|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Supplementary Table 1. Hazard ratios\* (95% CI) for the development of NAFLD by smoking pack-years after additional adjustment for potential mediating variables | | | | | | |
| Potential mediating  Variableb | **smoking pack-years** | | | | | *P for trend* |
| Men | **0** | <10 | 10-19.9 | ≥20 |
| Women | **0** | <5 | 5-9.9 | ≥10 |
| Men |  |  |  |  |  |  |
| Model 1 |  | 1.00 | 1.10 (1.07-1.14) | 1.25 (1.21-1.29) | 1.36 (1.30-1.42) | <0.001 |
| HOMA-IR |  | 1.00 | 1.11 (1.08-1.14) | 1.25 (1.21-1.29) | 1.36 (1.30-1.42) | <0.001 |
| LDL-C |  | 1.00 | 1.10 (1.07-1.14) | 1.24 (1.20-1.28) | 1.34 (1.28-1.40) | <0.001 |
| HDL-C |  | 1.00 | 1.09 (1.06-1.12) | 1.21 (1.17-1.25) | 1.31 (1.25-1.37) | <0.001 |
| Triglycerides |  | 1.00 | 1.07 (1.04-1.10) | 1.19 (1.15-1.23) | 1.28 (1.22-1.34) | <0.001 |
| hsCRP |  | 1.00 | 1.10 (1.07-1.14) | 1.25 (1.21-1.29) | 1.36 (1.30-1.42) | <0.001 |
| Women |  |  |  |  |  |  |
| Model 1 |  | 1.00 | 1.01 (0.91-1.12) | 1.25 (1.04-1.50) | 1.46 (1.17-1.81) | <0.001 |
| HOMA-IR |  | 1.00 | 1.01 (0.91-1.12) | 1.25 (1.04-1.50) | 1.46 (1.17-1.81) | <0.001 |
| LDL-C |  | 1.00 | 1.01 (0.91-1.13) | 1.23 (1.03-1.48) | 1.46 (1.18-1.82) | <0.001 |
| HDL-C |  | 1.00 | 1.02 (0.91-1.13) | 1.22 (1.02-1.47) | 1.38 (1.11-1.71) | 0.001 |
| Triglycerides |  | 1.00 | 1.00 (0.90-1.12) | 1.19 (1.00-1.43) | 1.35 (1.08-1.67) | 0.005 |
| hsCRP |  | 1.00 | 1.01 (0.91-1.12) | 1.25 (1.04-1.50) | 1.46 (1.17-1.81) | <0.001 |

aEstimated from parametric proportional hazard models. Multivariable model 1was adjusted for age, center, year of screening exam, BMI, alcohol intake, regular exercise, educational level, history of diabetes, and history of hypertension; model 2: model 1 plus adjustment for HOMA-IR, LDL-C, HDL-C, triglycerides, and hsCRP.

bA single potential mediating variable was included in the multivariable-adjusted model.

Supplementary Table 2**. Development of NAFLD by urinary cotinine levels among 44,036 never-smokers between 2011 and 2016.**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Cotinine (ng/mL) | Person-years | Incident  cases | Incidence density  (per 100 person-years) | Age adjusted HR  (95% CI) | Multivariable-adjusted HRa (95% CI) | | HR (95% CI)b  in the model using time-dependent variables |
| Model 1 | Model 2 |
| Men (n=10,966) |  |  |  |  |  |  |  |
| <50 | 32,416.6 | 2,511 | 7.7 | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| 50-99 | 64.0 | 5 | 7.8 | 1.10 (0.46-2.63) | 1.07 (0.45-2.58) | 0.96 (0.40-2.31) | 0.83 (0.42-1.67) |
| 100-499 | 159.3 | 15 | 9.4 | 1.25 (0.75-2.08) | 0.96 (0.58-1.60) | 1.00 (0.60-1.67) | 0.87 (0.59-1.29) |
| ≥.87 | 527.1 | 43 | 8.2 | 1.01 (0.75-1.37) | 0.79 (0.58-1.07) | 0.72 (0.53-0.97) | 0.98 (0.78-1.23) |
| *P for trend* |  |  |  | 0.713 | 0.148 | 0.045 | 0.646 |
| Women (n=33,250) |  |  |  |  |  |  |  |
| <50 | 102,653.9 | 2,143 | 2.1 | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| 50-99 | 273.3 | 7 | 2.6 | 1.16 (0.55-2.44) | 0.94 (0.45-1.99) | 0.84 (0.40-1.78) | 1.10 (0.61-2.00) |
| 100-499 | 574.8 | 24 | 4.2 | 2.04 (1.36-3.04) | 2.03 (1.35-3.03) | 2.04 (1.36-3.06) | 2.00 (1.46-2.73) |
| ≥.00 | 572.4 | 13 | 2.3 | 1.09 (0.63-1.87) | 1.28 (0.74-2.21) | 1.24 (0.72-2.14) | 1.00 (0.68-1.47) |
| *P for trend* |  |  |  | 0.027 | 0.009 | 0.014 | 0.026 |

The P-value for the interaction of sex and cotinine levels in the risk of NAFLD was 0.04

aEstimated from parametric proportional hazard models. Multivariable model 1was adjusted for age, center, year of screening exam, BMI, alcohol intake, regular exercise, educational level, history of diabetes, and history of hypertension; model 2: model 1 plus adjustment for HOMA-IR, LDL-C, HDL-C, triglycerides, and hsCRP.

bEstimated from parametric proportional hazard models with cotinine levels as a time-dependent categorical variable adjusted for age, sex, center, year of screening exam, education level, history of diabetes, history of hypertension, and other covariates (alcohol intake, regular exercise, BMI)as time-dependent variables.

Abbreviations: CI, confidence intervals; HR, hazards ratio.

Supplementary **Table 3. Hazard ratiosa (95% CI) of incident NAFLD according to smoking status in clinically relevant subgroups among men**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Subgroup** | Smoking status | | | ***P* for trend** | ***P* for interaction** |
| Never smoker | Ex-smoker | Current smoker |
| **Age** |  |  |  |  | <0.001 |
| <40 years (N=65,733) | reference | 0.97 (0.94-1.01) | 1.20 (1.16-1.23) | <0.001 |  |
| ≥40 years (N=21,944) | reference | 1.07 (1.01-1.14) | 1.36 (1.29-1.45) | <0.001 |  |
| **Alcohol intake** |  |  |  |  | 0.453 |
| <10 g/day (N=47,648) | reference | 0.98 (0.94-1.02) | 1.23 (1.19-1.28) | <0.001 |  |
| ≥10 g/day (N=38,360) | reference | 1.02 (0.97-1.07) | 1.23 (1.18-1.29) | <0.001 |  |
| **Vigorous exercise** |  |  |  |  | 0.101 |
| <3 times (N=73,642) | reference | 0.98 (0.95-1.02) | 1.22 (1.18-1.25) | <0.001 |  |
| ≥3 times (N=13,402) | reference | 1.05 (0.98-1.13) | 1.31 (1.22-1.41) | <0.001 |  |
| **BMI** |  |  |  |  | 0.016 |
| <25 kg/m2 (N=68,333) | reference | 1.03 (0.99-1.07) | 1.25 (1.21-1.29) | <0.001 |  |
| ≥25 kg/m2 (N=19,339) | reference | 0.96 (0.92-1.02) | 1.16 (1.10-1.21) | <0.001 |  |
| **Abdominal obesity** |  |  |  |  | 0.007 |
| No (N=52,011) | reference | 1.04 (1.00-1.08) | 1.24 (1.19-1.28) | <0.001 |  |
| Yes (N=5,719) | reference | 1.02 (0.92-1.12) | 1.08 (0.99-1.17) | 0.037 |  |
| **Weight change tertiles** |  |  |  |  | 0.003 |
| Q1 (<-0.2 Kg) (N=29,568) | reference | 1.04 (0.99-1.11) | 1.28 (1.22-1.35) | <0.001 |  |
| Q2 (-0.2-1.9 Kg) (N=29,572) | reference | 1.04 (0.99-1.10) | 1.22 (1.17-1.28) | <0.001 |  |
| Q3 (>1.9 Kg) (N=28,447) | reference | 0.97 (0.92-1.01) | 1.11 (1.07-1.16) | <0.001 |  |
| **HOMA-IR** |  |  |  |  | <0.001 |
| <2.5 (N=49,856) | reference | 1.00 (0.96-1.03) | 1.25 (1.21-1.29) | <0.001 |  |
| ≥2.5 (N=7,821) | reference | 0.99 (0.91-1.07) | 1.08 (1.01-1.16) | 0.003 |  |
| **hsCRP** |  |  |  |  | 0.407 |
| <1.0 mg/L (N=68,910) | reference | 0.99 (0.96-1.03) | 1.21 (1.18-1.25) | <0.001 |  |
| ≥1.0 mg/L (N=18,767) | reference | 1.01 (0.95-1.07) | 1.26 (1.20-1.33) | <0.001 |  |

Abbreviations: CI, confidence intervals; HOMA-IR, homeostasis model assessment of insulin resistance; BMI, body mass index; hsCRP, high sensitivity C-reactive protein.

aEstimated from parametric proportional hazard models adjusted for age, center, year of screening exam, BMI, alcohol intake, regular exercise, education level, history of diabetes and history of hypertension.

Weight changes were calculated for each subject as the differences in weight from visit 2 to baseline (visit 1) and were categorized into tertiles based on distribution: <−0.3 (weight loss group), −0.3–1.5 (weight stable group), and ≥1.5 kg (weight gain group).

Supplementary **Table 4. Hazard ratiosa (95% CI) of incident NAFLD according to smoking status in clinically relevant subgroups among women**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Subgroup** | Smoking status | | | ***P* for trend** | ***P* for interaction** |
| Never smoker | Ex-smoker | Current smoker |
| **Age** |  |  |  |  | 0.054 |
| <40 years (N=86,652) | reference | 0.97 (0.87-1.08) | 1.07 (0.94-1.23) | 0.738 |  |
| ≥40 years (N=25,139) | reference | 0.86 (0.70-1.06) | 1.37 (1.15-1.64) | 0.019 |  |
| **Alcohol intake** |  |  |  |  | 0.517 |
| <20 g/day (N=96,524) | reference | 0.91 (0.82-1.01) | 1.14 (1.00-1.29) | 0.466 |  |
| ≥20 g/day (N=7,556) | reference | 1.01 (0.77-1.34) | 1.30 (1.02-1.65) | 0.033 |  |
| **Vigorous exercise** |  |  |  |  | 0.391 |
| <3 times (N=97,355) | reference | 0.93 (0.84-1.03) | 1.14 (1.01-1.29) | 0.297 |  |
| ≥3 times (N=13,473) | reference | 1.02 (0.80-1.31) | 1.34 (1.07-1.68) | 0.045 |  |
| **BMI** |  |  |  |  | 0.258 |
| <25 kg/m2 (N=102,967) | reference | 0.96 (0.86-1.08) | 1.19 (1.05-1.34) | 0.013 |  |
| ≥25 kg/m2 (N=8,816) | reference | 1.03 (0.86-1.24) | 0.97 (0.77-1.23) | 0.510 |  |
| **Abdominal obesity** |  |  |  |  | 0.050 |
| No (N=68,170) | reference | 0.84 (0.71-0.98) | 1.05 (0.90-1.22) | 0.942 |  |
| Yes (N=11,692) | reference | 1.05 (0.88-1.26) | 1.29 (1.06-1.56) | 0.043 |  |
| **Weight change tertiles** |  |  |  |  | 0.307 |
| Q1 (<-0.3Kg) (N=38,731) | reference | 0.98 (0.82-1.18) | 1.26 (1.02-1.55) | 0.120 |  |
| Q2 (-0.3-1.5 Kg) (N=36,825) | reference | 0.96 (0.79-1.18) | 0.94 (0.75-1.19) | 0.620 |  |
| Q3 (>1.5 Kg) (N=35,549) | reference | 0.87 (0.76-1.00) | 1.16 (1.00-1.34) | 0.425 |  |
| **HOMA-IR** |  |  |  |  | 0.015 |
| <2.5 (N=101,652) | reference | 1.01 (0.91-1.12) | 1.21 (1.08-1.37) | 0.008 |  |
| ≥2.5 (N=10,139) | reference | 0.73 (0.59-0.91) | 1.00 (0.78-1.28) | 0.512 |  |
| **hsCRP** |  |  |  |  | 0.607 |
| <1.0 mg/L (N=94,618) | reference | 0.97 (0.87-1.09) | 1.18 (1.04-1.33) | 0.048 |  |
| ≥1.0 mg/L (N=17,173) | reference | 0.87 (0.73-1.05) | 1.19 (0.95-1.49) | 0.451 |  |

Abbreviations: CI, confidence intervals; HOMA-IR, homeostasis model assessment of insulin resistance; BMI, body mass index; hsCRP, high sensitivity C-reactive protein.

aEstimated from parametric proportional hazard models adjusted for age, center, year of screening exam, BMI, alcohol intake, regular exercise, education level, history of diabetes and history of hypertension.

Weight changes were calculated for each subject as the differences in weight from visit 2 to baseline (visit 1) and were categorized into tertiles based on its distribution: <−0.3 (weight loss group), −0.3–1.5 (weight stable group), and ≥1.5 kg (weight gain group).

Supplementary **Table 5. Prevalence ratios (PR) of NAFLD by self-reported smoking status and smoking pack-years among 264,481 participants at baseline.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Person | prevalent  cases | Prevalence rate ( % ) | Age adjusted PR  (95% CI) | Multivariable-adjusted PRa (95% CI) | |
| Model 1 | Model 2 |
| **Men (n=**140,527 **)** |  |  |  |  |  |  |
| Smoking status |  |  |  |  |  |  |
| Never smoker | 50,102 | 17,564 | 35.1 | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| Ex-smoker | 36,965 | 14,638 | 39.6 | 1.08 (1.07-1.10) | 1.08 (1.06-1.10) | 1.05 (1.03-1.07) |
| Current smoker | 53,460 | 20,648 | 38.6 | 1.09 (1.07-1.11) | 1.06 (1.04-1.08) | 0.98 (0.96-0.99) |
| Pack-years |  |  |  |  |  |  |
| 0 | 50,175 | 17,583 | 35.0 | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| <10 | 34,955 | 12,649 | 36.2 | 1.05 (1.03-1.07) | 1.05 (1.03-1.06) | 1.01 (0.99-1.03) |
| 10-19.9 | 23,418 | 9,476 | 40.5 | 1.13 (1.11-1.16) | 1.09 (1.07-1.11) | 0.99 (0.98-1.01) |
| ≥.9 | 12,414 | 5,681 | 45.8 | 1.18 (1.15-1.21) | 1.09 (1.06-1.11) | 0.98 (0.95-1.00) |
| *P for trend* |  |  |  | <0.001 | <0.001 | 0.089 |
| **Women ( n=**123,954 **)** |  |  |  |  |  |  |
| Smoking status |  |  |  |  |  |  |
| Never smoker | 117,146 | 11,478 | 9.8 | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| Ex-smoker | 4,042 | 399 | 9.9 | 1.14 (1.04-1.25) | 1.06 (0.96-1.18) | 1.04 (0.94-1.16) |
| Current smoker | 2,766 | 286 | 10.3 | 1.07 (0.96-1.20) | 1.07 (0.96-1.18) | 0.95 (0.85-1.05) |
| Pack-years |  |  |  |  |  |  |
| 0 | 117,161 | 11,479 | 9.8 | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| <5 | 3,751 | 346 | 9.2 | 1.17 (1.06-1.30) | 1.14 (1.04-1.26) | 1.10 (1.00-1.22) |
| 5-9.9 | 947 | 102 | 10.8 | 1.04 (0.87-1.25) | 0.98 (0.78-1.22) | 0.89 (0.74-1.07) |
| ≥.8 | 442 | 71 | 16.1 | 1.05 (0.85-1.29) | 0.91 (0.75-1.11) | 0.74 (0.59-0.93) |
| *P for trend* |  |  |  | 0.040 | 0.671 | 0.090 |

The P*-*value for the interaction of sex and smoking status on the risk of NAFLD was 0.638. The P-value for the interaction of sex and pack-years on the risk of NAFLD was 0.852.

a Estimated from Poisson regression with robust error. Multivariable model 1was adjusted for age, center, year of screening exam, BMI, alcohol intake, regular exercise, educational level, history of diabetes, and history of hypertension; model 2: model 1 plus adjustment for HOMA-IR, LDL-C, HDL-C, triglycerides, and hsCRP.