

SUPPLEMENTARY MATERIALS

Table of contents

S1-1. Selection of participants: exclusion criteria

S1-2. Measurements

S1-3. Assessment of hepatic steatosis

S1-4. Assessment of NAFLD severity

S1-5. Measurement of pelvic ultrasonography

S2-1. Statistical analysis: assessment of interaction

S2-2. Statistical analysis: calculations of NRI and IDI

Supplementary Table 1. Relative estimates of diabetes incidence for population strata based on sex, menopausal status, and NAFLD status after further adjustment for waist circumference as a continuous variable instead of BMI (N=244,377)

Supplementary Table 2. Comparison of discriminatory power of NAFLD for incident diabetes based on sex and menopausal status with the base model adjusted for age, family history of diabetes, hypertension, BMI, waist circumference, and triglyceride levels

Supplementary Table 3. Comparison of the discriminatory power of NAFLD for incident diabetes by sex and menopausal status using ADA risk score as the base model

Supplementary Table 4. Comparison of the discriminatory power of NAFLD for incident diabetes by sex and menopausal status using the Leicester Diabetes Risk Score (UK risk score) as the base model

Supplementary Table 5. Absolute and relative estimates of diabetes incidence for population strata defined by sex, menopausal status, and subgroups of NAFLD severity defined by the FIB-4 score

Supplementary Table 6. Absolute and relative estimates of diabetes incidence for population strata based on sex, menopausal status, and subgroups of NAFLD severity defined by NAFLD fibrosis score

Supplementary Table 7. Absolute and relative estimates of diabetes incidence for population strata defined by sex, menopausal status, and subgroups of NAFLD severity defined by APRI

Supplementary Table 8. Development of diabetes based on NAFLD and its severity based on Hepamet Fibrosis Score (HFS) by sex and menopausal status

Supplementary Table 9. Relative estimates of diabetes incidence for population strata based on sex, menopausal status, and subgroups of NAFLD severity defined by FIB-4, NFS, or APRI (109,810 premenopausal women, 4,958 postmenopausal women, and 130,286 men)

Supplementary Table 10. Relative estimates of diabetes incidence for population strata defined by sex, and menopausal and NAFLD status

Supplementary Table 11. Relative estimates of diabetes incidence for population strata based on sex, menopausal status, and subgroups of NAFLD severity defined by FIB-4, NFS, APRI, or HFS after excluding 57,521 participants with prediabetes or $\text{HOMA-IR} \geq 2.5$

Supplementary Table 12. Relative estimates of diabetes incidence for population strata based on sex, menopausal status, and subgroups of NAFLD severity defined by FIB-4, NFS, APRI, or HFS after excluding 7,256 participants with $\text{BMI} \geq 30 \text{ kg/m}^2$

Supplementary Table 13. Relative estimates of diabetes incidence for population strata based on sex, menopausal status, and subgroups of NAFLD severity defined by FIB-4, NFS, APRI, or HFS after including 1,306 women who took the oral contraceptive

Supplementary Table 14. Absolute and relative estimates of diabetes incidence based on NAFLD status and diagnosis of polycystic ovaries among 30,591 premenopausal women with available pelvic sonography data

Supplementary text

S1-1. Selection of participants: exclusion criteria

A total of 123,250 subjects were excluded on the basis of the following criteria (Figure 1): excessive alcohol consumption (n = 54,548); liver steatogenic medication (n = 2,175); hepatitis medication and history of hepatitis (n = 11,157); serologic positivity for hepatitis B and hepatitis C virus (n = 11,653); liver cirrhosis based on ultrasound (n = 105); history of cancer (n = 8,199); diabetes at baseline (n = 13,217); use of female hormone therapy (n = 3,449); use of oral contraceptives (n = 2,236); history of hysterectomy, bilateral oophorectomy, or radiation or chemotherapy-related menopause (n = 7,352); use of intrauterine device (n = 5,300); and missing information on menopausal status, alcohol consumption, metabolic parameters, or components of the Fibrosis-4 Index for Liver Fibrosis (FIB-4) score, nonalcoholic fatty liver disease (NAFLD) fibrosis score (NFS), or Hepamet fibrosis score (HFS). Some participants met more than one exclusion criterion, and the final sample included 245,054 participants without diabetes, comprising 109,810 premenopausal women, 4,958 postmenopausal women, and 130,286 men.

S1-2. Measurements

A family history of diabetes was defined as having a self-reported diagnosis of diabetes in one or more first-degree relatives, and the current average alcohol consumption per day was assessed using the frequency of alcohol consumption per week and the amount of alcohol consumed per drinking day. Physical activity levels were assessed using the validated Korean version of the International Physical Activity Questionnaire short form.(1) Physical activity levels were classified into three categories: inactive, minimally active, and health-enhancing physical activity (HEPA).(1, 2) HEPA was defined as follows: (1) vigorous activity ≥ 3 days/week, with $\geq 1,500$ accumulated metabolic equivalent (MET)-min/week, or (2) a combination of walking and moderate- or vigorous-intensity activities over 7 days for a total of $\geq 3,000$ MET-min/week.

S1-3. Assessment of hepatic steatosis

Fatty liver was diagnosed on the basis of an abdominal ultrasound performed by experienced radiologists who were unaware of the study aim, using standard criteria, including a diffuse increase in fine echoes in the liver parenchyma in comparison with the kidney or spleen, deep beam attenuation, and bright vessel walls.(3) The inter -and intra-observer reliability values for HS diagnosis were substantial (kappa statistic of 0.74) and excellent (kappa statistic of 0.94), respectively.(4)

S1-4. Assessment of NAFLD severity

The FIB-4 index was calculated using the following formula: $FIB-4 = (\text{age [years]} \times \text{aspartate transaminase [AST; U/L]}) / (\text{platelet count } [\times 10^9/\text{L}] \times \text{alanine aminotransferase [ALT; U/L]}^{1/2})$. The cutoff values of the FIB-4 index were used to define low ($FIB-4 < 1.30$), intermediate ($FIB-4 1.30-2.67$), and high ($FIB-4 \geq 2.67$) probabilities of advanced fibrosis.(5) The NFS was calculated on the basis of the following published formula: $NFS = -1.675 + 0.037 \times \text{age (years)} + 0.094 \times \text{body mass index (BMI; kg/m}^2) + 1.13 \times \text{impaired fasting glycemia or diabetes (yes = 1, no = 0)} + 0.99 \times \text{AST/ALT ratio} - 0.013 \times \text{platelet } (\times 10^9/\text{L}) - 0.66 \times \text{albumin (g/dL)}$.(6) The NFS scores were categorized into three groups: high ($NFS > 0.676$), intermediate ($NFS 0.676$ to -1.455), and low ($NFS < -1.455$).(6) The aspartate transaminase to platelet ratio index (APRI) was calculated on the basis of the following formula: $APRI = 100 \times (\text{AST/upper limit of normal})/\text{platelet count } (\times 10^9/\text{L})$. The upper limits of the AST reference intervals for women and men were 32 U/L and 40 U/L, respectively, at Kangbuk Samsung Hospital. The APRI cutoffs for low and high probability of advanced fibrosis were 0.5 and 1.5, respectively.(7) The HFS was assessed on the basis of the following equation: $1/(1 + e^{[5.390 - 0.986 \times \text{age [45-64 years of age]} - 1.719 \times \text{age } [\geq 65 \text{ years of age}] + 0.785 \times \text{male sex} - 0.896 \times \text{AST [35-69 IU/L]} - 2.126 \times \text{AST } [\geq 70 \text{ IU/L}] - 0.027 \times \text{albumin [4-4.49 g/dl]} - 0.897 \times \text{albumin } [< 4 \text{ g/dl}] - 0.899 \times \text{homeostasis model assessment [2-3.99 with no diabetes mellitus]} - 1.497 \times \text{homeostasis model assessment } [\geq 4 \text{ with no diabetes mellitus}] - 2.184 \times \text{diabetes mellitus} - 0.882 \times \text{platelets } \times 1,000/\mu\text{l [155-219]} - 2.233 \times \text{platelets } \times 1,000/\mu\text{l } [< 155]})$).(8) HFS was categorized as follows: high ($HFS > 0.47$), intermediate ($HFS 0.12$ to 0.47), and low ($HFS < 0.12$).(8)

S1-5. Measurement of pelvic ultrasonography

In a subsample of women who underwent pelvic ultrasonographic examinations, experienced gynecologists who were blinded to the study aim routinely asked examinees if they had been diagnosed with any gynecological disorders, including polycystic ovary syndrome (PCOS), and examined them for the presence of ovarian cysts, including size, echogenicity, echotexture, internal pattern, and content. Previous gynecological disorders or abnormal findings on pelvic ultrasonographic examinations have been described in previous reports.(9, 10) The incidence of diabetes among women was analyzed while considering those with a suspected PCOS diagnosis or polycystic ovaries based on ultrasonographic findings.

S2-1. Statistical analysis: assessment of interaction

To assess the interaction effect by menopausal status and sex, the multivariable model included the presence of NAFLD, sex, menopausal status, and the product term, as well as the potential confounders in Model 2. We calculated stratum-specific effect estimates with confidence intervals using the `-lincom` command in STATA after performing multivariable analysis. The interactions between NAFLD status and sex on the risk of diabetes were assessed using likelihood ratio tests, comparing models with and without multiplicative interaction terms.

S2-2. Statistical analysis: calculations of NRI and IDI

In addition to the area under the receiver operating characteristic curve (AUROC), we further calculated the net reclassification improvement (NRI) and integrated discrimination improvement (IDI) to quantify the incremental predictive ability by adding NAFLD status to the conventional risk factors(11) including age, family history of diabetes, hypertension, BMI, and waist circumference in all three groups. We also assessed the added predictive value of NAFLD status to the American Diabetes Association (ADA) and Leicester Diabetes Risk Scores.(12, 13) We calculated category-based NRI (cutoffs at 5% and 10%), and IDI, a category-free measure.(14) Along with the incremental AUROC, NRI and IDI are useful measures for assessing the added value of new biomarkers in predicting clinical diseases.(14)

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Supplementary Table 1. Relative estimates of diabetes incidence for population strata based on sex, menopausal status, and NAFLD status after further adjustment for waist circumference as a continuous variable instead of BMI (N=244,377)

Multivariable-adjusted HR (95% CI)		
	^a With adjustment for waist circumference instead of BMI	^b With adjustment for BMI and waist circumference
Premenopausal women (N= 109,150)		
No NAFLD	1.00 (reference)	1.00 (reference)
NAFLD	3.33 (2.99-3.70)	3.11 (2.80-3.47)
Postmenopausal women (N= 4,953)		
No NAFLD	1.00 (reference)	1.00 (reference)
NAFLD	2.17 (1.65-2.85)	2.13 (1.62-2.80)
Men (N= 130,274)		
No NAFLD	1.00 (reference)	1.00 (reference)
NAFLD	1.58 (1.48-1.68)	1.56 (1.46-1.65)

The *P*-value for the interaction between sex, menopausal status, and NAFLD status and the risk of diabetes was <0.001.

^a Estimated from Cox proportional hazards models. The multivariable model was adjusted for age; center; year of screening examination; alcohol consumption; smoking status; physical activity; education level; hyperlipidemia medication; family history of diabetes; history of hypertension; SBP; total cholesterol, HDL-C, and triglyceride levels; HOMA-IR; hs-CRP level; and waist circumference.

^b Estimated from Cox proportional hazards models. The multivariable model was adjusted for age; center; year of screening examination; alcohol consumption; smoking status; physical activity; education level; hyperlipidemia medication; family history of diabetes; history of hypertension; SBP; total cholesterol, HDL-C, and triglyceride levels; HOMA-IR; hs-CRP level; BMI; and waist circumference.

Abbreviations: BMI, body mass index; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein; NAFLD, nonalcoholic fatty liver disease; PY, person-years; SBP, systolic blood pressure.

Supplementary Table 2. Comparison of discriminatory power of NAFLD for incident diabetes based on sex and menopausal status with the base model adjusted for age, family history of diabetes, hypertension, BMI, waist circumference, and triglyceride levels

	AUROC (95% CI)		NRI ^a		IDI	
	Harrell's C (95% CI)	<i>P</i> value	Index	<i>P</i> value	Index	<i>P</i> value
Premenopausal women						
Base model	0·831 (0·820–0·843)	reference		reference		reference
+ NAFLD	0·841 (0·830–0·852)	< 0·001	0·137	< 0·001	0·010	< 0·001
Postmenopausal women						
Base model	0·739 (0·705–0·774)	reference		reference		reference
+ NAFLD	0·758 (0·724–0·793)	0·014	0·155	< 0·001	0·012	< 0·001
Men						
Base model ^a	0·754 (0·748–0·760)	reference		reference		reference

+ NAFLD	0.764 (0.758–0.770)	< 0.001	0.057	< 0.001	0.003	< 0.001
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^a Risk cutoffs of 5% and 10% were used.

Abbreviations: AUROC, area under the receiver operating characteristic curve; BMI, body mass index; CI, confidence interval; IDI, integrated discrimination improvement; NAFLD, nonalcoholic fatty liver disease; NRI, net reclassification improvement.

Supplementary table 3. Comparison of the discriminatory power of NAFLD for incident diabetes by sex and menopausal status using ADA risk score as the base model

	AUROC (95% CI)		NRI ^a		IDI	
	Harrell's C (95% CI)	<i>P</i> value	Index	<i>P</i> value	Index	<i>P</i> value
Premenopausal women						
Base model ^a	0·777 (0·764–0·789)	reference		reference		reference
+ NAFLD	0·816 (0·804–0·828)	< 0·001	0·315	< 0·001	0·022	< 0·001
Postmenopausal women						
Base model ^a	0·675 (0·638–0·711)	reference		reference		reference
+ NAFLD	0·731 (0·696–0·767)	< 0·001	0·244	< 0·001	0·020	< 0·001
Men						
Base model ^a	0·707 (0·701–0·714)	reference		reference		reference

+ NAFLD	0.742 (0.736–0.748)	< 0.001	0.183	< 0.001	0.011	< 0.001
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^a Risk cutoffs of 5% and 10% were used.

Abbreviations: ADA, American Diabetes Association; AUROC, area under the receiver operating characteristic curve; BMI, body mass index; CI, confidence interval; IDI, integrated discrimination improvement; NRI, net reclassification improvement; NAFLD, nonalcoholic fatty liver disease.

Supplementary table 4. Comparison of the discriminatory power of NAFLD for incident diabetes by sex and menopausal status using the Leicester Diabetes Risk Score (UK risk score) as the base model

	AUROC (95% CI)		NRI ^a		IDI	
	Harrell's C (95% CI)	<i>P</i> value	Index	<i>P</i> value	Index	<i>P</i> value
Premenopausal women						
Base model ^a	0·763 (0·750–0·776)	reference		reference		reference
+ NAFLD	0·810 (0·797–0·822)	<0·001	0·223	<0·001	0·018	<0·001
Postmenopausal women						
Base model ^a	0·681 (0·643–0·719)	reference		reference		reference
+ NAFLD	0·739 (0·704–0·774)	<0·001	0·253	<0·001	0·020	<0·001
Men						
Base model ^a	0·712 (0·705–0·718)	reference		reference		reference

+ NAFLD	0.740 (0.734–0.747)	<0.001	0.097	<0.001	0.009	<0.001
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^a Risk cutoffs of 5% and 10% were used.

Abbreviations: AUROC, area under the receiver operating characteristic curve; BMI, body mass index; CI, confidence interval; IDI, integrated discrimination improvement; NRI, net reclassification improvement; NAFLD, nonalcoholic fatty liver disease.

Supplementary Table 5. Absolute and relative estimates of diabetes incidence for population strata defined by sex, menopausal status, and subgroups of NAFLD severity defined by the FIB-4 score

	Person-years	Incident cases	Incidence density (/ 10 ³ PY)	Age adjusted HR (95% CI)	Multivariable-adjusted HR ^a (95% CI)		HR (95% CI) ^b in a model with time-dependent variables
					Model 1	Model 2	
Premenopausal women							
(N= 109,810)							
No NAFLD	527,498	803	1.5	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
NAFLD, low FIB-4	44,447	820	18.4	11.02 (10.00-12.15)	4.60 (4.14-5.11)	3.09 (2.77-3.44)	3.16 (2.85-3.50)
NAFLD, intermediate or high FIB-4	695	22	31.7	13.08 (8.55-20.01)	5.34 (3.48-8.19)	4.05 (2.64-6.22)	4.28 (3.10-5.91)
<i>P</i> for trend				< 0.001	< 0.001	< 0.001	< 0.001
Postmenopausal women							
(N= 4,958)							
No NAFLD	13,208	82	6.2	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)

NAFLD, low FIB-4	3,569	96	26.9	4.55 (3.39-6.11)	2.98 (2.22-4.00)	2.32 (1.73-3.13)	1.95 (1.47-2.59)
NAFLD, intermediate or high FIB-4	1,635	47	28.7	3.85 (2.69-5.52)	2.16 (1.51-3.10)	1.84 (1.29-2.64)	1.53 (1.09-2.14)
<i>P</i> for trend				< 0.001	< 0.001	< 0.001	0.008
Men (N= 130,286)							
No NAFLD	427,315	1,941	4.5	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
NAFLD, low FIB-4	265,285	4,315	16.3	3.53 (3.34-3.72)	2.17 (2.05-2.30)	1.57 (1.47-1.66)	1.75 (1.65-1.86)
NAFLD, intermediate or high FIB-4	10,382	255	24.6	3.15 (2.75-3.62)	1.96 (1.70-2.25)	1.48 (1.29-1.70)	1.70 (1.51-1.91)
<i>P</i> for trend				< 0.001	< 0.001	< 0.001	< 0.001

The *P* value for the interaction of sex, menopausal status, and NAFLD categories for the risk of diabetes was <0.001 (Model 2).

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

^b Estimated from Cox proportional hazard models with NAFLD categories, smoking status, alcohol consumption, physical activity, BMI, hyperlipidemia medication, history of hypertension, SBP, total cholesterol, HDL-C, triglyceride, HOMA-IR, and hs-CRP as time-dependent categorical variables, and baseline age, center, year of screening examination, family history of diabetes, and education level as time-fixed variables

Abbreviations: BMI, body mass index; CI, confidence interval; FIB-4, Fibrosis-4 index for liver fibrosis; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein; HOMA-IR, homeostasis model assessment of insulin resistance; NAFLD, nonalcoholic fatty liver disease; PY, person-years; SBP, systolic blood pressure

Supplementary Table 6. Absolute and relative estimates of diabetes incidence for population strata based on sex, menopausal status, and subgroups of NAFLD severity defined by NAFLD fibrosis score

	Person- years (PY)	Incident cases	Incidence density (/ 10 ³ PY)	Age adjusted HR (95% CI)	Multivariable-adjusted HR ^a (95% CI)		HR (95% CI) ^b in a model with time-dependent variables
					Model 1	Model 2	
					Premenopausal women (N=109,810)		
No NAFLD	527,498	803	1.5	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
NAFLD, low NFS	43,225	765	17.7	10.79 (9.77-11.92)	4.7 (4.23-5.23)	3.12 (2.80-3.48)	2.94 (2.65-3.27)
NAFLD, intermediate or high NFS	1,916	77	40.2	20.82 (16.46- 26.33)	5.83 (4.57-7.44)	4.14 (3.25-5.28)	4.71 (3.85-5.76)
<i>P</i> for trend				< 0.001	< 0.001	< 0.001	< 0.001
Postmenopausal women (N=4,958)							
No NAFLD	13,208	82	6.2	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)

NAFLD, low NFS	3,775	80	21.2	3.52 (2.59-4.79)	2.42 (1.78-3.3)	1.90 (1.39-2.59)	1.40 (1.05-1.87)
NAFLD, intermediate or high NFS	1,429	63	44.1	6.10 (4.39-8.48)	3.14 (2.26-4.37)	2.62 (1.88-3.65)	2.10 (1.56-2.82)
<i>P</i> for trend				< 0.001	< 0.001	< 0.001	< 0.001
Men (N=130,286)							
No NAFLD	427,315	1,941	4.5	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
NAFLD, low NFS	256,911	3,874	15.1	3.28 (3.11-3.47)	2.09 (1.97-2.21)	1.50 (1.41-1.60)	1.50 (1.41-1.59)
NAFLD, intermediate or high NFS	18,757	696	37.1	5.96 (5.44-6.53)	3.01 (2.73-3.31)	2.19 (1.99-2.42)	2.18 (2.00-2.38)
<i>P</i> for trend				< 0.001	< 0.001	< 0.001	< 0.001

The *P* value for the interaction of sex, menopausal status, and NAFLD categories for the risk of diabetes was <0.001 (Model 2).

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

^b Estimated from Cox proportional hazard models with NAFLD categories, smoking status, alcohol consumption, physical activity, BMI, hyperlipidemia medication, history of hypertension, SBP, total cholesterol, HDL-C, triglyceride, HOMA-IR, and hs-CRP as time-dependent categorical variables, and baseline age, center, year of screening examination, family history of diabetes, and education level as time-fixed variables.

Abbreviations: BMI, body mass index; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein; NAFLD, nonalcoholic fatty liver disease; NFS, NAFLD fibrosis score; PY, person-years; SBP, systolic blood pressure.

Supplementary Table 7. Absolute and relative estimates of diabetes incidence for population strata defined by sex, menopausal status, and subgroups of NAFLD severity defined by APRI

	Person- years (PY)	Incident cases	Incidence density (/ 10 ³ PY)	Age adjusted HR (95% CI)	Multivariable-adjusted HR ^a (95% CI)		HR (95% CI) ^b in a model with time-dependent variables
					Model 1	Model 2	
Premenopausal women (N=109,810)							
No NAFLD	527,498	803	1.5	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
NAFLD, low APRI	43,624	752	17.2	10.23 (9.26- 11.30)	4.49 (4.03-5.00)	3.04 (2.72-3.39)	2.97 (2.68-3.30)
NAFLD, intermediate or high APRI	1,518	90	59.3	36.73 (29.54- 45.68)	11.32 (9.04- 14.17)	7.06 (5.63-8.86)	5.80 (4.67-7.21)
<i>P</i> for trend				< 0.001	< 0.001	< 0.001	< 0.001
Postmenopausal women (N=4,958)							

No NAFLD	13,208	82	6.2	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
NAFLD, low APRI	4,834	127	26.3	4.12 (3.12-5.44)	2.70 (2.05-3.57)	2.16 (1.63-2.85)	1.66 (1.29-2.15)
NAFLD, intermediate or high APRI	369	16	43.3	6.55 (3.83-11.2)	2.71 (1.58-4.66)	2.35 (1.37-4.03)	1.80 (1.12-2.91)
<i>P</i> for trend				< 0.001	< 0.001	< 0.001	< 0.001
Men (N=130,286)							
No NAFLD	427,315	1,941	4.5	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
NAFLD, low APRI	259,269	3,944	15.2	3.21 (3.04-3.39)	2.05 (1.93-2.17)	1.50 (1.41-1.60)	1.50 (1.41-1.59)
NAFLD, intermediate or high APRI	16,398	626	38.2	8.49 (7.76-9.29)	4.15 (3.77-4.57)	2.66 (2.41-2.94)	3.06 (2.78-3.36)
<i>P</i> for trend				< 0.001	< 0.001	< 0.001	< 0.001

The *P* value for the interaction of sex, menopausal status, and NAFLD categories for the risk of diabetes was <0.001 (Model 2).

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

^b Estimated from Cox proportional hazard models with NAFLD categories, smoking, alcohol consumption, physical activity, BMI, medication for hyperlipidemia, history of hypertension, SBP, total cholesterol, HDL-C, triglyceride, HOMA-IR, and hs-CRP as time-dependent categorical variables and baseline age, center, year of screening examination, family history of diabetes, and education level as time-fixed variables.

Abbreviations: APRI, aspartate transaminase to platelet ratio index; BMI, body mass index; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein; NAFLD, nonalcoholic fatty liver disease; PY, person-years; SBP, systolic blood pressure.

Supplementary Table 8. Development of diabetes based on NAFLD and its severity based on Hepamet Fibrosis Score (HFS) by sex and menopausal status

	Person-years (PY)	Incident cases	Incidence density (/ 10 ³ PY)	Age adjusted HR (95% CI)	Multivariable-adjusted HR ^a (95% CI)		HR (95% CI) ^b in a model with time-dependent variables
					Model 1	Model 2	
Premenopausal women (N=109,810)							
No NAFLD	526,408	798	1.5	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
NAFLD, low HFS	44,785	814	18.2	10.90 (9.88- 12.02)	4.59 (4.13-5.10)	3.44 (3.09-3.84)	3.26 (2.94-3.62)
NAFLD, intermediate or high HFS	216	26	120.3	71.50 (48.34- 105.75)	15.78 (10.62- 23.46)	10.53 (7.08- 15.68)	7.09 (5.15-9.77)
<i>P</i> for trend				< 0.001	< 0.001	< 0.001	< 0.001
Postmenopausal women (N=4,958)							

No NAFLD	12,202	74	6.1	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
NAFLD, low HFS	4,612	119	25.8	4.16 (3.12-5.57)	2.68 (2.00-3.58)	2.34 (1.75-3.13)	1.80 (1.38-2.33)
NAFLD, intermediate or high HFS	196	12	61.2	8.19 (4.45-15.08)	2.47 (1.34-4.57)	2.59 (1.40-4.79)	1.81 (1.05-3.12)
<i>P</i> for trend				< 0.001	< 0.001	< 0.001	< 0.001
Men (N=130,286)							
No NAFLD	426,127	1,925	4.5	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
NAFLD, low HFS	274,325	4,511	16.4	3.50 (3.32-3.69)	2.17 (2.05-2.30)	1.78 (1.68-1.89)	1.78 (1.67-1.88)
NAFLD, intermediate or high HFS	577	47	81.4	13.03 (9.74-17.44)	4.69 (3.49-6.29)	3.52 (2.62-4.73)	3.29 (2.66-4.07)
<i>P</i> for trend				< 0.001	< 0.001	< 0.001	< 0.001

The *P* value for the interaction of sex, menopausal status, and NAFLD categories for the risk of diabetes was <0.001 (Model 2).

^a Estimated from Cox proportional hazards models; multivariable Model 1 was adjusted for age, center, year of screening examination, alcohol

consumption, smoking status, physical activity, education level, hyperlipidemia medication, family history of diabetes, history of hypertension, and BMI.

Model 2: Model 1 plus adjustments for SBP; total cholesterol, HDL-C, and triglyceride levels; and hs-CRP level.

^b Estimated from Cox proportional hazard models with NAFLD categories, smoking, alcohol consumption, physical activity, BMI, medication for hyperlipidemia, history of hypertension, SBP, total cholesterol, HDL-C, triglyceride, and hs-CRP as time-dependent categorical variables and baseline age, center, year of screening examination, family history of diabetes, and education level as time-fixed variables.

Abbreviations: APRI, aspartate transaminase to platelet ratio index; BMI, body mass index; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein; NAFLD, nonalcoholic fatty liver disease; PY, person-years; SBP, systolic blood pressure.

Supplementary Table 9. Relative estimates of diabetes incidence for population strata based on sex, menopausal status, and subgroups of NAFLD severity defined by FIB-4, NFS, or APRI (109,810 premenopausal women, 4,958 postmenopausal women, and 130,286 men)

	Multivariable-adjusted HR (95% CI)			Multivariable-adjusted HR (95% CI)		
	^a with adjustment for waist circumference instead of			^b with adjustment for BMI and waist circumference		
	BMI					
	Based on FIB-4	Based on NFS	Based on APRI	Based on FIB-4	Based on NFS	Based on APRI
Premenopausal women						
No NAFLD	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
NAFLD, Low	3.31 (2.97-3.68)	3.31 (2.97-3.69)	3.24 (2.90-3.61)	3.09 (2.77-3.44)	3.12 (2.80-3.48)	3.04 (2.72-3.39)
NAFLD, Intermediate or high	4.03 (2.63-6.19)	4.68 (3.67-5.96)	7.74 (6.18-9.70)	4.02 (2.62-6.18)	4.12 (3.23-5.26)	7.07 (5.64-8.87)
<i>P</i> for trend	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Postmenopausal women						
No NAFLD	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
NAFLD, Low	2.37 (1.77-3.19)	1.90 (1.39-2.59)	2.18 (1.65-2.88)	2.32 (1.73-3.12)	1.89 (1.39-2.58)	2.15 (1.63-2.85)
NAFLD, Intermediate or high	1.84 (1.28-2.64)	2.71 (1.95-3.78)	2.44 (1.42-4.17)	1.83 (1.28-2.62)	2.61 (1.88-3.63)	2.34 (1.37-4.01)

high						
<i>P</i> for trend	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Men						
No NAFLD	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
NAFLD, Low	1.58 (1.49-1.68)	1.51 (1.42-1.61)	1.52 (1.43-1.61)	1.56 (1.47-1.66)	1.50 (1.41-1.59)	1.50 (1.41-1.59)
NAFLD, Intermediate or high	1.48 (1.29-1.70)	2.28 (2.07-2.51)	2.72 (2.46-3.00)	1.47 (1.28-1.69)	2.19 (1.98-2.41)	2.66 (2.41-2.93)
<i>P</i> for trend	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
<i>P</i> for interaction	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

The *P*-value for the interaction of sex, menopausal status, and NAFLD status with the risk of diabetes was < 0.001.

^a After further adjustment for waist circumference as a continuous variable instead of BMI, estimated using Cox proportional hazards models. The multivariable model was adjusted for age; center; year of screening examination; alcohol consumption; smoking status; physical activity; education level; hyperlipidemia medication; family history of diabetes; history of hypertension; SBP; total cholesterol, HDL-C, and triglyceride levels; HOMA-IR; hs-CRP level; and waist circumference.

^b After adjustment for both BMI and waist circumference as continuous variables

Abbreviations: APRI, aspartate transaminase to platelet ratio index; BMI, body mass index; CI, confidence interval; FIB-4, Fibrosis-4 index for liver fibrosis; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein; NAFLD, nonalcoholic fatty liver disease; NFS, NAFLD fibrosis score; PY, person-years; SBP, systolic blood pressure.

Supplementary Table 10. Relative estimates of diabetes incidence for population strata defined by sex, and menopausal and NAFLD status

	Multivariable-adjusted HR^a (95% CI) after including 1,306 women who took oral contraceptives	Multivariable-adjusted HR^a (95% CI) after excluding 7,256 participants with BMI ≥30 kg/m²	Multivariable-adjusted HR^a (95% CI) after excluding 57,521 participants with prediabetes or HOMA-IR ≥2.5
Premenopausal women			
No NAFLD	1.00 (reference)	1.00 (reference)	1.00 (reference)
NAFLD	3.11 (2.80-3.47)	3.29 (2.93-3.69)	3.08 (2.72-3.49)
Postmenopausal women			
No NAFLD	1.00 (reference)	1.00 (reference)	1.00 (reference)
NAFLD	2.14 (1.63-2.81)	2.16 (1.63-2.86)	2.12 (1.58-2.86)
Men			
No NAFLD	1.00 (reference)	1.00 (reference)	1.00 (reference)
NAFLD	1.56 (1.47-1.66)	1.55 (1.45-1.64)	1.54 (1.44-1.64)
<i>P</i> for interaction	< 0.001	< 0.001	< 0.001

^a Estimated from Cox proportional hazards models; multivariable Model 1 was adjusted for age, center, year of screening examination, alcohol consumption, smoking status, physical activity, education level, hyperlipidemia medication, family history of diabetes, history of hypertension, BMI, SBP, HOMA-IR, and total cholesterol, HDL-C, triglyceride, and hs-CRP levels.

Abbreviations: BMI, body mass index; CI, confidence interval; HOMA-IR, homeostasis model assessment of insulin resistance; HR, hazard ratio; NAFLD, nonalcoholic fatty liver disease; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; SBP, systolic blood pressure.

Supplementary Table 11. Relative estimates of diabetes incidence for population strata based on sex, menopausal status, and subgroups of NAFLD severity defined by FIB-4, NFS, APRI, or HFS after excluding 57,521 participants with prediabetes or HOMA-IR ≥ 2.5

	Multivariable-adjusted HR (95% CI)			
	Based on FIB-4	Based on NFS	Based on APRI	Based on HFS
Premenopausal women				
No NAFLD	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
NAFLD, Low	3.07 (2.71-3.48)	3.05 (2.69-3.46)	3.02 (2.66-3.43)	3.29 (2.91-3.73)
NAFLD, Intermediate or high	3.16 (1.82-5.50)	4.58 (3.20-6.58)	6.53 (4.71-9.04)	5.56 (2.30-13.45)
<i>P</i> for trend	<0.001	<0.001	<0.001	<0.001
Postmenopausal women				
No NAFLD	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
NAFLD, Low	2.32 (1.67-3.22)	1.92 (1.38-2.68)	2.09 (1.54-2.84)	2.14 (1.56-2.95)
NAFLD, Intermediate or high	1.81 (1.21-2.72)	2.61 (1.76-3.86)	2.74 (1.45-5.16)	3.22 (1.40-7.44)
<i>P</i> for trend	<0.001	<0.001	<0.001	<0.001

Men				
No NAFLD	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
NAFLD, Low	1.55 (1.45-1.66)	1.47 (1.38-1.58)	1.50 (1.40-1.60)	1.67 (1.56-1.78)
NAFLD, Intermediate or high	1.34 (1.14-1.59)	2.31 (2.04-2.60)	2.38 (2.10-2.70)	2.74 (1.58-4.75)
<i>P</i> for trend	<0.001	<0.001	<0.001	<0.001
<i>P</i> for interaction	<0.001	<0.001	<0.001	<0.001

Estimated from Cox proportional hazards models. The multivariable model was adjusted for age; center; year of screening examination; alcohol consumption; smoking status; physical activity; education level; hyperlipidemia medication; family history of diabetes; history of hypertension; BMI; SBP; total cholesterol, HDL-C, hs-CRP, and triglyceride levels; and HOMA-IR (not for HFS).

Abbreviations: APRI, aspartate transaminase to platelet ratio index; BMI, body mass index; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein; NAFLD, nonalcoholic fatty liver disease; SBP, systolic blood pressure; HFS, Hepamet Fibrosis Score; NFS, NAFLD fibrosis score; FIB-4, FIB-4, fibrosis-4 index for liver fibrosis.

Supplementary Table 12. Relative estimates of diabetes incidence for population strata based on sex, menopausal status, and subgroups of NAFLD severity defined by FIB-4, NFS, APRI, or HFS after excluding 7,256 participants with BMI ≥ 30 kg/m²

	Multivariable-adjusted HR (95% CI)			
	Based on FIB-4	Based on NFS	Based on APRI	Based on HFS
Premenopausal women				
No NAFLD	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
NAFLD, Low	3.29 (2.93-3.69)	3.22 (2.86-3.62)	3.21 (2.85-3.61)	3.67 (3.26-4.12)
NAFLD, Intermediate or high	3.09 (1.81-5.27)	5.51 (4.15-7.31)	7.67 (5.71-10.30)	9.22 (4.76-17.86)
<i>P</i> for trend	<0.001	<0.001	<0.001	<0.001
Postmenopausal women				
No NAFLD	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
NAFLD, Low	2.23 (1.64-3.05)	1.83 (1.33-2.52)	2.12 (1.59-2.82)	2.31 (1.71-3.13)
NAFLD, Intermediate or high	2.03 (1.40-2.95)	2.89 (2.04-4.10)	3.04 (1.69-5.47)	3.62 (1.86-7.02)
<i>P</i> for trend	<0.001	<0.001	<0.001	<0.001

Men				
No NAFLD	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
NAFLD, Low	1.56 (1.46-1.66)	1.50 (1.40-1.60)	1.49 (1.40-1.59)	1.74 (1.64-1.85)
NAFLD, Intermediate or high	1.42 (1.22-1.64)	2.11 (1.89-2.35)	2.62 (2.34-2.94)	3.18 (2.12-4.78)
<i>P</i> for trend	<0.001	<0.001	<0.001	<0.001
<i>P</i> for interaction	<0.001	<0.001	<0.001	<0.001

Estimated from Cox proportional hazards models. The multivariable model was adjusted for age; center; year of screening examination; alcohol consumption; smoking status; physical activity; education level; hyperlipidemia medication; family history of diabetes; history of hypertension; BMI; SBP; total cholesterol, HDL-C, hs-CRP, and triglyceride levels; and HOMA-IR (not for HFS).

Abbreviations: APRI, aspartate transaminase to platelet ratio index; BMI, body mass index; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein; NAFLD, nonalcoholic fatty liver disease; SBP, systolic blood pressure; HFS, Hepamet Fibrosis Score; NFS, NAFLD fibrosis score; FIB-4, FIB-4, fibrosis-4 index for liver fibrosis.

Supplementary Table 13. Relative estimates of diabetes incidence for population strata based on sex, menopausal status, and subgroups of NAFLD severity defined by FIB-4, NFS, APRI, or HFS after including 1,306 women who took the oral contraceptive

	Multivariable-adjusted HR (95% CI)			
	Based on FIB-4	Based on NFS	Based on APRI	Based on HFS
Premenopausal women				
No NAFLD	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
NAFLD, Low	3.09 (2.77-3.44)	3.12 (2.80-3.48)	3.04 (2.72-3.39)	3.45 (3.10-3.84)
NAFLD, Intermediate or high	4.23 (2.78-6.44)	4.19 (3.29-5.33)	7.17 (5.73-8.97)	10.53 (7.07-15.67)
<i>P</i> for trend	< 0.001	< 0.001	< 0.001	< 0.001
Postmenopausal women				
No NAFLD	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
NAFLD, Low	2.32 (1.73-3.12)	1.90 (1.39-2.59)	2.16 (1.63-2.85)	2.34 (1.75-3.13)
NAFLD, Intermediate or high	1.84 (1.29-2.64)	2.62 (1.88-3.65)	2.36 (1.38-4.04)	2.60 (1.41-4.79)
<i>P</i> for trend	< 0.001	< 0.001	< 0.001	< 0.001

Men				
No NAFLD	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
NAFLD, Low	1.56 (1.47-1.66)	1.50 (1.42-1.60)	1.50 (1.41-1.60)	1.78 (1.68-1.89)
NAFLD, Intermediate or high	1.48 (1.29-1.70)	2.19 (1.99-2.41)	2.66 (2.41-2.94)	3.52 (2.62-4.72)
<i>P</i> for trend	< 0.001	< 0.001	< 0.001	< 0.001
<i>P</i> for interaction	< 0.001	< 0.001	< 0.001	< 0.001

Estimated from Cox proportional hazards models. The multivariable model was adjusted for age; center; year of screening examination; alcohol consumption; smoking status; physical activity; education level; hyperlipidemia medication; family history of diabetes; history of hypertension; BMI; SBP; total cholesterol, HDL-C, hs-CRP, and triglyceride levels; and HOMA-IR (not for HFS).

Abbreviations: APRI, aspartate transaminase to platelet ratio index; BMI, body mass index; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein; NAFLD, nonalcoholic fatty liver disease; SBP, systolic blood pressure; HFS, Hepamet Fibrosis Score; NFS, NAFLD fibrosis score; FIB-4, FIB-4, fibrosis-4 index for liver fibrosis.

Supplementary Table 14. Absolute and relative estimates of diabetes incidence by NAFLD status and diagnosis of polycystic ovaries among 30,591 premenopausal women with available pelvic sonography data

		Person- years (PY)	Incident cases	Incidence density (/ 10 ³ PY)	Age adjusted HR (95% CI)	Multivariable-adjusted HR ^a (95% CI)		HR (95% CI) ^b in a model with time- dependent variables
						Model 1	Model 2	
NAFLD	Polycystic ovaries							
No	No	147,998	215	1.5	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
No	Yes	1,255	3	2.4	2.40 (0.76-7.52)	2.10 (0.67-6.58)	1.76 (0.56-5.56)	0.60 (0.08-4.27)
Yes	No	11,376	189	16.6	9.81 (8.03- 12.00)	8.85 (7.21-10.86)	2.95 (2.30-3.79)	3.01 (2.40-3.79)
Yes	Yes	188	8	42.5	40.23 (19.77- 81.85)	36.13 (17.65-73.93)	8.33 (3.95-17.56)	9.35 (5.07-17.22)

^a Estimated from Cox proportional hazards models; multivariable Model 1 was adjusted for age, center, year of screening examination, alcohol consumption, smoking status, physical activity, education level, hyperlipidemia medication, family history of diabetes, history of hypertension, and BMI.

Model 2: Model 1 was adjusted for SBP, HOMA-IR, and total cholesterol, HDL-C, triglyceride, and hs-CRP levels.

Abbreviations: BMI, body mass index; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein; NAFLD, nonalcoholic fatty liver disease; SBP, systolic blood pressure.