

**Supplementary Figure 1** Distribution of body weight change at the 2-year landmark time-point from baseline

**Supplementary Table 1** Questionnaire for health check-up

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Q1. Which medical conditions do you have currently? What treatments are you receiving? Please choose all relevant options from the following list. | | | | |
| Q2. Which medical conditions have you had in the past? What treatments did you receive? Please choose all that apply from the following list. | | | | |
|  | | | | |
| Disease | | | | |
| Cerebrovascular, Nervous system | Cerebral infarction |  | Digestive | Esophageal cancer |
| Subarachnoid hemorrhage |  | Esophageal varices |
| Intracerebral hemorrhage |  | Reflux esophagitis |
| Transient cerebral ischemic attack |  | Esophageal polyp |
| Parkinson’s disease |  | Gastric cancer |
| Psychiatry | Depression |  | Gastric polyp |
| Ophthalmic | Glaucoma |  | Gastric ulcer |
| Cataract |  | Duodenal ulcer |
| Diabetic retinopathy |  | Helicobacter pylori infection |
| Respiratory | Lung cancer |  | Colon cancer |
| Pneumonia |  | Colon polyp |
| Tuberculosis |  | Appendicitis |
| Bronchial asthma |  | Bowel obstruction |
| COPD |  | Ulcerative colitis |
| Interstitial pneumonia |  | Crohn’s disease |
| Pneumothorax |  | Ischemic Colitis |
| Sleep apnea syndrome |  | Hemorrhoids |
| Nontuberculous mycobacterial infection |  | Liver cancer |
| Endocrine | Hyperlipidemia |  | Hepatitis B |
| Diabetes mellitus  hyperglycemia |  | Hepatitis C |
| Gout  hyperuricemia |  | Alcoholic liver disease |
| Hypothyroidism |  | Liver cirrhosis |
| Hyperthyroidism |  | Fatty liver |
| Circulatory | Hypertension |  | Gallstone disease |
| Angina pectoris |  | Gallbladder polyp |
| Myocardial infarction |  | Chronic pancreatitis |
| Arrhythmia |  | Men | Prostatic cancer |
| Valvular disease |  | Prostatic Hypertrophy |
| Atrial septal defect |  | Women | Cervical cancer |
| Ventricular septal defect |  | Endometrial cancer |
| Aortic aneurysm |  | Uterine myoma |
| Blood | Anemia |  | Endometriosis interna |
| Other blood disease |  | Endometriosis externa |
| ENT | Deafness |  | Malignant ovarian tumor |
| Orthopedic | Fracture |  | Benign ovarian tumor |
| Osteoporosis |  | Breast cancer |
| Renal, Urinary | Nephritis/Nephrosis |  | mastopathy |
| Chronic renal failure |  |  |  |
| Kidney stone |  |  |  |
| Urinary tract stone |  |  |  |
|  | | | | |
| Treatment | | | | |
| Treatment with medication | | | | |
| Consultation without medication | | | | |
| Treatment concluded | | | | |
| Treatment with surgery | | | | |
| Treatment with endoscopic resection | | | | |
| Treatment laparoscopy | | | | |
| Treatment suspended or unattended | | | | |
| Treatment with dialysis | | | | |
|  | | | | |
| Q3. What was your weight at age of 20 years? | | | | |
| Q4. How often do you have a drink containing alcohol?   1. Drink habitually (☐ days per week) (2) Sometimes (3) Never | | | | |
| Q5. If you drink habitually, approximately how much do you drink per day? Please fill in the blank.  ☐ bottles (633 ml of beer per bottle) ☐ cans (350 ml of beer) ☐ cans (500 ml of beer)  ☐ gous of sake (180ml of sake) ☐ glasses (120 ml of wine) ☐ glasses (30 ml of whiskey) | | | | |
| Q6. What is your smoking status?   1. Current smoker (2) Former smoker (3) Never smoked | | | | |

**Supplementary Table 2** Baseline and year 2 characteristics of non-obese participants who did and did not develop NAFLD

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Did not develop NAFLD  (N=16,504) | | |  | Did develop NAFLD  (N=1326) | | |
|  | Baseline | Year 2 | P value‡ |  | Baseline | Year 2 | P value‡ |
| Men |  |  |  |  |  |  |  |
| Waist (cm)\* | 78.0 (5.8) | 78.2 (5.9) | < 0.001 |  | 80.4 (4.9) | 81.4 (5) | < 0.001 |
| AST (U/L)† | 20 (17–23) | 19 (17–23) | < 0.001 |  | 20 (18–23) | 19 (17–23) | < 0.001 |
| ALT (U/L)† | 19 (15–24) | 18 (15–23) | < 0.001 |  | 20 (16–27) | 21 (16–27) | 0.28 |
| APRI† | 0.23 (0.19–0.28) | 0.23 (0.19–0.28) | < 0.001 |  | 0.22 (0.18–0.28) | 0.23 (0.18–0.29) | 0.03 |
| FIB-4† | 0.92 (0.71–1.20) | 0.98 (0.75–1.29) | < 0.001 |  | 0.89 (0.69–1.16) | 0.93 (0.74–1.21) | < 0.001 |
| Women |  |  |  |  |  |  |  |
| Waist (cm)\* | 72.7 (6.1) | 72.7 (6.3) | < 0.001 |  | 78.4 (5.7) | 79.3 (5.9) | < 0.001 |
| AST (U/L)† | 18 (16–21) | 18 (16–21) | < 0.001 |  | 19 (16–22) | 18 (16–21) | < 0.001 |
| ALT (U/L)† | 15 (12–18) | 14 (12–18) | < 0.001 |  | 16 (13–20) | 16 (13–20) | 0.78 |
| APRI† | 0.20 (0.17–0.25) | 0.20 (0.16–0.25) | 0.78 |  | 0.19 (0.16–0.24) | 0.19 (0.16–0.24) | 0.14 |
| FIB-4† | 0.92 (0.72–1.21) | 0.97 (0.76–1.29) | < 0.001 |  | 0.91 (0.74–1.15) | 0.97 (0.74–1.29) | < 0.001 |

Data are presented as the \*mean (standard deviation) or †median (interquartile range).

‡Statistical differences between the parameters at baseline and year 2 were analyzed using Wilcoxon signed-rank tests.

**Supplementary Table 3** Association between the risk factors of NAFLD and the development of NAFLD in non-obese participants using landmark analysis (Model 1)

|  |  |  |
| --- | --- | --- |
|  | Men | Women |
|  | HR (95% CI) | HR (95% CI) |
| Weight change at 2-year landmark point |  |  |
| Gain of 3-kg unit | 1.60 (1.46–1.76) | 1.66 (1.51–1.83) |
| Weight change from age 20 to baseline |  |  |
| < −2.5 kg | 0.68 (0.46–1.02) | 0.63 (0.45–0.89) |
| −2.5 to 2.4 kg | 1.00 (Ref) | 1.00 (Ref) |
| 2.5 to 9.9 kg | 1.37 (1.12–1.68) | 2.06 (1.69–2.51) |
| 10 kg | 1.97 (1.53–2.55) | 2.68 (2.00–3.59) |
| Age |  |  |
| 30–39 years | 1.00 (Ref) | 1.00 (Ref) |
| 40–49 years | 0.99 (0.82–1.20) | 1.53 (1.21–1.93) |
| 50–59 years | 1.04 (0.83–1.30) | 1.94 (1.51–2.51) |
| 60–69 years | 0.83 (0.63–1.09) | 1.74 (1.29–2.34) |
| BMI |  |  |
| < 18.5 kg/m² | 0.31 (0.14–0.70) | 0.31 (0.20–0.48) |
| 18.5 to 22.9 kg/m2 | 1.00 (Ref) | 1.00 (Ref) |
| 23.0 to 24.9 kg/m² | 1.27 (1.07–1.51) | 1.46 (1.19–1.80) |
| Smoking Status |  |  |
| Never smoked | 1.00 (Ref) | 1.00 (Ref) |
| Former smoker | 0.93 (0.78–1.11) | 1.01 (0.78–1.30) |
| Current Smoker | 1.37 (1.12–1.67) | 1.47 (1.09–1.99) |
| Abdominal obesity |  |  |
| No | 1.00 (Ref) | 1.00 (Ref) |
| Yes | 1.05 (0.64–1.72) | 2.04 (1.69–2.47) |
| Hyperglycemia |  |  |
| No | 1.00 (Ref) | 1.00 (Ref) |
| Yes | 1.20 (1.03–1.41) | 1.15 (0.96–1.39) |
| Dyslipidemia |  |  |
| No | 1.00 (Ref) | 1.00 (Ref) |
| Yes | 1.84 (1.52–2.23) | 1.68 (1.33–2.11) |
| Hypertension |  |  |
| No | 1.00 (Ref) | 1.00 (Ref) |
| Yes | 1.15 (0.96–1.39) | 1.03 (0.84–1.27) |
| Hyperuricemia |  |  |
| No | 1.00 (Ref) | 1.00 (Ref) |
| Yes | 1.31 (1.09–1.57) | 2.20 (0.98–4.94) |

HR, hazard ratio; CI, confidence interval; NAFLD, non-alcoholic fatty liver disease; BMI, body mass index

**Supplementary Table 4** Association between the risk factors of NAFLD and the development of NAFLD in non-obese participants using landmark analysis (Model 2)

|  |  |
| --- | --- |
|  | HR (95% CI) |
| Weight change at 2-year landmark point |  |
| Gain of 3-kg unit | 1.63 (1.53–1.75) |
| Weight change from age 20 to baseline |  |
| < −2.5 kg | 0.64 (0.49–0.83) |
| −2.5 to 2.4 kg | 1.00 (Ref) |
| 2.5 to 9.9 kg | 1.71 (1.48–1.97) |
| 10 kg | 2.26 (1.86–2.74) |
| Sex |  |
| Women | 1.00 (Ref) |
| Men | 1.64 (1.42–1.89) |
| Age |  |
| 30–39 years | 1.00 (Ref) |
| 40–49 years | 1.17 (1.01–1.35) |
| 50–59 years | 1.33 (1.13–1.57) |
| 60–69 years | 1.12 (0.92–1.36) |
| BMI |  |
| < 18.5 kg/m² | 0.28 (0.19–0.41) |
| 18.5 to 22.9 kg/m2 | 1.00 (Ref) |
| 23.0 to 24.9 kg/m² | 1.30 (1.14–1.49) |
| Smoking Status |  |
| Never smoked | 1.00 (Ref) |
| Former smoker | 0.91 (0.79–1.05) |
| Current Smoker | 1.41 (1.19–1.66) |
| Abdominal obesity |  |
| No | 1.00 (Ref) |
| Yes | 2.09 (1.78–2.45) |
| Hyperglycemia |  |
| No | 1.00 (Ref) |
| Yes | 1.18 (1.05–1.33) |
| Dyslipidemia |  |
| No | 1.00 (Ref) |
| Yes | 1.77 (1.53–2.05) |
| Hypertension |  |
| No | 1.00 (Ref) |
| Yes | 1.12 (0.98–1.29) |
| Hyperuricemia |  |
| No | 1.00 (Ref) |
| Yes | 1.31 (1.1–1.57) |

HR, hazard ratio; CI, confidence interval; NAFLD, non-alcoholic fatty liver disease; BMI, body mass index

**Supplementary Table 5** Association between the risk factors of NAFLD and the development of NAFLD in non-obese participants using landmark analysis (Model 3)

|  |  |  |
| --- | --- | --- |
|  | Men | Women |
|  | HR (95% CI) | HR (95% CI) |
| Waist circumference gain at 2-year landmark point | 1.00 (0.96–1.04) | 1.05 (1.01–1.08) |
| Weight change at 2-year landmark point |  |  |
| Gain of 3-kg unit | 1.60 (1.38–1.85) | 1.46 (1.28–1.67) |
| Weight change from age 20 to baseline |  |  |
| < −2.5 kg | 0.68 (0.46–1.02) | 0.63 (0.45–0.89) |
| −2.5 to 2.4 kg | 1.00 (Ref) | 1.00 (Ref) |
| 2.5 to 9.9 kg | 1.37 (1.12–1.68) | 2.04 (1.67–2.49) |
| 10 kg | 1.97 (1.52–2.55) | 2.66 (1.98–3.56) |
| Age |  |  |
| 30–39 years | 1.00 (Ref) | 1.00 (Ref) |
| 40–49 years | 0.99 (0.82–1.20) | 1.52 (1.20–1.92) |
| 50–59 years | 1.04 (0.83–1.30) | 1.91 (1.48–2.46) |
| 60–69 years | 0.83 (0.63–1.09) | 1.71 (1.27–2.30) |
| BMI |  |  |
| < 18.5 kg/m² | 0.31 (0.14–0.70) | 0.31 (0.20–0.49) |
| 18.5 to 22.9 kg/m2 | 1.00 (Ref) | 1.00 (Ref) |
| 23.0 to 24.9 kg/m² | 1.27 (1.07–1.51) | 1.42 (1.16–1.75) |
| Smoking Status |  |  |
| Never smoked | 1.00 (Ref) | 1.00 (Ref) |
| Former smoker | 0.93 (0.78–1.11) | 1.01 (0.78–1.31) |
| Current Smoker | 1.37 (1.12–1.67) | 1.48 (1.09–2.00) |
| Abdominal obesity |  |  |
| No | 1.00 (Ref) | 1.00 (Ref) |
| Yes | 1.05 (0.64–1.72) | 2.16 (1.78–2.62) |
| Hyperglycemia |  |  |
| No | 1.00 (Ref) | 1.00 (Ref) |
| Yes | 1.20 (1.03–1.41) | 1.15 (0.96–1.39) |
| Dyslipidemia |  |  |
| No | 1.00 (Ref) | 1.00 (Ref) |
| Yes | 1.84 (1.52–2.23) | 1.67 (1.33–2.11) |
| Hypertension |  |  |
| No | 1.00 (Ref) | 1.00 (Ref) |
| Yes | 1.15 (0.96–1.39) | 1.03 (0.83–1.26) |
| Hyperuricemia |  |  |
| No | 1.00 (Ref) | 1.00 (Ref) |
| Yes | 1.31 (1.09–1.57) | 2.13 (0.95–4.77) |

HR, hazard ratio; CI, confidence interval; NAFLD, non-alcoholic fatty liver disease; BMI, body mass index