

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 of Contents

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)

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

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

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 (%) [†]	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 (%) [‡]	81.3 (81.1-81.6)	86.5 (85.4-87.5)	73 (72.1-73.8)	78.7 (75.7-81.7)
HEPA (%) [§]	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 (%)	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 ²)	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; [†]≥10 g/day; [‡]≥college graduate; [§] health-enhancing physical activity; ^{||} BMI ≥25 kg/m²

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 ³ PY)	Cumulative Incidence (/10 ³ persons)		Age adjusted HR (95% CI)	Multivariable-adjusted HR* (95% CI)		HR (95% CI) [†] 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.

[†]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)	<i>P</i> -value	Value	<i>P</i> value
Base model	0.780 (0.767–0.792)	reference		reference
+ pGDM only	0.793 (0.781–0.805)	<0.001	0.004	<0.001
+ NAFLD only	0.816 (0.804–0.828)	<0.001	0.018	<0.001
+ Both pGDM and NAFLD	0.825 (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