholesterol, triglyceride, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol (HDL-C), gamma-glutamyltransferase (GGT), insulin, exercise, and smoking status.
MASLD, metabolic dysfunction-associated steatotic liver disease; NAFLD, nonalcoholic fatty liver disease.
[a]For MASLD, NAFLD, and NAFLD$^{\text{-cardiometabolic}}$, because certain variables did not meet the Cox proportional hazards assumption (ALT for MASLD; FBS, HDL-C, ALT, and GGT for NAFLD; and GGT for NAFLD$^{\text{-cardiometabolic}}$), we introduced interaction terms involving these variables over time to account for non-proportional hazards in our analysis.

**Supplementary Table 3.** Hazard ratios for MASLD, NAFLD, and NAFLD$^{\text{-cardiometabolic}}$ by adiponectin levels across different models in females

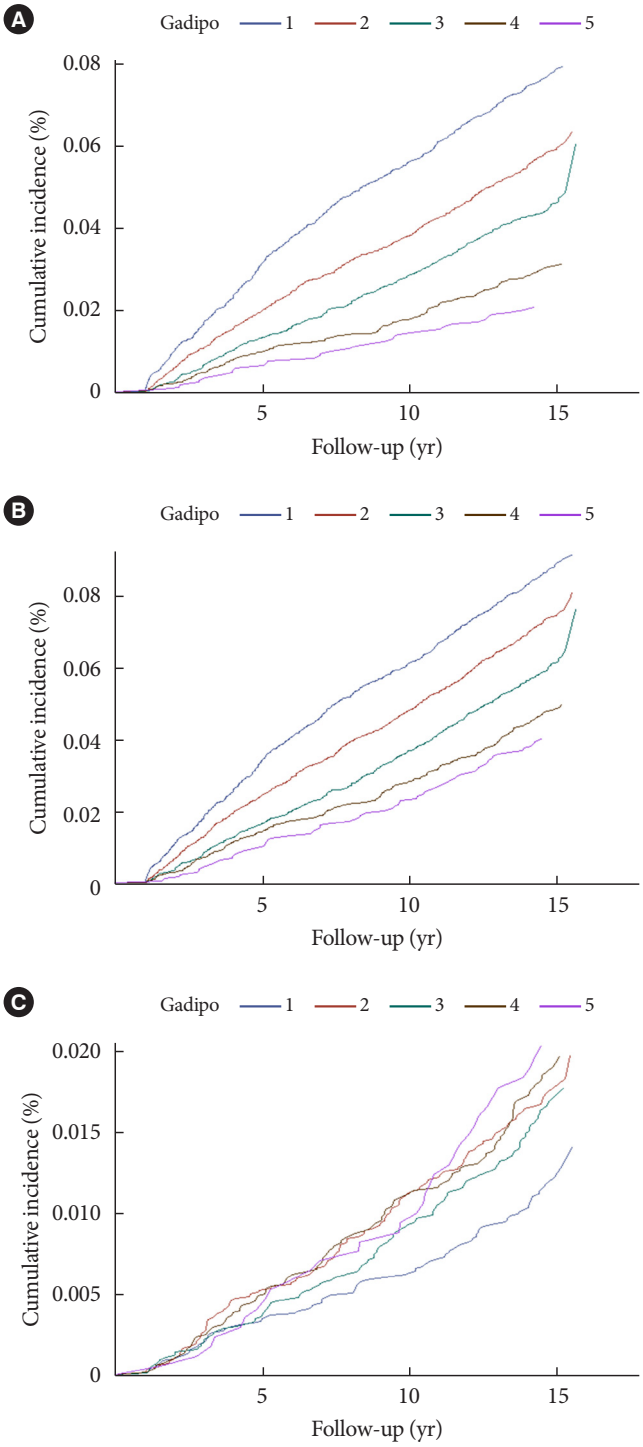
| Analysis | Adiponectin level, μg/mL | | | | |
|---|---|---|---|---|---|
| | ≥17.21 | 9.95–17.20 | 6.46–9.94 | 4.45–6.45 | ≤4.44 |
| NAFLD | | | | | |
| Model 1 | Ref. | 1.09 (0.80–1.49) | 1.48 (1.09–2.00) | 2.00 (1.47–2.73) | 2.24 (1.62–3.10) |
| Model 2 | Ref. | 1.16 (0.85–1.58) | 1.54 (1.13–2.09) | 2.01 (1.48–2.75) | 2.23 (1.61–3.08) |
| Model 3[a] | Ref. | 1.42 (0.99–2.04) | 1.75 (1.21–2.52) | 2.52 (1.74–3.66) | 2.98 (2.01–4.41) |
| MASLD | | | | | |
| Model 1 | Ref. | 1.37 (0.88–2.14) | 2.20 (1.42–3.40) | 3.26 (2.10–5.05) | 3.65 (2.32–5.74) |
| Model 2 | Ref. | 1.50 (0.96–2.35) | 2.36 (1.53–3.65) | 3.34 (2.15–5.17) | 3.69 (2.34–5.80) |
| Model 3[a] | Ref. | 1.57 (0.92–2.68) | 2.17 (1.28–3.68) | 3.13 (1.85–5.32) | 3.42 (1.97–5.93) |
| NAFLD$^{\text{-cardiometabolic}}$ | | | | | |
| Model 1 | Ref. | 0.86 (0.56–1.33) | 0.88 (0.57–1.37) | 0.97 (0.61–1.56) | 1.09 (0.65–1.81) |
| Model 2 | Ref. | 0.87 (0.57–1.34) | 0.89 (0.57–1.38) | 0.97 (0.60–1.56) | 1.08 (0.65–1.80) |
| Model 3[a] | Ref. | 1.37 (0.83–2.26) | 1.50 (0.88–2.56) | 2.14 (1.22–3.75) | 2.88 (1.56–5.33) |

Values are presented as hazard ratio (95% confidence interval). Model 1: crude model; Model 2: further adjusted for age, sex; Model 3: further adjusted for body mass index, fasting blood sugar (FBS), aspartate aminotransferase, alanine aminotransferase (ALT), alkaline phosphatase, systolic blood pressure, diastolic blood pressure, total cholesterol, triglyceride, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol (HDL-C), gamma-glutamyltransferase (GGT), insulin, exercise, and smoking status.
MASLD, metabolic dysfunction-associated steatotic liver disease; NAFLD, nonalcoholic fatty liver disease.
[a]For MASLD, NAFLD, and NAFLD$^{\text{-cardiometabolic}}$, because certain variables did not meet the Cox proportional hazards assumption (ALT for MASLD; FBS, HDL-C, ALT, and GGT for NAFLD; and GGT for NAFLD$^{\text{-cardiometabolic}}$), we introduced interaction terms involving these variables over time to account for non-proportional hazards in our analysis.

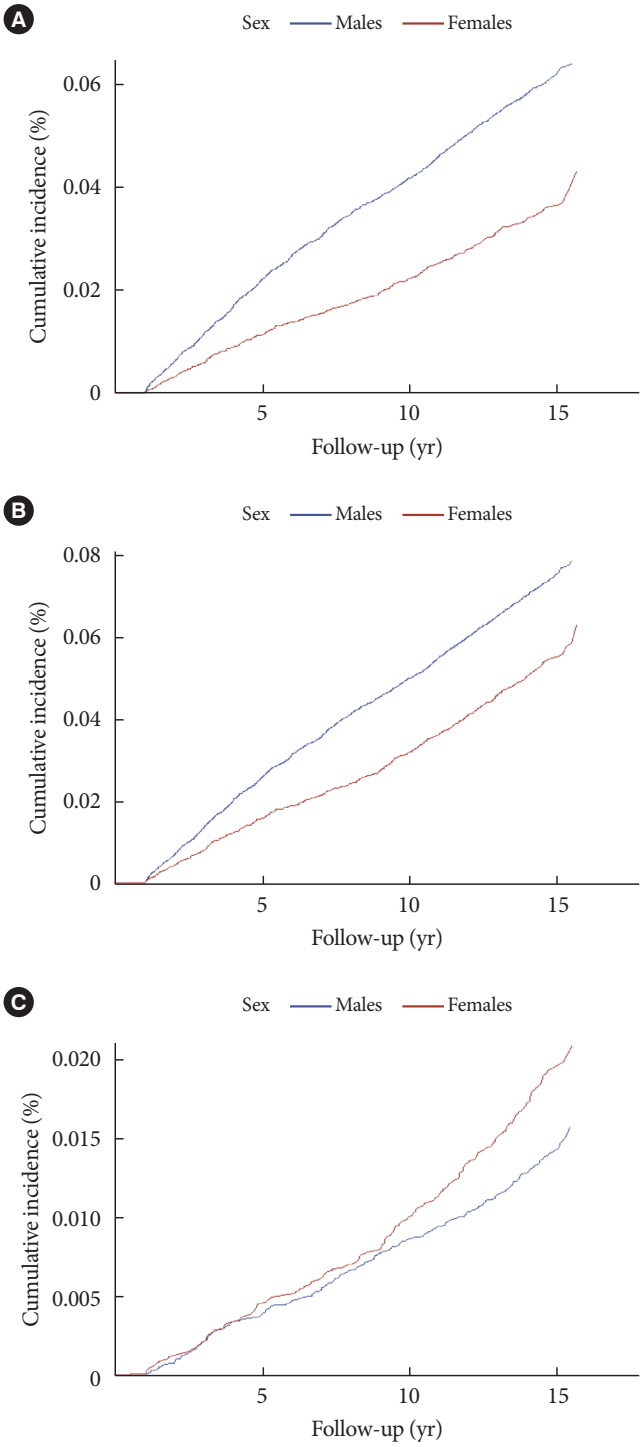
**Supplementary Table 4.** Association between adiponectin levels and NAFLD incidence, including lean obesity, across models with different variables and the fully adjusted model

| Analysis | Lean obese | Adiponectin level, μg/mL | | | | |
|---|---|---|---|---|---|---|
| | | ≥17.21 | 9.95–17.20 | 6.46–9.94 | 4.45–6.45 | ≤4.44 |
| Model 1 | 1.49 (1.00–2.23) | - | - | - | - | - |
| Model 2 | 1.53 (1.02–2.29) | Ref. | 1.16 (0.89–1.50) | 1.29 (1.00–1.66) | 1.44 (1.13–1.85) | 1.49 (1.16–1.90) |
| Model 3 | 1.59 (1.05–2.40) | Ref. | 1.29 (0.99–1.69) | 1.49 (1.14–1.93) | 1.83 (1.41–2.38) | 2.16 (1.66–2.81) |

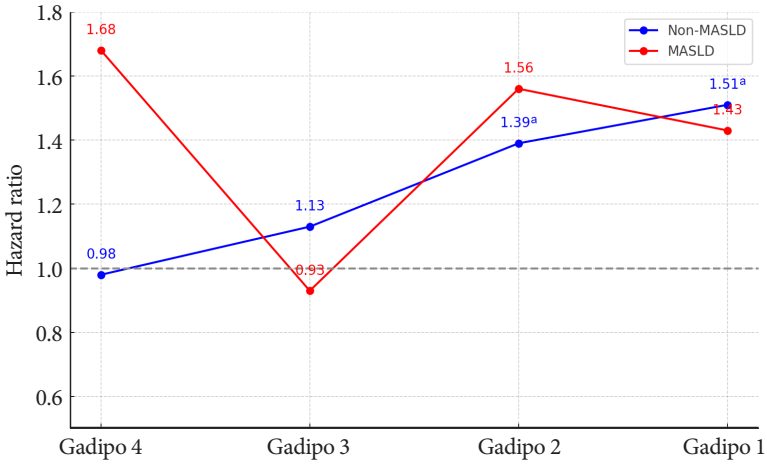
Values are presented as hazard ratio (95% confidence interval). Model 1: crude model; Model 2: further adjusted for adiponectin level; Model 3: further adjusted for age, sex, body mass index, fasting blood sugar, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase.
NAFLD, nonalcoholic fatty liver disease.




**Supplementary Fig. 1.** Cumulative incidence of metabolic dysfunction-associated steatotic liver disease (MASLD), nonalcoholic fatty liver disease (NAFLD), and NAFLD$^{\text{-cardiometabolic}}$ by adiponectin levels. (A) Cumulative incidence of MASLD over the follow-up period, stratified by adiponectin levels. (B) Cumulative incidence of NAFLD over the follow-up period, stratified by adiponectin levels. (C) Cumulative incidence of NAFLD$^{\text{-cardiometabolic}}$ over the follow-up period, stratified by adiponectin levels. Adiponectin groups are categorized as follows: Gadipo 1 (≤4.44 μg/mL), Gadipo 2 (4.45–6.45 μg/mL), Gadipo 3 (6.46–9.94 μg/mL), Gadipo 4 (9.95–17.20 μg/mL), and Gadipo 5 (≥17.21 μg/mL).




**Supplementary Fig. 2.** Cumulative incidence of metabolic dysfunction-associated steatotic liver disease (MASLD), nonalcoholic fatty liver disease (NAFLD), and NAFLD$^{\text{-cardiometabolic}}$ by sex. (A) Cumulative incidence of MASLD over the follow-up period, stratified by sex. (B) Cumulative incidence of NAFLD over the follow-up period, stratified by sex. (C) Cumulative incidence of NAFLD$^{\text{-cardiometabolic}}$ over the follow-up period, stratified by sex.




**Supplementary Fig. 3.** Cardiovascular disease risk by adiponectin group according to metabolic dysfunction-associated steatotic liver disease (MASLD) status. Hazard ratios for cardiovascular disease (CVD) across adiponectin groups, stratified by MASLD status. In the non-MASLD group (blue line), CVD risk decreased with increasing adiponectin levels. In contrast, in the MASLD group (red line), higher adiponectin groups were associated with increased CVD risk, indicating a non-linear pattern. Reference group: Gadipo 5 (≥17.18 μg/mL). Error bars represent 95% confidence intervals. [a]Statistically significant ($P<0.05$).