

**Synergistic effect of non-alcoholic fatty liver disease and history of gestational diabetes to increase risk of type 2 diabetes**

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**Table 1.** Estimated\* mean values (95% CI) and adjusted\* proportions (95% CI) of baseline characteristics for population strata-defined by prior gestational diabetes mellitus and NAFLD status (n = 97,347)

| Characteristics                                    | Neither pGDM nor NAFLD | pGDM without NAFLD  | NAFLD without pGDM  | Both pGDM and NAFLD |
|--|------------------------|---------------------|---------------------|---------------------|
| Number of participants                             | 82,681                 | 3,887               | 10,088              | 691                 |
| Age (years)  | 38.5 (38.5-38.6)       | 39.0 (38.7-39.2)    | 43.3 (43.2-43.5)    | 40.5 (39.9-41)      |
| Alcohol intake (%) <sup>†</sup>                    | 10.4 (10.2-10.6)       | 8.8 (7.9-9.7)       | 11.5 (10.8-12.2)    | 8.8 (6.6-10.9)      |
| Current smoker (%)                                 | 1.3 (1.2-1.3)          | 1.1 (0.7-1.4)       | 1.7 (1.4-2.0)       | 1.9 (0.9-3.0)       |
| Education level (%) <sup>‡</sup>                   | 81.3 (81.1-81.6)       | 86.5 (85.4-87.5)    | 73 (72.1-73.8)      | 78.7 (75.7-81.7)    |
| HEPA (%) <sup>§</sup>                              | 12.8 (12.6-13.1)       | 12.4 (11.4-13.5)    | 11.6 (11-12.2)      | 10.4 (8.2-12.6)     |
| History of hypertension (%)                        | 2.2 (2.1-2.3)          | 2.7 (2.1-3.2)       | 5.3 (5.0-5.6)       | 6.2 (4.6-7.9)       |
| History of CVD (%)                                 | 0.6 (0.6-0.7)          | 0.7 (0.4-1.0)       | 0.6 (0.5-0.8)       | 1.0 (0.3-1.8)       |
| Anti-lipid medication use (%)                      | 1.2 (1.1-1.3)          | 1.2 (0.8-1.6)       | 2.4 (2.2-2.6)       | 2.9 (1.7-4.0)       |
| Family history of diabetes (%)                     | 14.1 (13.9-14.3)       | 20.6 (19.3-21.8)    | 18.8 (18.1-19.6)    | 25.3 (22.1-28.5)    |
| Obesity (%) <sup>  </sup>                          | 7.9 (7.7-8.1)          | 8.1 (7.3-9.0)       | 54.9 (53.9-55.9)    | 55.5 (51.8-59.2)    |
| Body mass index (kg/m <sup>2</sup> ) <sup>  </sup> | 21.3 (21.3-21.3)       | 21.4 (21.3-21.5)    | 25.9 (25.8-25.9)    | 25.7 (25.5-25.9)    |
| Waist circumference (cm)                           | 73.4 (73.3-73.4)       | 74.2 (73.9-74.4)    | 84.4 (84.3-84.5)    | 84.8 (84.3-85.3)    |
| SBP (mmHg)   | 102.1 (102.1-102.2)    | 101.9 (101.6-102.2) | 110 (109.8-110.2)   | 109.4 (108.6-110.1) |
| DBP (mmHg)   | 65.0 (64.9-65.0)       | 65.1 (64.8-65.3)    | 69.6 (69.5-69.8)    | 69.4 (68.9-70.0)    |
| Fasting glucose (mg/dl)                            | 90.5 (90.5-90.6)       | 92.4 (92.2-92.6)    | 95.2 (95-95.3)      | 98.3 (97.8-98.9)    |
| HbA1c (%)  | 5.4 (5.4-5.4)          | 5.5 (5.5-5.5)       | 5.6 (5.6-5.6)       | 5.7 (5.7-5.7)       |
| Total cholesterol (mg/dl)                          | 185.1 (184.9-185.3)    | 185.1 (184.2-186.1) | 196.7 (196.1-197.3) | 197.7 (195.4-199.9) |
| LDL-C (mg/dl)                                      | 112.7 (112.5-112.9)    | 113.9 (113-114.8)   | 130.7 (130.1-131.2) | 132.8 (130.7-134.9) |
| HDL-C (mg/dl)                                      | 69.5 (69.4-69.6)       | 67.9 (67.5-68.4)    | 56.4 (56.1-56.7)    | 54.9 (53.8-56.0)    |
| Triglycerides (mg/dl)                              | 76.1 (75.8-76.4)       | 78.7 (77.4-79.9)    | 122.8 (122-123.6)   | 132.7 (129.6-135.7) |
| GTP (U/L)  | 15.4 (15.3-15.6)       | 15.8 (15.3-16.4)    | 24.9 (24.5-25.2)    | 25.6 (24.3-26.8)    |
| ALT (U/L)  | 14.5 (14.4-14.6)       | 14.6 (14.3-15.0)    | 23.9 (23.7-24.1)    | 24.9 (24.0-25.8)    |
| AST (U/L)  | 18.3 (18.2-18.3)       | 17.9 (17.6-18.2)    | 21.5 (21.3-21.7)    | 21.4 (20.6-22.1)    |
| hs-CRP (mg/L)                                      | 0.70 (0.68-0.72)       | 0.72 (0.65-0.80)    | 1.57 (1.52-1.63)    | 1.76 (1.57-1.95)    |
| HOMA-IR  | 1.28 (1.27-1.29)       | 1.35 (1.31-1.39)    | 2.53 (2.50-2.55)    | 2.58 (2.49-2.67)    |

\*Adjusted for age; <sup>†</sup>≥10 g/day; <sup>‡</sup>≥college graduate; <sup>§</sup> health-enhancing physical activity; <sup>||</sup> BMI ≥25 kg/m<sup>2</sup>

Abbreviations: NAFLD, non-alcoholic fatty liver disease; pGDM, prior gestational diabetes mellitus; ALT, alanine aminotransferase; AST, aspartate transaminase; GTP, glutamyl transpeptidase; BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; HOMA-IR, homeostasis model assessment of insulin resistance

**Table 2.** Absolute and relative estimates of diabetes incidence for population strata defined by prior gestational diabetes mellitus and NAFLD status

| Group                  | Person-years | Incident cases | Incidence rate (/10 <sup>3</sup> PY) | Cumulative Incidence (/10 <sup>3</sup> persons) |        | Age adjusted HR (95% CI) | Multivariable-adjusted HR* (95% CI) |                  | HR (95% CI) <sup>†</sup> in model 2 with time-dependent variables |
|------------------------|--------------|----------------|--------------------------------------|---|--------|--------------------------|-------------------------------------|------------------|---|
|                        |              |                |                                      | 2-Year  | 5-Year |                          | Model 1                             | Model 2          |   |
| Neither pGDM nor NAFLD | 296,518      | 609            | 2.1                                  | 2.9   | 10.9   | 1.00 (reference)         | 1.00 (reference)                    | 1.00 (reference) | 1.00 (reference)  |
| pGDM without NAFLD     | 13,885       | 78             | 5.6                                  | 9.4   | 28.9   | 2.78 (2.20-3.52)         | 2.71 (2.14-3.43)                    | 2.61 (2.06-3.31) | 2.92 (2.29-3.72)  |
| NAFLD without pGDM     | 33,846       | 712            | 21.0                                 | 40.9  | 102.3  | 8.28 (7.40-9.27)         | 3.67 (3.22-4.18)                    | 2.26 (1.96-2.59) | 2.39 (2.09-2.74)  |
| Both pGDM and NAFLD    | 2,218        | 116            | 52.3                                 | 91.6  | 229.2  | 24.37 (19.98-29.73)      | 11.02 (8.94-3.57)                   | 6.45 (5.19-8.00) | 7.85 (6.36-9.68)  |

The *P*-value for the multiplicative interaction of GDM and NAFLD status with the risk of diabetes was 0.561 (Model 2).

The *P*-value for the additive interaction of GDM and NAFLD status with the risk of diabetes was <0.001 (Model 2); the relative excess risk due to interaction (PERI) was 2.58 (95% CI, 1.21-3.95), attributable proportion due to interaction (AP) was 0.40 (95%CI, 0.25-0.55), and synergistic index was 1.90 (95%CI, 1.32-2.48).

\* Estimated from Cox proportional hazards models; multivariable Model 1 was adjusted for age, centre, year of screening examination, alcohol consumption, smoking status, physical activity, education level, hyperlipidaemia medication, family history of diabetes, history of hypertension, and BMI. Model 2: Model 1 plus adjustments for SBP; total cholesterol, HDL-C, triglyceride levels; HOMA-IR; and hs-CRP level.

<sup>†</sup>Estimated from Cox proportional hazard models with group status, smoking status, alcohol consumption, physical activity, BMI, hyperlipidaemia medication, history of hypertension, SBP, total cholesterol, HDL-C, triglyceride, HOMA-IR, and hs-CRP as time-dependent categorical variables; baseline age, centre, year of screening examination, family history of diabetes, and education level as time-fixed variables

Abbreviations: NAFLD, non-alcoholic fatty liver disease; pGDM, prior gestational diabetes mellitus; HR, hazard ratio; CI, confidence interval; PY, person-years

**Table 3.** Comparison of the discriminatory power of prior gestational diabetes mellitus and NAFLD individually and combined for diabetes incidence, with the base model adjusted for age, family history of diabetes, hypertension, BMI, and waist circumference

|                       | Harrell's C index      |           | IDI   |           |
|-----------------------|------------------------|-----------|-------|-----------|
|                       | Value (95% CI)         | P-value   | Value | P value   |
| Base model            | 0.780<br>(0.767–0.792) | reference |       | reference |
| + pGDM only           | 0.793<br>(0.781–0.805) | <0.001    | 0.004 | <0.001    |
| + NAFLD only          | 0.816<br>(0.804–0.828) | <0.001    | 0.018 | <0.001    |
| + Both pGDM and NAFLD | 0.825<br>(0.813–0.836) | <0.001    | 0.023 | <0.001    |

Abbreviations: BMI, body mass index; CI, confidence interval; IDI, integrated discrimination improvement; NAFLD, non-alcoholic fatty liver disease; pGDM, prior gestational diabetes mellitus