SUPPLEMENTAL MATERIAL

Metabolic Dysfunction-Associated Fatty Liver Disease Increases Colon Cancer Risk: A Nationwide Cohort Study

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CONTENTS

Table S1. Definitions of fatty liver disease, advanced fibrosis, and metabolic dysfunction

Table S2. Baseline characteristics by combination of NAFLD and/or MAFLD

Table S3. Colorectal cancer risk according to presence and combination of NAFLD and/or MAFLD with or without advanced fibrosis

Table S4. Colorectal cancer risk according to combination of NAFLD and/or MAFLD using different biochemical steatosis scores

Table S5. Colorectal cancer risk according to presence and combination of NAFLD and/or MAFLD when metabolic abnormality was defined as meeting ≥1 out of 5 criteria

Table S6. Association of MAFLD with colorectal cancer risk after further covariable adjustment or balancing

Figure S1. Flowchart of inclusion and exclusion criteria

Figure S2. Covariable balance between the MAFLD and non-MAFLD groups before and after propensity score weighting

Reference
### Table S1. Definitions of fatty liver disease, advanced fibrosis, and metabolic dysfunction

| Definition               | Criteria                                                                 |
|-------------------------|--------------------------------------------------------------------------|
| **Hepatic steatosis**   | Fatty liver index (FLI) ≥30 (1)                                          |
|                         | FLI = 1 / (1 + e^{-x}) × 100; where                                       |
|                         | x = 0.953 × log_{10} triglyceride + 0.139 × body mass index              |
|                         | + 0.718 × log_{10} γ-glutamyl-transferase + 0.053 × waist circumference  |
|                         | − 15.745                                                                |
| **NAFLD**               | The presence of hepatic steatosis without:                               |
|                         | 1. excessive alcohol consumption (≥210 g/week in men and ≥140 g/week      |
|                         | in women) (2); or                                                        |
|                         | 2. any of the following concomitant liver diseases*—viral hepatitis (B15-|
|                         | B19), alcoholic liver disease (K70), toxic liver disease (K71), biliary  |
|                         | cholangitis (K74.3-K74.5), autoimmune hepatitis (K75.4), Wilson’s        |
|                         | disease (E83.0), or hemochromatosis (E83.1)                              |
| **MAFLD**               | The presence of hepatic steatosis with one or more of the following (3): |
|                         | 1. overweight or obese (body mass index ≥23 kg/m\(^2\)) (4);             |
|                         | 2. diabetes mellitus; or                                                |
|                         | 3. at least 2 metabolic abnormalities†,                                   |
|                         | a. waist circumference ≥90 cm in men and ≥80 cm women;                   |
|                         | b. blood pressure ≥130/85 mmHg or specific drug treatment                |
|                         | c. triglycerides ≥150 mg/dL or specific drug treatment                   |
|                         | d. high-density lipoprotein cholesterol <40 mg/dL in men and <50          |
|                         | mg/dL in women or specific drug treatment;                              |
|                         | e. fasting glucose ≥100 mg/dL                                           |
| **Advanced fibrosis**   | BARD score ≥2                                                           |
|                         | BARD score is the sum of the following (5):                             |
|                         | body mass index ≥28 = 1 point                                            |
|                         | aspartate transaminase/alanine transaminase ratio ≥0.8 = 2 points        |
|                         | diabetes mellitus = 1 point                                              |
| **Diabetes mellitus**   | Fasting glucose ≥126 mg/dL or specific drug treatment                   |
| **Hypertension**        | Systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg  |
|                         | or specific drug treatment                                              |
| **Dyslipidemia**        | One or more of the following:                                           |
|                         | 1. total cholesterol ≥240 mg/dL;                                        |
|                         | 2. triglyceride ≥200 mg/dL;                                             |
|                         | 3. high-density lipoprotein cholesterol <40 mg/dL;                       |
|                         | 4. low-density lipoprotein cholesterol ≥160 mg/dL; or                    |
|                         | 5. specific drug treatment                                               |

*International classification of diseases, 10th revision codes in parentheses.
†Fasting insulin or C-reactive protein levels were not available in this study.
| Variable                        | Neither FLD (N=5,543,716) | NAFLD only (N=52,179) | MAFLD only (N=2,465,151) | Both FLD (N=871,971) |
|--------------------------------|---------------------------|-----------------------|--------------------------|--------------------|
| Age, years                     | 50 [44-56]                | 49 [44-54]            | 51 [46-57]               | 50 [45-56]        |
| Sex                            |                           |                       |                          |                   |
| Female                         | 3,646,902 (65.8)          | 5,451 (10.4)          | 829,114 (33.6)           | 107,180 (12.3)    |
| Male                           | 1,896,814 (34.2)          | 46,728 (89.6)         | 1,636,037 (66.4)         | 764,791 (87.7)    |
| Household income*              |                           |                       |                          |                   |
| Q4, highest                    | 1,972,485 (35.6)          | 20,470 (39.2)         | 635,360 (25.8)           | 231,996 (26.6)    |
| Q3                             | 1,342,038 (24.2)          | 13,545 (26.0)         | 452,784 (18.4)           | 166,479 (19.1)    |
| Q2                             | 1,080,525 (19.5)          | 9,667 (18.5)          | 326,204 (13.5)           | 127,228 (14.8)    |
| Q1, lowest                     | 1,148,668 (20.7)          | 8,497 (16.3)          | 231,996 (9.8)            | 85,692 (9.8)      |
| Residential area               |                           |                       |                          |                   |
| Metropolitan                   | 2,601,828 (46.9)          | 24,221 (46.4)         | 1,094,373 (44.4)         | 377,897 (43.3)    |
| Urban                          | 1,969,351 (35.5)          | 18,426 (35.3)         | 869,689 (35.3)           | 304,580 (34.9)    |
| Rural                          | 972,537 (17.5)            | 9,532 (18.3)          | 501,089 (20.3)           | 189,494 (21.7)    |
| Charlson Comorbidity Index     |                           |                       |                          |                   |
| 0                              | 3,991,109 (72.0)          | 40,860 (78.3)         | 1,762,651 (71.5)         | 631,067 (72.4)    |
| 1                              | 1,389,194 (25.1)          | 10,638 (20.4)         | 605,893 (24.6)           | 205,136 (23.5)    |
| ≥2                             | 163,413 (2.9)             | 681 (1.3)             | 96,907 (3.9)             | 35,768 (4.1)      |
| Overweight/Obese               | 2,384,773 (43.0)          | 0                     | 2,319,290 (94.1)         | 782,087 (89.7)    |
| Diabetes mellitus              | 310,075 (5.6)             | 0                     | 388,616 (15.8)           | 171,301 (19.6)    |
| Hypertension                   | 1,165,191 (21.0)          | 4,216 (8.1)           | 1,049,655 (42.6)         | 421,086 (48.3)    |
| Dyslipidemia                   | 1,416,360 (25.5)          | 24,229 (46.4)         | 1,554,768 (63.1)         | 543,610 (62.3)    |
| Viral hepatitis                | 198,503 (3.6)             | 0                     | 0                        | 134,241 (15.4)    |
| Alcoholic liver disease†       | 101,676 (1.8)             | 0                     | 0                        | 743,785 (85.3)    |
| Other liver disease‡           | 52,426 (0.9)              | 0                     | 0                        | 47,272 (5.4)      |
| Regular aspirin use            | 265,876 (4.8)             | 602 (1.2)             | 270,085 (11.0)           | 101,164 (11.6)    |
| Regular NSAID use              | 131,432 (2.4)             | 694 (1.3)             | 81,502 (3.3)             | 21,218 (2.4)      |
| Alcohol consumption            |                           |                       |                          |                   |
| None                           | 3,562,233 (64.3)          | 17,398 (33.3)         | 1,306,711 (53.0)         | 114,788 (13.2)    |
| Moderate                       | 1,589,932 (28.7)          | 34,781 (66.7)         | 1,158,440 (47.0)         | 108,485 (12.4)    |
| Excessive                      | 391,551 (7.1)             | 0                     | 0                        | 648,698 (74.4)    |
| Tobacco use                    |                           |                       |                          |                   |
| Never                          | 4,086,654 (73.7)          | 15,883 (30.4)         | 1,280,491 (51.9)         | 235,449 (27.0)    |
| Past                           | 589,183 (10.6)            | 10,564 (20.2)         | 509,841 (20.7)           | 239,191 (27.4)    |
| Current                        | 867,879 (15.7)            | 25,732 (49.3)         | 674,819 (27.4)           | 397,331 (45.6)    |
| Exercise frequency             |                           |                       |                          |                   |
| ≥3/week                        | 1,429,614 (25.8)          | 10,525 (20.2)         | 589,952 (23.9)           | 228,706 (26.2)    |
| 1-2/week                       | 1,385,642 (25.0)          | 17,323 (33.2)         | 706,830 (28.7)           | 251,839 (28.9)    |
| None                           | 2,728,460 (49.2)          | 24,331 (46.6)         | 1,168,369 (47.4)         | 391,426 (44.9)    |
| BARD score ≥2                  | NA                        | 0                     | 0                        | 648,698 (74.4)    |
| Follow-up, years               | 10.1 [9.4-10.4]           | 10.1 [9.4-10.4]       | 10.1 [9.4-10.4]          | 10.1 [9.4-10.4]   |

Values as frequency (%), median [interquartile range], or mean ± standard deviation.

*Household income categorized based on quartiles among the entire Korean population.
†Diagnosed as alcoholic liver disease or fatty liver with excessive alcohol consumption.
‡Other liver disease including toxic liver disease, autoimmune hepatitis, biliary cholangitis, Wilson’s disease, or hemochromatosis.

FLD, fatty liver disease; MAFLD, metabolic dysfunction-associated fatty liver disease; NAFLD, nonalcoholic fatty liver disease; NSAID, nonsteroidal anti-inflammatory drug.
Table S3. Colorectal cancer risk according to presence and combination of NAFLD and/or MAFLD with or without advanced fibrosis

| Presence of FLD and fibrosis | Events | Person-yrs | Rate* | Hazard ratio (95% confidence interval) |
|-----------------------------|--------|------------|-------|-------------------------------------|
|                             |        |            |       | Model 1 | Model 2 | Model 3 | Model 4 |
| **NAFLD**                   |        |            |       |         |         |         |         |
| No steatosis                | 39,780 | 62,898,545 | 63.2  | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| Simple steatosis            | 5,937  | 7,888,983  | 75.3  | 1.19 (1.16-1.22) | 1.05 (1.02-1.08) | 1.06 (1.03-1.09) | 1.02 (0.99-1.05) |
| Advanced fibrosis           | 15,171 | 16,736,003 | 90.6  | 1.43 (1.41-1.46) | 1.11 (1.09-1.13) | 1.12 (1.10-1.14) | 1.08 (1.06-1.10) |
| **MAFLD**                   |        |            |       |         |         |         |         |
| No steatosis                | 31,603 | 54,940,578 | 57.5  | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| Simple steatosis            | 7,726  | 10,057,684 | 76.8  | 1.34 (1.30-1.37) | 1.14 (1.11-1.17) | 1.15 (1.12-1.18) | 1.15 (1.12-1.18) |
| Advanced fibrosis           | 21,559 | 22,525,270 | 95.7  | 1.66 (1.64-1.69) | 1.23 (1.21-1.25) | 1.23 (1.21-1.25) | 1.20 (1.18-1.23) |
| **Combination**             |        |            |       |         |         |         |         |
| Neither FLD                 | 31,177 | 54,433,056 | 57.3  | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| NAFLD only, without fibrosis| 99     | 150,153    | 65.9  | 1.15 (0.94-1.40) | 1.06 (0.87-1.30) | 1.05 (0.86-1.27) | - |
| Both FLD, without fibrosis  | 5,838  | 7,738,830  | 75.4  | 1.32 (1.28-1.35) | 1.13 (1.10-1.16) | 1.14 (1.11-1.17) | - |
| MAFLD only, without fibrosis| 1,888  | 2,318,853  | 81.4  | 1.42 (1.36-1.49) | 1.23 (1.17-1.29) | 1.22 (1.16-1.28) | - |
| NAFLD only, with advanced fibrosis | 327 | 357,369 | 91.5 | 1.60 (1.43-1.78) | 1.25 (1.12-1.39) | 1.20 (1.08-1.34) | - |
| Both FLD, with advanced fibrosis | 14,844 | 16,378,634 | 90.6 | 1.58 (1.55-1.61) | 1.19 (1.16-1.21) | 1.19 (1.17-1.22) | - |
| MAFLD only, with advanced fibrosis | 6,715 | 6,146,636 | 109.2 | 1.91 (1.86-1.96) | 1.37 (1.34-1.41) | 1.35 (1.31-1.39) | - |

*Rate per 100,000 person-years.

Model 1 was unadjusted.
Model 2 was adjusted for age and sex.
Model 3 was further adjusted for household income quartile, residential area, Charlson Comorbidity Index, aspirin use, nonsteroidal anti-inflammatory drug use, tobacco smoking, and exercise frequency.
For the NAFLD analyses, Model 4 was adjusted for overweight/obesity, diabetes, hypertension, and dyslipidemia in addition to Model 3.
For the MAFLD analyses, Model 4 was adjusted for alcohol intake and concomitant liver diseases in addition to Model 3.

FLD, fatty liver disease; MAFLD, metabolic dysfunction-associated fatty liver disease; NAFLD, nonalcoholic fatty liver disease.
| Steatosis model and Presence of FLD | Events | Person-yrs | Rate*  | HR (95% CI)   |
|-----------------------------------|--------|------------|--------|--------------|
| **FLI ≥30**                       |        |            |        |              |
| Neither FLD                       | 31,177 | 54,433,056 | 57.3   | 1.00 (reference) |
| NAFLD only                        | 426    | 507,522    | 83.9   | 1.16 (1.06-1.28) |
| Both FLD                          | 20,682 | 24,117,464 | 85.8   | 1.18 (1.16-1.20) |
| MAFLD only                        | 8,603  | 8,465,489  | 101.6  | 1.32 (1.28-1.35) |
| **HSI ≥36**                       |        |            |        |              |
| Neither FLD                       | 45,022 | 66,892,456 | 67.3   | 1.00 (reference) |
| NAFLD only                        | 130    | 290,643    | 44.7   | 0.91 (0.77-1.08) |
| Both FLD                          | 12,416 | 16,479,942 | 75.3   | 1.11 (1.09-1.14) |
| MAFLD only                        | 3,320  | 3,860,491  | 86.0   | 1.18 (1.14-1.22) |
| **SNS ≥8**                        |        |            |        |              |
| Neither FLD                       | 33,181 | 55,474,519 | 59.8   | 1.00 (reference) |
| NAFLD only                        | 2      | 2,031      | 98.5   | 1.10 (0.28-4.41) |
| Both FLD                          | 20,721 | 25,069,560 | 82.7   | 1.14 (1.12-1.16) |
| MAFLD only                        | 6,984  | 6,977,421  | 100.1  | 1.26 (1.22-1.29) |

*Rate per 100,000 person-years.

All models were adjusted for age, sex, household income quartile, residential area, Charlson Comorbidity Index, aspirin use, nonsteroidal anti-inflammatory drug use, tobacco smoking, and exercise frequency.

CI, confidence interval; FLD, fatty liver disease; FLI, fatty liver index; HR, hazard ratio; HSI, hepatic steatosis index; MAFLD, metabolic dysfunction-associated fatty liver disease; NAFLD, nonalcoholic fatty liver disease; SNS, simple nonalcoholic fatty liver disease score.
Table S5. Colorectal cancer risk according to presence and combination of NAFLD and/or MAFLD when metabolic abnormality was defined as meeting ≥1 out of 5 criteria

| Presence of FLD | Events | Person-yrs | Rate* | HR (95% CI) |
|-----------------|--------|------------|-------|-------------|
| **MAFLD**       |        |            |       |             |
| No              | 30,978 | 54,266,801 | 57.1  | 1.00 (reference) |
| Yes             | 29,910 | 33,256,731 | 89.9  | 1.21 (1.19-1.24) |
| **Combination** |        |            |       |             |
| Neither FLD     | 30,903 | 54,176,255 | 57.0  | 1.00 (reference) |
| NAFLD only      | 75     | 90,545     | 82.8  | 1.18 (0.94-1.48) |
| Both FLD        | 21,033 | 24,534,442 | 85.7  | 1.18 (1.16-1.20) |
| MAFLD only      | 8,877  | 8,722,289  | 101.8 | 1.32 (1.29-1.36) |

*Rate per 100,000 person-years.

All models were adjusted for age, sex, household income quartile, residential area, Charlson Comorbidity Index, aspirin use, nonsteroidal anti-inflammatory drug use, tobacco smoking, and exercise frequency.

CI, confidence interval; FLD, fatty liver disease; HR, hazard ratio; MAFLD, metabolic dysfunction-associated fatty liver disease; NAFLD, nonalcoholic fatty liver disease.
Table S6. Association of MAFLD with colorectal cancer risk after further covariable adjustment or balancing

| Model                                                                 | HR (95% CI)      |
|----------------------------------------------------------------------|------------------|
| Multivariable base model                                             | 1.21 (1.19-1.23) |
| Multivariable + alcohol consumption + past liver disease            | 1.19 (1.17-1.21) |
| Multivariable + overweight + diabetes + hypertension + dyslipidemia | 1.18 (1.16-1.21) |
| Multivariable + all above risk factors                               | 1.16 (1.13-1.18) |
| Propensity score weighting                                           | 1.14 (1.12-1.17) |

Multivariable base model was adjusted age, sex, household income quartile, residential area, Charlson Comorbidity Index, aspirin use, nonsteroidal anti-inflammatory drug use, tobacco smoking, and exercise frequency. Subsequent 3 models were further adjusted for the designated risk factors. For the last model, propensity score overlap weighting was used to balance covariables (all variables in Figure S2) between the MAFLD and non-MAFLD groups.

CI, confidence interval; HR, hazard ratio; MAFLD, metabolic dysfunction-associated fatty liver disease.
Figure S1. Flowchart of inclusion and exclusion criteria.

*The Medical Aid program covers approximately 3% of Korean population with financial needs or under special provisions (e.g., meritorious persons, refugees, etc.). Medical Aid beneficiaries were excluded from this study, because some sociodemographic variables (e.g. income) or claims information were incomplete for these individuals.

CRC, colorectal cancer; IBD, inflammatory bowel disease.
Figure S2. Covariable balance between the MAFLD and non-MAFLD groups before and after propensity score weighting.

For categorical variables with ≥3 levels, the largest absolute standardized difference was plotted. MAFLD, metabolic dysfunction-associated fatty liver disease; NSAID, nonsteroidal anti-inflammatory drug.
Reference

1. Bedogni G, Bellentani S, Miglioli L, et al. The Fatty Liver Index: a simple and accurate predictor of hepatic steatosis in the general population. BMC Gastroenterol 2006;6:33.

2. European Association for the Study of the Liver, European Association for the Study of Diabetes, European Association for the Study of Obesity. EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol 2016;64:1388-402.

3. Eslam M, Newsome PN, Sarin SK, et al. A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. J Hepatol 2020;73:202-9.

4. World Health Organization. The Asia-Pacific Perspective: Redefining Obesity and Its Treatment. 2000.

5. Harrison SA, Oliver D, Arnold HL, et al. Development and validation of a simple NAFLD clinical scoring system for identifying patients without advanced disease. Gut 2008;57:1441-7.