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Liver enzymes, body mass index, and the risk of diabetes

Bo Mi Song, M.P.H.

The Graduate School

Yonsei University

Department of Public Health

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Liver enzymes, body mass index, and the risk of diabetes

A Dissertation

Submitted to the Department of Public Health

and the Graduate School of Yonsei University

in partial fulfillment of the

requirements for the degree of

Doctor of Philosophy of Public Health

Bo Mi Song, M.P.H.

June 2016

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YONSEI UNIVERSITY

This certifies that the dissertation of Bo Mi Song is approved.

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Thesis Supervisor: Hyeon Chang Kim

_____

Il Suh: Thesis Committee Member #1

_____

Dae Jung Kim: Thesis Committee Member #2

_____

Song Vogue Ahn: Thesis Committee Member #3

_____

Kyoung Min Kim: Thesis Committee Member #4

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ABSTRACT

Liver enzymes, body mass index, and the risk of diabetes

Bo Mi Song, M.P.H.

Department of Public Health

The Graduate School of Yonsei University

(Directed by Professor Hyeon Chang Kim, M.D., Ph.D.)

INTRODUCTION

Prevalence and incidence of diabetes have increased alarmingly worldwide and across all age, sex, and race groups. Obesity is an important risk factor for diabetes. Meanwhile, there have been several reports about the association between liver enzyme levels and diabetes. However, only few studies investigated the association of liver enzymes, obesity, and the incident diabetes. This study was performed to investigate whether the relationship between body mass index (BMI) and the incident diabetes is modified by ALT or AST levels.

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METHODS

This study used data from the Korean Genome Epidemiology Study_cardiovascular disease association study (KoGES_CAVAS) which enrolled 10,615 participants aged 40 years or older from rural communities between 2005 and 2011. I carried out a prospective analysis of 6,484 participants (2,497 men and 3,987 women) who completed follow-up examinations until 2014. Serum ALT and AST were measured using the enzymatic methods. BMI was analyzed as both a continuous and categorized variable. Diabetes was defined as fasting blood glucose ≥ 126 mg/dL or current treatment for diabetes. To examine the associations of BMI with the incident diabetes according to ALT or AST levels, multiple logistic regression models were used after stratification into the low and high groups based on the median ALT or AST levels.

RESULTS

The median follow-up time was 4.5 years, during which 304 participants (4.7%) developed diabetes. In people with high ALT levels, compared with the first BMI quartile, the adjusted odds ratios (ORs) for incident diabetes of the second, third, and fourth BMI quartiles were 1.88 (95% CI, 0.98 – 3.62), 2.24 (1.21 – 4.13), and 3.32 (1.84 – 5.99), respectively (p-trend < 0.001) after adjustment for age, sex, study year, residential area, hypertension, family history of diabetes, smoking status, alcohol intake, exercise, fasting glucose, and ALT, while in people with low ALT levels, high BMI was not independently associated with the incident diabetes. Similarly, in people with high AST levels, the adjusted ORs for incident diabetes of the second, third, and fourth BMI quartiles, were 2.14 (1.13 – 4.08), 2.44 (1.32 – 4.53), and 3.65 (2.02 – 6.60), respectively (p-trend < 0.001), while in people with low AST levels,

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categorized BMI was not significantly associated with the incident diabetes but the adjusted OR per 1 kg/m^2 increase in BMI was 1.10 (1.02 – 1.19).

CONCLUSION

These findings suggest that there was a strong association between BMI and incident diabetes among people with high liver enzyme levels, but the association was only modest among those with low liver enzyme levels.

Keywords: ALT, AST, body mass index, obesity, diabetes

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Ⅰ. INTRODUCTION

A. Backgrounds

Serum alanine aminotransferases (ALT, formerly called as GPT: glutamic pyruvic transaminase) and aspartate aminotransferases (AST, formerly called as GOT: glutamic oxaloacetic transaminase), found primarily in the liver, are considered indicators of hepatocellular health (Craxi, and Almasio 1996, 47-51, Pratt, and Kaplan 2000, 1266-71). The liver plays an important role in maintaining normal glucose concentrations during fasting as well as postprandially. It is also a major site of insulin clearance (Duckworth, Hamel, and Peavy 1988, 71-6). The loss of a direct effect of insulin to suppress hepatic glucose production and glycogenolysis in the liver causes an increase in hepatic glucose production (Michael et al. 2000, 87-97).

Recently, the prevalence and incidence of diabetes have increased alarmingly worldwide and across all age, sex, and race groups (Danaei et al. 2011, 31-40, Jayawardena et al. 2012, 380). Obesity is an important risk factor for diabetes (Ford, Williamson, and Liu 1997, 214-22). Meanwhile, there have been several reports about the association between liver enzyme levels and diabetes (Goessling et al. 2008, 1935-44, 1944.e1, Hanley et al. 2004, 2623-32, Lee et al. 2003, 359-64, Lee et al. 2003, 1358-66, Sattar et al. 2004, 2855-60, Vozarova et al. 2002, 1889-95, Wannamethee et al. 2005, 2913-8). However, only few studies investigated the association of liver enzymes, obesity, and the incident diabetes.

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B. Objectives

The aim of this study was to investigate whether the relationship between body mass index (BMI) and the incident diabetes is modified by serum ALT or AST levels in Korean general population.

Specifically,

1) To investigate whether BMI and serum ALT or AST levels are associated with the incident diabetes

2) To investigate whether the association between BMI and incident diabetes differs according to serum ALT and AST levels

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Ⅱ. MATERIALS AND METHODS

A. Study Population

This study used data from the Korean Genome Epidemiology Study_cardiovascular disease association study (KoGES_CAVAS), which was initiated to investigate risk factors for cardiovascular diseases by setting up a community-based prospective cohort in 11 rural counties in South Korea. The current study used the data of 3 rural counties (Gangwha, Pyeongchang, and Wonju) where demographic shifts are infrequent and high long-term follow up rates are expected.

The baseline survey, carried out from 2005 to 2011, included 10,615 participants aged 40 years or older. Of them, 7,445 (70.1%) participants completed follow-up health questionnaires and health examinations until 2014. The sampling and data collection procedures have been described in detail elsewhere (Kim, and Han 2016). I excluded those who had missing key variables (n = 61); had fasting blood glucose ≥ 126 mg/dL, or were receiving treatment by oral antidiabetic drugs or insulin (n = 700); or had a history of stroke, angina pectoris, or myocardial infarction (n = 200) at the baseline survey. Finally, I conducted a prospective analysis of 6,484 participants (2,497 men and 3,987 women).

All participants provided written informed consent, and the study protocol was approved by the Institutional Review Boards of Severance Hospital at Yonsei University College of Medicine and Wonju Severance Christian Hospital.

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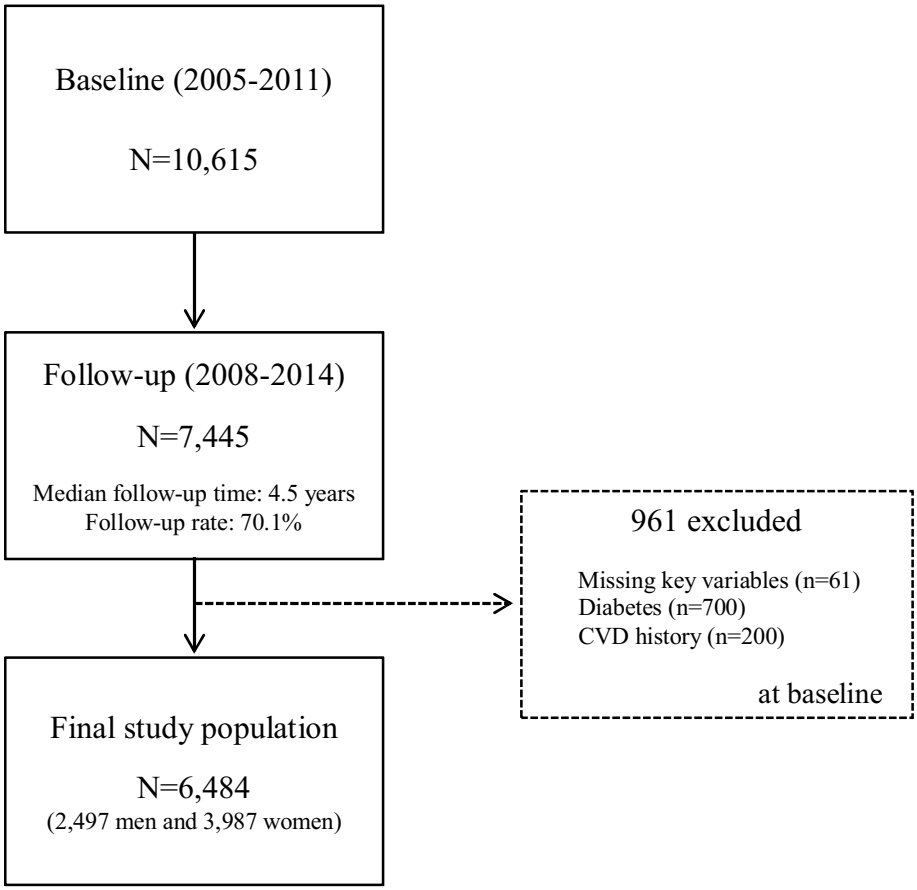

Figure 1. Framework of the selection criteria for the final study population

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B. Data Collection

i. Questionnaire

All participants were individually interviewed using standardized questionnaires to acquire information about their demographics, personal and family medical history, medication usage, health behaviors, and menopausal status (for women). Trained interviewers individually carried out the questionnaire surveys according to a predefined protocol. Smoking status was classified into current smokers, past smokers, and never smokers. Alcohol intake was categorized as current drinkers, past drinkers and never drinkers. However, they were dichotomized as current smokers or current nonsmokers (past smokers or never smokers), and current drinkers or current nondrinkers (past drinkers or never drinkers) for the statistical analysis. Heavy alcohol intake was defined as at least 50 grams per day by self-report. Regular exercise was indicated as “yes” for participants who exercised on a regular basis regardless of indoor or outdoor exercise and “no” for those who did not. Menopause was defined as cessation of menses ≥1 year. Lastly, the designated field director double-checked whether responses were inappropriate or missing.

ii. Physical Examination

Participants wore lightweight clothing for convenient and reliable examinations. Standing height was measured to the nearest 0.1 cm using a stadiometer and body weight was measured to the nearest 0.1 kg using a digital scale. The participants stood on the floor with the heels of both feet together and the toes pointed slightly outward at approximately a 60˚ angle. The position of the heel, the buttocks, shoulder blades and the back of the head were checked for contact with the vertical backboard. Once correctly positioned, the participant

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took a deep breath and the headboard was lowered and positioned firmly on top of the head with sufficient pressure to compress the hair. When the participant was properly positioned, the height and weight were recorded by examiners. Subsequently, BMI was calculated as body weight in kilograms divided by standing height in meters squared (kg/m^2). Waist circumference was measured to the nearest 0.1 cm at the midpoint between the lower borders of the rib cage and the iliac crest with an ergonomic circumference measuring tape (SECA 200 and SECA 201; SECA, Hamburg, Germany). Blood pressure was measured using a standard mercury sphygmomanometer (Baumanometer; Copiague, USA) in Pyeongchang and Wonju and an automatic sphygmomanometer (Dinamap 1846 SX/P; GE Healthcare, USA) in Gangwha. Participants were seated for at least five minutes, and a suitably sized cuff was applied closely around the right upper arm. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were taken at least twice with intervals of five minutes, and the last two measurements were averaged for analysis.

iii. Laboratory Test

Blood samples of all participants were collected from the antecubital vein after an overnight fast. All of the laboratory tests were performed at the same facility. Total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were measured with the enzymatic methods (ADVIA 1800; Siemens medical Sol., USA). Low-density lipoprotein (LDL) cholesterol levels were calculated using the Friedewald formula (Friedewald, Levy, and Fredrickson 1972, 499-502). Fasting blood glucose levels were measured using the colorimetry method (ADVIA 1800; Siemens medical Sol., USA), and fasting insulin levels were measured in accordance with the immunoradiometric assay (SR-300; Stratec, Germany).

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Additionally, insulin resistance was estimated using the homeostasis model assessment for insulin resistance (HOMA-IR), defined as the product of fasting glucose level (mg/dL) and serum insulin level (uIU/mL) divided by 405. Homeostasis model assessment of beta-cell function (HOMA-β) was caluculated as 360 × serum insulin / (fasting glucose − 63) (Matthews et al. 1985, 412-9). Serum ALT, AST, and γ-GTP were measured using the enzymatic methods (ADVIA 1800; Siemens medical Sol., USA). The inter-assay coefficient of variation of ALT was 3.1% at 37 U/L and 1.6% at 152 U/L, and the inter-assay coefficient of variation of AST was 3.3% at 42 U/L and 2.3% at 188 U/L.

C. Definition of Diseases

Diabetes was defined as fasting blood glucose ≥ 126 mg/dL or current treatment using oral antidiabetic agents or insulin. Hypertension was defined as SBP ≥ 140 mmHg, DBP ≥ 90 mmHg, or current treatment by anti-hypertensive agents. Dyslipidemia was defined as total cholesterol ≥ 230 mg/dL, HDL cholesterol < 40 mg/dL, LDL cholesterol ≥ 150 mg/dL, triglycerides ≥ 200 mg/dL, or current treatment by antilipidemic agents. A family history of diabetes was defined as parents, brothers, or sisters of the participants being diagnosed with diabetes by a physician.

D. Statistical Analysis

I evaluated differences in the baseline characteristics of respondents and non-respondents to follow-up evaluation (Table 1) and in the baseline characteristics of study participants according to sex, ALT or AST levels, and the development of diabetes at follow-up, respectively (Tables 2, 3, and 4). Continuous variables were described as means and standard

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deviation (for normally distributed variables) or as median and interquartile range (for skewed variables), and tested by independent t-test and Wilcoxon rank sum test, respectively. Categorical variables were described as numbers (percentages) and tested by chi-square tests.

Multiple logistic regression analyses were used to assess the independent association of the incident diabetes with BMI and liver enzyme levels in two adjusted models; firstly adjusted for age, sex, study year, and residential area (Gangwha, Pyeongchang, and Wonju), then secondly additionally adjusted for hypertension, family history of diabetes, smoking status, alcohol intake, regular exercise, fasting blood glucose, and ALT (when the association between BMI and diabetes was assessed) or BMI (when the association between ALT or AST and diabetes was assessed). Menopausal status was adjusted only for analysis of women. BMI was analyzed as both a continuous variable (1 kg/m^2) and quartile groups (<22.4, 22.4-<24.2, 24.2-<26.4, and ≥26.4 kg/m^2). Serum ALT and AST were analyzed as both a continuous (10 U/L) and quartile groups, respectively (ALT, < 16, 16 -< 20, 20 -< 27, and ≥ 27 U/L; AST, < 20, 20 -< 24, 24 -< 28, and ≥ 28 U/L) (Tables 5 and 6).

To assess whether the association between BMI and incident diabetes differs according to serum ALT or AST levels, multiple logistic regression models were used after stratification into the two groups with the median (ALT, 20 U/L; AST, 24 U/L) or the three groups with the tertiles (ALT, 17 and 24 U/L; AST, 21 and 27 U/L) of ALT and AST, respectively (Tables 7, 12 and 13).

Furthermore, I performed the several sensitivity analyses to test the robustness of the associations as follows. Waist circumference was used instead of BMI. Waist circumference was analyzed as both a continuous (1 cm) and sex-specific quartile groups (men, < 81.5, 81.5

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-< 87.0, 87.0 -< 91.4, and ≥ 91.4 cm; women, < 76.0, 76.0 -< 82.0, 82.0 -< 88.2, and ≥ 88.2 cm) (Table 8). Participants with excess alcohol consumption, ≥ 50 grams/day, were excluded to avoid the presence of alcoholic liver disease (Table 9). Sex-specific analyses were performed (Tables 10 and 11).

SAS version 9.2 (SAS Institute, Cary, NC, USA) was used for all statistical analyses and statistical significance was defined as p-value<0.05, two-tailed.

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Ⅲ. RESULTS

A. Baseline Characteristics of Respondents and Non-respondents to Follow-up Evaluation

Table 1 presents baseline characteristics of respondents and non-respondents to follow-up evaluation. Respondents to follow-up evaluation were relatively younger, had significantly higher height, weight, BMI, waist circumference, DBP, and LDL cholesterol levels, and reported higher frequency of regular exercise than non-respondents at baseline. However, HDL cholesterol, triglycerides, γ-GTP, and insulin levels, HOMA-IR, and HOMA-β, and the frequency of cigarette smoking were lower in respondents than in non-respondents. Meanwhile, SBP, total cholesterol, ALT, AST, and fasting glucose levels, the prevalences of hypertension, dyslipidemia, and family history of diabetes, and the frequency of alcohol drinking were similar between respondents and non-respondents.

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Table 1. Comparison of baseline characteristics of respondents and non-respondents to follow-up evaluation

Variables	Respondents to f/u (n=7,445)	Non-respondents to f/u (n=3,170)	*p*-value
Men	2955 (39.7)	1200 (37.9)	0.080
Age, years	55.5 ± 8.2	56.2 ± 9.4	<0.001
Height, cm	158.8 ± 8.3	158.2 ± 8.4	0.001
Weight, kg	62.1 ± 9.9	61.3 ± 10.2	<0.001
Body mass index, kg/m^2	24.6 ± 3.1	24.4 ± 3.3	0.014
Waist circumference, cm	84.5 ± 8.7	83.4 ± 9.0	<0.001
Systolic BP, mmHg	125.2 ± 17.7	124.8 ± 18.6	0.318
Diastolic BP, mmHg	79.4 ± 11.6	78.1 ± 12.1	<0.001
Total cholesterol, mg/dL	198.7 ± 36.8	198.2 ± 35.7	0.507
HDL cholesterol, mg/dL	44.9 ± 10.7	45.3 ± 11.6	0.048
LDL cholesterol, mg/dL	126.1 ± 32.2	124.0 ± 31.9	0.003
Triglycerides, mg/dL	120 [85, 175]	125 [89, 179]	0.002
ALT, U/L	21 [16, 28]	21 [16, 28]	0.258
AST, U/L	24 [20, 29]	24 [20, 28]	0.188
γ-GTP, U/L	19 [13, 34]	19 [13, 36]	0.024
Glucose, mg/dL	92 [86, 100]	92 [86, 100]	0.976
Insulin, uIU/mL	7.5 [5.8, 10.0]	7.7 [6.0, 10.6]	<0.001
HOMA-IR	1.7 [1.3, 2.5]	1.8 [1.3, 2.6]	<0.001
HOMA-β	95 [70, 131]	98 [69, 142]	0.002
Hypertension	3303 (44.4)	1387 (43.8)	0.576
Dyslipidemia	4279 (57.5)	1835 (57.9)	0.710
Family history of diabetes	996 (13.4)	437 (13.8)	0.595
Current smokers	1072 (14.4)	537 (16.9)	<0.001
Current alcohol drinkers	3075 (41.3)	1317 (41.6)	0.080
Regular exercisers	2591 (34.9)	921 (29.2)	<0.001
Residential area			
Gangwha	2705 (36.3)	1513 (47.7)	
Pyeongchang	2051 (27.6)	729 (23.0)	<0.001
Wonju	2689 (36.1)	928 (29.3)	

Data are expressed as numbers (percent), means ± standard deviation, or medians [inter quartile range].

p-value was derived from chi-square test, independent t-test, or Willcoxon rank sum test.

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B. Baseline Characteristics of the Study Participants

Table 2 presents the baseline characteristics of the study participants. This study consisted of 2,497 men with a mean age of 56.4 years and 3,987 women with a mean age of 54.2 years. The mean BMI in men was significantly lower than that in women (24.3 versus 24.5 kg/m^2, p = 0.012) and the mean waist circumference was significantly higher than that in women (86.4 versus 82.4 cm, $p < 0.001$). The median serum ALT and AST in men were significantly higher than that in women (ALT, 24 versus 18 U/L, $p < 0.001$; AST, 26 versus 23 U/L, $p < 0.001$). The median fasting glucose concentration in men was significantly higher than that in women (93 versus 89 mg/dL, $p < 0.001$). The prevalence of hypertension in men was significantly higher than that in women (45.9 versus 39.0%, $p < 0.001$) and the prevalence of family history of diabetes in men was significantly lower than that in women (9.3 versus 13.5%, $p < 0.001$). Cigarette smoking and alcohol drinking were more frequent in men than in women. But the frequency of regular exercise was similar between men and women.

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Table 2. Baseline characteristics of the study participants

Variables	Total (N=6,484)	Men (n=2,497)	Women (n=3,987)	*p*-value
Age, years	55.1 ± 8.1	56.4 ± 8.3	54.2 ± 8.0	<0.001
Height, cm	158.7 ± 8.2	166.3 ± 5.7	153.9 ± 5.5	<0.001
Weight, kg	61.7 ± 9.8	67.4 ± 9.2	58.2 ± 8.3	<0.001
Body mass index, kg/m^2	24.5 ± 3.0	24.3 ± 2.9	24.5 ± 3.2	0.012
Waist circumference, cm	83.9 ± 8.6	86.4 ± 7.5	82.4 ± 8.9	<0.001
Systolic BP, mmHg	124.5 ± 17.5	126.4 ± 16.8	123.3 ± 17.8	<0.001
Diastolic BP, mmHg	79.3 ± 11.6	81.7 ± 11.0	77.8 ± 11.7	<0.001
Total cholesterol, mg/dL	198.8 ± 36.0	194.6 ± 34.6	201.4 ± 36.6	<0.001
HDL cholesterol, mg/dL	45.2 ± 10.7	43.3 ± 10.7	46.3 ± 10.5	<0.001
LDL cholesterol, mg/dL	126.5 ± 31.8	121.0 ± 30.5	129.8 ± 32.1	<0.001
Triglycerides, mg/dL	117 [83, 171]	131 [93, 196]	110 [79, 156]	<0.001
ALT, U/L	20 [16, 27]	24 [18, 33]	18 [15, 24]	<0.001
AST, U/L	24 [20, 28]	26 [22, 32]	23 [19, 26]	<0.001
γ-GTP, U/L	19 [13, 32]	31 [20, 54]	15 [11, 21]	<0.001
Glucose, mg/dL	91 [85, 97]	93 [87, 100]	89 [85, 95]	<0.001
Insulin, uIU/mL	7.2 [5.7, 9.5]	6.8 [5.4, 8.9]	7.5 [5.9, 9.8]	<0.001
HOMA-IR	1.6 [1.3, 2.2]	1.6 [1.2, 2.1]	1.7 [1.3, 2.2]	<0.001
HOMA-β	97 [73, 129]	84 [64, 112]	105 [81, 138]	<0.001
Hypertension	2700 (41.6)	1145 (45.9)	1555 (39.0)	<0.001
Dyslipidemia	3598 (55.5)	1497 (60.0)	2101 (52.7)	<0.001
Family history of diabetes	770 (11.9)	232 (9.3)	538 (13.5)	<0.001
Current smokers	919 (14.2)	854 (34.2)	65 (1.6)	<0.001
Current alcohol drinkers	2705 (41.7)	1661 (66.5)	1044 (26.2)	<0.001
Regular exercisers	2210 (34.1)	875 (35.0)	1335 (33.5)	0.207
Residential area				
Gangwha	2354 (36.3)	904 (36.2)	1450 (36.4)	
Pyeongchang	1797 (27.7)	682 (27.3)	1115 (28.0)	0.766
Wonju	2333 (36.0)	911 (36.5)	1422 (35.7)	
Menopause	NA	NA	2720 (68.2)	NA

p-value was derived from independent t-test, Willcoxon rank sum test, or chi-square test.

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C. Baseline Characteristics of the Study Participants according to ALT or AST Levels

Tables 3A and 3B present the baseline characteristics of the study participants according to ALT or AST levels, respectively. The low and high groups were classified based on the median of ALT or AST concentrations (ALT, 20 U/L; AST, 24 U/L). Compared to people with low ALT level, people with high ALT level were older and had higher BMI, bigger waist circumference, and higher fasting glucose and insulin levels and HOMA-IR. The prevalence of hypertension and the frequencies of cigarette smoking and alcohol drinking were higher in the high ALT group than in the low ALT group. Regular exercising was less frequent in the high ALT group than in the low ALT group. But the prevalence of family history of diabetes was similar between the two groups.

Meanwhile, people with high AST level were older and had higher BMI, bigger waist circumference, and higher fasting glucose and insulin levels and HOMA-IR than that in people with low AST level. The prevalence of hypertension and the frequencies of cigarette smoking and alcohol drinking were higher in the high AST group than in the low AST group. The prevalence of family history of diabetes and the frequency of regular exercising were lower in the high AST group than in the low AST group.

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Table 3A. Baseline characteristics of the study participants according to ALT levels

Variables	Low ALT < 20 U/L (n=3,206)	High ALT ≥ 20 U/L (n=3,458)	*p*-value
Men	767 (25.4)	1730 (50.0)	<0.001
Age, years	54.7 ± 8.4	55.4 ± 7.9	<0.001
Height, cm	157.3 ± 7.6	159.9 ± 8.5	<0.001
Weight, kg	58.9 ± 8.5	64.2 ± 10.1	<0.001
Body mass index, kg/m^2	23.8 ± 2.8	25.1 ± 3.1	<0.001
Waist circumference, cm	81.5 ± 8.4	86.0 ± 8.2	<0.001
Systolic BP, mmHg	121.9 ± 17.2	126.8 ± 17.4	<0.001
Diastolic BP, mmHg	77.4 ± 11.4	81.0 ± 11.6	<0.001
Total cholesterol, mg/dL	194.1 ± 33.2	202.9 ± 37.8	<0.001
HDL cholesterol, mg/dL	45.7 ± 10.7	44.7 ± 10.7	<0.001
LDL cholesterol, mg/dL	124.9 ± 29.2	127.9 ± 33.9	<0.001
Triglycerides, mg/dL	103 [75, 144]	132 [93, 197]	<0.001
AST, U/L	21 [18, 23]	27 [24, 33]	<0.001
γ-GTP, U/L	14 [11, 20]	26 [17, 46]	<0.001
Glucose, mg/dL	89 [84, 95]	92 [87, 99]	<0.001
Insulin, uIU/mL	6.8 [5.5, 8.7]	7.7 [6.0, 10.2]	<0.001
HOMA-IR	1.5 [1.2, 2.0]	1.8 [1.3, 2.4]	<0.001
HOMA-β	96 [74, 126]	98 [73, 132]	0.078
Hypertension	1071 (35.4)	1629 (47.1)	<0.001
Dyslipidemia	1434 (47.4)	2164 (62.6)	<0.001
Family history of diabetes	373 (12.3)	397 (11.5)	0.312
Current smokers	297 (9.8)	622 (18.0)	<0.001
Current alcohol drinkers	1059 (35.0)	1646 (47.6)	<0.001
Regular exercisers	1073 (35.5)	1137 (32.9)	0.031
Residential area			
Gangwha	1192 (39.4)	1162 (33.6)	
Pyeongchang	718 (23.7)	1079 (31.2)	<0.001
Wonju	1116 (36.9)	1217 (35.2)	

Data are expressed as numbers (percent), means ± standard deviation, or medians [inter quartile range].

p-value was derived from chi-square test, independent t-test, or Willcoxon rank sum test.

The ALT groups were classified based on the median (20 U/L).

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Table 3B. Baseline characteristics of the study participants according to AST levels

Variables	Low AST < 24 U/L (n=3,148)	High AST ≥ 24 U/L (n=3,336)	*p*-value
Men	872 (27.7)	1625 (48.7)	<0.001
Age, years	53.8 ± 8.1	56.3 ± 8.0	<0.001
Height, cm	157.8 ± 7.7	159.5 ± 8.6	<0.001
Weight, kg	60.5 ± 8.9	62.9 ± 10.4	<0.001
Body mass index, kg/m^2	24.3 ± 2.9	24.7 ± 3.2	<0.001
Waist circumference, cm	83.1 ± 8.4	84.7 ± 8.7	<0.001
Systolic BP, mmHg	122.2 ± 17.1	126.6 ± 17.6	<0.001
Diastolic BP, mmHg	77.5 ± 11.3	81.0 ± 11.7	<0.001
Total cholesterol, mg/dL	195.7 ± 34.2	201.6 ± 37.4	<0.001
HDL cholesterol, mg/dL	44.4 ± 10.0	45.9 ± 11.2	<0.001
LDL cholesterol, mg/dL	126.0 ± 30.0	127.0 ± 33.5	0.216
Triglycerides, mg/dL	111 [80, 156]	124 [87, 188]	<0.001
ALT, U/L	17 [14, 20]	26 [20, 35]	<0.001
γ-GTP, U/L	15 [11, 22]	24 [15, 46]	<0.001
Glucose, mg/dL	90 [85, 96]	92 [86, 98]	<0.001
Insulin, uIU/mL	7.1 [5.7, 9.3]	7.3 [5.7, 9.7]	0.007
HOMA-IR	1.6 [1.2, 2.1]	1.7 [1.3, 2.3]	<0.001
HOMA-β	98 [76, 130]	96 [71, 129]	0.013
Hypertension	1116 (35.5)	1584 (47.5)	<0.001
Dyslipidemia	1634 (51.9)	1964 (58.9)	<0.001
Family history of diabetes	419 (13.3)	351 (10.5)	<0.001
Current smokers	347 (11.0)	572 (17.2)	<0.001
Current alcohol drinkers	1123 (35.7)	1582 (47.4)	<0.001
Regular exercisers	1140 (36.2)	1070 (32.1)	<0.001
Residential area			
Gangwha	1397 (44.4)	957 (28.7)	
Pyeongchang	655 (20.8)	1142 (34.2)	<0.001
Wonju	1096 (34.8)	1237 (37.1)	

Data are expressed as numbers (percent), means ± standard deviation, or medians [inter quartile range].

p-value was derived from chi-square test, independent t-test, or Willcoxon rank sum test.

The AST groups were classified based on the median (24 U/L).

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D. Baseline Characteristics of the Study Population according to the Development of Diabetes at Follow-up

Table 4 presents the baseline characteristics of the study population according to the development of diabetes at follow-up. The median follow-up time was 4.5 years. During this period, 304 participants (4.7%) developed incident diabetes. People who developed diabetes were older, and had higher BMI, bigger waist circumference, higher serum ALT, AST, fasting glucose, and insulin levels and HOMA-IR and lower HOMA-β than those who did not. The prevalences of hypertension and family history of diabetes and the frequency of cigarette smoking in those who developed diabetes was higher than those who did not. However, the frequencies of alcohol drinking and regular exercise were similar between subjects who developed diabetes and those who did not.

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Table 4. Baseline characteristics of the study participants according to the development of diabetes at follow-up

Variables	Non-diabetes at f/u (n=6,180, 95.3%)	Diabetes at f/u (n=304, 4.7%)	*p*-value
Men	2348 (38.0)	149 (49.0)	<0.001
Age, years	55.0 ± 8.2	57.0 ± 7.8	<0.001
Height, cm	158.6 ± 8.2	159.8 ± 8.5	0.016
Weight, kg	61.5 ± 9.7	66.5 ± 10.0	<0.001
Body mass index, kg/m^2	24.4 ± 3.0	26.0 ± 3.2	<0.001
Waist circumference, cm	83.7 ± 8.6	88.9 ± 7.8	<0.001
Systolic BP, mmHg	124.3 ± 17.5	129.1 ± 17.7	<0.001
Diastolic BP, mmHg	79.2 ± 11.7	81.5 ± 11.0	<0.001
Total cholesterol, mg/dL	198.4 ± 35.7	205.3 ± 40.6	0.004
HDL cholesterol, mg/dL	45.3 ± 10.7	42.1 ± 9.4	<0.001
LDL cholesterol, mg/dL	126.4 ± 31.7	127.8 ± 33.5	0.482
Triglycerides, mg/dL	115 [83, 169]	155 [111, 230]	<0.001
ALT, U/L	20 [16, 27]	25 [19, 36]	<0.001
AST, U/L	24 [20, 28]	26 [22, 32]	<0.001
γ-GTP, U/L	18 [13, 31]	29 [20, 52]	<0.001
Glucose, mg/dL	90 [85, 96]	106 [99, 115]	<0.001
Insulin, uIU/mL	7.2 [5.7, 9.4]	8.2 [6.4, 11.3]	<0.001
HOMA-IR	1.6 [1.2, 2.2]	2.1 [1.7, 3.1]	<0.001
HOMA-β	98 [75, 130]	73 [56, 101]	<0.001
Hypertension	2537 (41.1)	163 (53.6)	<0.001
Dyslipidemia	3381 (54.7)	217 (71.4)	<0.001
Family history of diabetes	722 (11.7)	48 (15.8)	0.038
Current smokers	850 (13.8)	69 (22.7)	<0.001
Current alcohol drinkers	2577 (41.7)	128 (42.1)	0.936
Regular exercisers	2120 (34.3)	90 (29.6)	0.104
Residential area			
Gangwha	2247 (36.4)	107 (35.2)	
Pyeongchang	1720 (27.8)	77 (25.3)	0.398
Wonju	2213 (35.8)	120 (39.5)	

Data are expressed as means ± standard deviation, medians [inter quartile range], or numbers (percent).

p-value was derived from independent t-test, Willcoxon rank sum test, or chi-square test.

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E. Associations between Obesity and the Incident Diabetes

Independent associations between BMI and the incident diabetes were assessed by multiple logistic regression models (Table 5). The adjusted odds ratio (OR) for incident diabetes per one kg/m^2 increase in BMI was 1.13 (95% CI, 1.09-1.18) after adjusting for age, sex, study year, residential area, hypertension, family history of diabetes, smoking status, alcohol intake, exercise, fasting blood glucose, and ALT. Compared with the first BMI quartile, the adjusted ORs for incident diabetes of the second, third, and fourth BMI quartiles were 1.61 (0.99 – 2.63), 2.12 (1.33 – 3.36), and 2.93 (1.87 – 4.59), respectively (p-trend < 0.001) in the fully adjusted model. When I analyzed with three groups (< 23, 23 -< 25, ≥ 25 kg/m^2) by World Health Organization classification instead of quartiles of BMI, similar results were observed (data not shown).

In sensitivity analysis, waist circumference was used instead of BMI. The adjusted OR for incident diabetes per one cm increase in waist circumference was 1.04 (1.02 – 1.06) in the same logistic regression model. Compared with the first waist circumference quartile, the fully adjusted ORs for incident diabetes of the second, third, and fourth waist circumference quartiles were 1.90 (1.12 – 3.23), 1.95 (1.17 – 3.23), and 2.95 (1.80 – 4.84), respectively (p-trend < 0.001)

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Table 5. Odds ratio for incident diabetes according to baseline obesity

Obesity	Case/no. of participants (%)	Model 1		Model 2	
		OR	(95% CI)	OR	(95% CI)
BMI					
Q1 (<22.4 kg/m^2)	31 / 1622 (1.9)	reference		reference	
Q2 (22.4-<24.2 kg/m^2)	57 / 1620 (3.5)	1.94	(1.24 – 3.02)	1.61	(0.99 – 2.63)
Q3 (24.2-<26.4 kg/m^2)	86 / 1621 (5.3)	2.94	(1.93 – 4.47)	2.12	(1.33 – 3.36)
Q4 (≥26.4 kg/m^2)	130 / 1321 (8.0)	4.67	(3.13 – 6.97)	2.93	(1.87 – 4.59)
p-trend		<0.001		<0.001	
per 1 kg/m^2		1.19	(1.15 – 1.23)	1.13	(1.09 – 1.18)
Waist circumference*					
Q1	23 / 1539 (1.5)	reference		reference	
Q2	59 / 1642 (3.6)	2.49	(1.53 – 4.06)	1.90	(1.12 – 3.23)
Q3	89 / 1677 (5.3)	3.61	(2.26 – 5.75)	1.95	(1.17 – 3.23)
Q4	133 / 1626 (8.2)	5.55	(3.53 – 8.74)	2.95	(1.80 – 4.84)
p-trend		<0.001		<0.001	
per 1 cm		1.07	(1.05 – 1.08)	1.04	(1.02 – 1.06)

Model 1: adjusted for age, sex, study year, and residential area

Model 2: additionally adjusted for hypertension, family history of diabetes, smoking status, alcohol intake, exercise, fasting glucose, and ALT

*Waist circumference was classified into sex-specific quartile groups (Men, < 81.5, 81.5 -< 87.0, 87.0 -< 91.4, ≥ 91.4 cm; Women, < 76.0, 76.0 -< 82.0, 82.0 -< 88.2, ≥ 88.2 cm).

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F. Associations between Serum ALT or AST and the Incident Diabetes

Table 6 presents the associations between serum ALT or AST and the incident diabetes using the multiple logistic regression models. First, the adjusted OR for incident diabetes per 10 U/L increase in ALT was 1.06 (1.02 – 1.09) in age, sex, study year, and residential area–adjusted model. However, the association was disappeared after further adjustment for hypertension, family history of diabetes, smoking status, alcohol intake, exercise, fasting glucose, and BMI. When I analyzed ALT level as quartiles, the fully adjusted ORs for incident diabetes of the second, third, and fourth ALT quartiles were 1.51 (0.91 – 2.50), 1.66 (1.03 – 2.69), and 1.97 (1.23 – 3.16), respectively (p-trend = 0.006), compared with the first ALT quartile.

When I analyzed with AST, similar results were observed. The adjusted ORs for incident diabetes per 10 U/L increase in AST were not significant. When AST level was analyzed as quartiles, in the fully adjusted model, the adjusted ORs for incident diabetes of the second, third, and fourth AST quartiles were 1.50 (0.95 – 2.37), 1.64 (1.03 – 2.60), and 1.60 (1.02 – 2.51), respectively (p-trend = 0.083), compared with the first AST quartile.

Compared with low ALT and AST group, the fully adjusted ORs for incident diabetes of ‘high ALT and low AST’ or ‘low ALT and high AST’ group and high ALT and AST group were 1.60 (1.08 – 2.35) and 1.53 (1.07 – 2.17), respectively.

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Table 6. Odds ratio for incident diabetes according to baseline ALT or AST

Liver enzymes	Case/no. of participants (%)	Model 1		Model 2	
		OR	(95% CI)	OR	(95% CI)
ALT					
Q1 (<16 U/L)	28 / 1471 (1.9)		reference		reference
Q2 (16-<20 U/L)	56 / 1555 (3.6)	1.85	(1.16 – 2.93)	1.51	(0.91 – 2.50)
Q3 (20-<27 U/L)	86 / 1698 (5.1)	2.53	(1.64 – 3.93)	1.66	(1.03 – 2.69)
Q4 (≥27 U/L)	134 / 1760 (7.6)	3.99	(2.61 – 6.10)	1.97	(1.23 – 3.16)
p-trend			<0.001		0.006
per 10 U/L		1.06	(1.02 – 1.09)	1.03	(0.99 – 1.07)
AST					
Q1 (<20 U/L)	36 / 1292 (2.8)		reference		reference
Q2 (20-<24 U/L)	77 / 1856 (4.2)	1.38	(0.92 – 2.07)	1.50	(0.95 – 2.37)
Q3 (24-<28 U/L)	75 / 1469 (5.1)	1.61	(1.06 – 2.44)	1.64	(1.03 – 2.60)
Q4 (≥28 U/L)	116 / 1867 (6.2)	1.84	(1.23 – 2.75)	1.60	(1.02 – 2.51)
p-trend			0.002		0.083
per 10 U/L		1.01	(0.99 – 1.03)	1.00	(0.96 – 1.05)
ALT & AST					
Both low	60 / 2305 (2.6)		reference		reference
Either high*	77 / 1564 (4.9)	1.76	(1.24 – 2.50)	1.60	(1.08 – 2.35)
Both high	167 / 2615 (6.4)	2.24	(1.64 – 3.07)	1.53	(1.07 – 2.17)
p-trend			<0.001		0.026

Model 1: adjusted for age, sex, study year, and residential area

Model 2: additionally adjusted for hypertension, family history of diabetes, smoking status, alcohol intake, exercise, fasting glucose, and body mass index

* 'High ALT and low AST' or 'low ALT and high AST'

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G. Associations between Obesity and the Incident Diabetes according to Serum ALT or AST Levels

In Table 7, the multiple logistic regression models were used to examine the independent associations of BMI with the incident diabetes after stratification into the low and high groups based on the median liver enzyme levels. In people with high ALT levels, compared with the first BMI quartile, the adjusted ORs for incident diabetes of the second, third, and fourth BMI quartiles were 1.88 (0.98 – 3.62), 2.24 (1.21 – 4.13), and 3.32 (1.84 – 5.99), respectively (p-trend < 0.001) after adjustment for all potential confounders previously defined, while in people with low ALT levels, high BMI was not significantly associated with the incident diabetes. Nevertheless, the interaction terms failed to reach statistical significance possibly due to the small number of cases.

Similarly, in people with high AST levels, the adjusted ORs for incident diabetes of the second, third, and fourth BMI quartiles were 2.14 (1.13 – 4.08), 2.44 (1.32 – 4.53), and 3.65 (2.02 – 6.60), respectively (p-trend < 0.001), while in people with low AST levels, the adjusted OR for incident diabetes per 1 kg/m^2 increase in BMI was 1.10 (1.02 – 1.19). However, when the BMI was analyzed as quartiles in the low AST group, the associations was not significant.

In sensitivity analysis, I used waist circumference instead of BMI (Table 8). In people with high ALT levels, compared with the first waist circumference quartile, the fully adjusted ORs for incident diabetes of the second, third, and fourth waist circumference quartiles were 1.51 (0.84 – 2.73), 1.81 (1.04 – 3.15), and 2.53 (1.48 – 4.34), respectively (p-trend < 0.001), while in people with low ALT levels, the relatively weak associations between waist circumference and the incident diabetes were observed.

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Similarly, in people with high AST levels, the fully adjusted ORs for incident diabetes of the second, third, and fourth waist circumference quartiles were 1.77 (0.98 – 3.19), 2.08 (1.18 – 3.68), and 2.84 (1.64 – 4.92), respectively (p-trend < 0.001), while in people with low AST levels, the relatively weak associations between waist circumference and the incident diabetes were also observed. When the analysis was restricted to non-heavy alcohol drinkers, similar results were observed (Table 9).

Additionally, I performed these analyses separately in men and women (Tables 10 and 11). In men with high ALT levels, the fully adjusted ORs for incident diabetes of the second, third, and fourth BMI quartiles were 2.43 (0.81 – 7.27), 3.48 (1.22 – 9.89), and 3.64 (1.30 – 10.16), respectively (p-trend = 0.012), while in men with low ALT levels, the fully adjusted ORs for incident diabetes of the second, third, and fourth BMI quartiles were 1.58 (0.61 – 4.06), 1.33 (0.49 – 3.62), and 3.43 (1.33 – 8.85), respectively (p-trend = 0.018). Similarly, in men with high AST levels, the fully adjusted ORs for incident diabetes of the second, third, and fourth BMI quartiles were 2.23 (0.89 – 5.61), 2.77 (1.13 – 6.77), and 3.94 (1.66 – 9.38), respectively (p-trend = 0.001), while in men with low AST levels, the fully adjusted ORs for incident diabetes of the second, third, and fourth BMI quartiles were 1.75 (0.59 – 5.21), 2.32 (0.81 – 6.59), and 2.94 (1.04 – 8.28), respectively (p-trend = 0.033). In women with high ALT levels, the fully adjusted ORs for incident diabetes of the second, third, and fourth BMI quartiles were 0.89 (0.38 – 2.10), 1.30 (0.61 – 2.76), and 2.37 (1.18 – 4.78), respectively (p-trend = 0.001), while in women with low ALT levels, high BMI was not significantly associated with the incident diabetes. Similarly, in women with high AST levels, the fully adjusted ORs for incident diabetes of the second, third, and fourth BMI quartiles were 1.58 (0.64 – 3.88), 1.50 (0.64 – 3.54), and 3.50 (1.59 – 7.73), respectively (p-trend < 0.001), while in women with

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low AST levels, high BMI was not significantly associated with the incident diabetes.

I assessed the relationships of obesity with the incident diabetes after stratification into the three groups based on the tertiles of liver enzyme levels (Tables 12 and 13). In the lower liver enzyme groups, the associations between high BMI and the incident diabetes were significant in the middle and upper liver enzyme groups but not significant. Meanwhile, the associations between big waist circumference and the incident diabetes were significant only in the upper liver enzyme groups.

Figure 2 displays the combined effects of obesity and liver enzymes on the incident diabetes. The adjusted ORs for incident diabetes became higher as obesity increased and were higher in high liver enzyme groups than in low liver enzyme groups.

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Table 7. Odds ratio for incident diabetes according to baseline BMI after stratification into the two groups of liver enzymes

BMI	Case/no. of participants (%)	OR (95% CI)*	Case/no. of participants (%)	OR (95% CI)*
	Low ALT < 20 U/L (n=3,026)		**High ALT ≥ 20 U/L (n=3,458)**	
Q1 (<22.4 kg/m^2)	15 / 962 (1.6)	reference	16 / 660 (2.4)	reference
Q2 (22.4-<24.2 kg/m^2)	18 / 840 (2.1)	1.17 (0.54 – 2.53)	39 / 780 (5.0)	1.88 (0.98 – 3.62)
Q3 (24.2-<26.4 kg/m^2)	24 / 698 (3.4)	1.77 (0.84 – 3.72)	62 / 923 (6.7)	2.24 (1.21 – 4.13)
Q4 (≥26.4 kg/m^2)	27 / 526 (5.1)	1.78 (0.84 – 3.78)	103 / 1095 (9.4)	3.32 (1.84 – 5.99)
p-trend		0.079		<0.001
per 1 kg/m^2		1.08 (0.99 – 1.18)		1.13 (1.08 – 1.19)
p-interaction		0.829		
	Low AST < 24 U/L (n=3,148)		**High AST ≥ 24 U/L (n=3,336)**	
Q1 (<22.4 kg/m^2)	15 / 825 (1.8)	reference	16 / 797 (2.0)	reference
Q2 (22.4-<24.2 kg/m^2)	19 / 845 (2.3)	1.07 (0.49 – 2.32)	38 / 775 (4.9)	2.14 (1.13 – 4.08)
Q3 (24.2-<26.4 kg/m^2)	36 / 782 (4.6)	1.61 (0.79 – 3.29)	50 / 839 (6.0)	2.44 (1.32 – 4.53)
Q4 (≥26.4 kg/m^2)	43 / 696 (6.2)	1.90 (0.93 – 3.85)	87 / 925 (9.4)	3.65 (2.02 – 6.60)
p-trend		0.032		<0.001
per 1 kg/m^2		1.10 (1.02 – 1.19)		1.14 (1.08 – 1.20)
p-interaction		0.380		

*Adjusted for age, sex, study year, residential area, hypertension, family history of diabetes, smoking status, alcohol intake, exercise, fasting glucose, and ALT or AST.

The low and high liver enzyme groups were classified based on the median.

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Table 8. Odds ratio for incident diabetes according to baseline waist circumference after stratification into the two groups of liver enzymes

Waist circumference*	Case/no. of participants (%)	OR (95% CI)†	Case/no. of participants (%)	OR (95% CI)†
	Low ALT < 20 U/L (n=3,026)		**High ALT ≥ 20 U/L (n=3,458)**	
Q1	11 / 930 (1.2)	reference	12 / 609 (2.0)	reference
Q2	22 / 840 (2.6)	1.92 (0.87 – 4.23)	37 / 802 (4.6)	1.87 (0.91 – 3.83)
Q3	29 / 729 (4.0)	1.45 (0.66 – 3.20)	60 / 948 (6.3)	2.05 (1.03 – 4.05)
Q4	22 / 527 (4.2)	1.61 (0.70 – 3.72)	111 / 1099 (10.1)	3.30 (1.70 – 6.39)
p-trend		0.465		<0.001
per 1 cm		1.02 (0.98 – 1.05)		1.05 (1.02 – 1.07)
p-interaction		0.539		
	Low AST < 24 U/L (n=3,148)		**High AST ≥ 24 U/L (n=3,336)**	
Q1	12 / 768 (1.6)	reference	11 / 771 (1.4)	reference
Q2	23 / 842 (2.7)	1.33 (0.61 – 2.91)	36 / 800 (4.5)	2.57 (1.24 – 5.33)
Q3	36 / 835 (4.3)	1.09 (0.51 – 2.32)	53 / 842 (6.3)	2.93 (1.46 – 5.91)
Q4	42 / 703 (6.0)	1.40 (0.65 – 3.01)	91 / 923 (9.9)	4.64 (2.35 – 9.16)
p-trend		0.520		<0.001
per 1 cm		1.02 (0.99 – 1.05)		1.05 (1.03 – 1.08)
p-interaction		0.572		

*Waist circumference was classified into sex-specific quartile groups (Men, < 81.5, 81.5 -< 87.0, 87.0 -< 91.4, ≥ 91.4 cm; Women, < 76.0, 76.0 -< 82.0, 82.0 -< 88.2, ≥ 88.2 cm).

†Adjusted for age, sex, study year, residential area, hypertension, family history of diabetes, smoking status, alcohol intake, exercise, fasting glucose, and ALT or AST.

The low and high liver enzyme groups were classified based on the median.

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Table 9. Odds ratio for incident diabetes according to baseline BMI after stratification into the two groups of liver enzymes in non-heavy alcohol drinkers

BMI	Case/no. of participants (%)	OR (95% CI)*	Case/no. of participants (%)	OR (95% CI)*
	Low ALT < 20 U/L (n=2,927)		**High ALT ≥ 20 U/L (n=3,149)**	
Q1 (<22.4 kg/m²)	14 / 925 (1.5)	reference	14 / 594 (2.4)	reference
Q2 (22.4-<24.2 kg/m²)	18 / 812 (2.2)	1.25 (0.57 – 2.74)	34 / 707 (4.8)	1.78 (0.89 – 3.59)
Q3 (24.2-<26.4 kg/m²)	23 / 676 (3.4)	1.79 (0.83 – 3.86)	58 / 843 (6.9)	2.17 (1.13 – 4.17)
Q4 (≥26.4 kg/m²)	27 / 514 (5.3)	1.84 (0.85 – 4.00)	93 / 1005 (9.3)	3.24 (1.73 – 6.09)
p-trend		0.080		<0.001
per 1 kg/m²		1.08 (0.99 – 1.18)		1.13 (1.07 – 1.19)
p-interaction		0.879		
	Low AST < 24 U/L (n=2,627)		**High AST ≥ 24 U/L (n=3,449)**	
Q1 (<22.4 kg/m²)	12 / 688 (1.7)	reference	16 / 831 (1.9)	reference
Q2 (22.4-<24.2 kg/m²)	13 / 699 (1.9)	0.92 (0.38 – 2.26)	39 / 820 (4.8)	2.21 (1.16 – 4.23)
Q3 (24.2-<26.4 kg/m²)	29 / 664 (4.4)	1.70 (0.77 – 3.78)	52 / 855 (6.1)	2.33 (1.25 – 4.36)
Q4 (≥26.4 kg/m²)	30 / 576 (5.2)	1.66 (0.73 – 3.76)	90 / 943 (9.5)	3.74 (2.06 – 6.81)
p-trend		0.092		<0.001
per 1 kg/m²		1.07 (0.98 – 1.17)		1.14 (1.09 – 1.21)
p-interaction		0.266		

*Adjusted for age, sex, study year, residential area, hypertension, family history of diabetes, smoking status, alcohol intake, exercise, fasting glucose, and ALT or AST.

The low and high liver enzyme groups were classified based on the median.

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Table 10. Odds ratio for incident diabetes according to baseline BMI after stratification into the two groups of liver enzymes in men

BMI	Case/no. of participants (%)	OR (95% CI)*	Case/no. of participants (%)	OR (95% CI)*
	Low ALT < 24 U/L (n=1,183)		**High ALT ≥ 24 U/L (n=1,314)**	
Q1 (<22.4 kg/m²)	10 / 413 (2.4)	reference	5 / 212 (2.4)	reference
Q2 (22.4-<24.3 kg/m²)	13 / 325 (4.0)	1.58 (0.61 – 4.06)	19 / 299 (6.4)	2.43 (0.81 – 7.27)
Q3 (24.3-<26.2 kg/m²)	11 / 262 (4.2)	1.33 (0.49 – 3.62)	29 / 363 (8.0)	3.48 (1.22 – 9.89)
Q4 (≥26.2 kg/m²)	21 / 183 (11.5)	3.43 (1.33 – 8.85)	41 / 440 (9.3)	3.64 (1.30 – 10.16)
p-trend		0.018		0.012
per 1 kg/m²		1.14 (1.01 – 1.30)		1.13 (1.03 – 1.23)
p-interaction		0.183		
	Low AST < 26 U/L (n=1,161)		**High AST ≥ 26 U/L (n=1,336)**	
Q1 (<22.4 kg/m²)	7 / 304 (2.3)	reference	8 / 321 (2.5)	reference
Q2 (22.4-<24.3 kg/m²)	14 / 310 (4.5)	1.75 (0.59 – 5.21)	18 / 314 (5.7)	2.23 (0.89 – 5.61)
Q3 (24.3-<26.2 kg/m²)	17 / 302 (5.6)	2.32 (0.81 – 6.59)	23 / 323 (7.1)	2.77 (1.13 – 6.77)
Q4 (≥26.2 kg/m²)	24 / 245 (9.8)	2.94 (1.04 – 8.28)	38 / 378 (10.1)	3.94 (1.66 – 9.38)
p-trend		0.033		0.001
per 1 kg/m²		1.11 (0.99 – 1.25)		1.17 (1.08 – 1.28)
p-interaction		0.944		

*Adjusted for age, study year, residential area, hypertension, family history of diabetes, smoking status, alcohol intake, exercise, fasting glucose, and ALT or AST.

The low and high liver enzyme groups were classified based on the median.

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Table 11. Odds ratio for incident diabetes according to baseline BMI after stratification into the two groups of liver enzymes in women

BMI	Case/no. of participants (%)	OR (95% CI)*	Case/no. of participants (%)	OR (95% CI)*
	Low ALT < 18 U/L (n=1,760)		**High ALT ≥ 18 U/L (n=2,227)**	
Q1 (<22.3 kg/m²)	4 / 549 (0.7)	reference	13 / 447 (2.9)	reference
Q2 (22.3-<24.2 kg/m²)	10 / 522 (1.9)	2.66 (0.73 – 9.72)	14 / 476 (2.9)	0.89 (0.38 – 2.10)
Q3 (24.2-<26.5 kg/m²)	10 / 406 (2.5)	2.02 (0.56 – 7.27)	31 / 590 (5.3)	1.30 (0.61 – 2.76)
Q4 (≥26.5 kg/m²)	12 / 283 (4.2)	2.34 (0.63 – 8.68)	61 / 714 (8.5)	2.37 (1.18 – 4.78)
p-trend		0.351		0.001
per 1 kg/m²		1.02 (0.89 – 1.17)		1.14 (1.07 – 1.21)
p-interaction		0.604		
	Low AST < 23 U/L (n=1,965)		**High AST ≥ 23 U/L (n=2,022)**	
Q1 (<22.3 kg/m²)	7 / 509 (1.4)	reference	10 / 487 (2.1)	reference
Q2 (22.3-<24.2 kg/m²)	8 / 529 (1.5)	0.97 (0.31 – 3.10)	16 / 469 (3.4)	1.58 (0.64 – 3.88)
Q3 (24.2-<26.5 kg/m²)	18 / 492 (3.7)	1.59 (0.57 – 4.41)	23 / 504 (4.6)	1.50 (0.64 – 3.54)
Q4 (≥26.5 kg/m²)	23 / 435 (5.3)	1.86 (0.67 – 5.17)	50 / 562 (8.9)	3.50 (1.59 – 7.73)
p-trend		0.126		<0.001
per 1 kg/m²		1.08 (0.97 – 1.20)		1.16 (1.08 – 1.24)
p-interaction		0.714		

*Adjusted for age, study year, residential area, menopause, hypertension, family history of diabetes, smoking status, alcohol intake, exercise, fasting glucose, and ALT or AST.

The low and high groups were classified based on the median.

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Table 12. Odds ratio for incident diabetes according to baseline BMI after stratification into the three groups of liver enzymes

BMI	Case/no. of participants (%)	OR (95% CI)*	Case/no. of participants (%)	OR (95% CI)*	Case/no. of participants (%)	OR (95% CI)*
	Lower ALT < 17 U/L (n=1,860)		**17 ≤ Middle ALT < 24 U/L (n=2,241)**		**Upper ALT ≥ 24 U/L (n=2,383)**	
Q1 (<22.4 kg/m^2)	7 / 636 (1.1)	reference	13 / 593 (2.2)	reference	11 / 393 (2.8)	reference
Q2 (22.4-<24.2 kg/m^2)	9 / 545 (1.7)	1.37 (0.45 – 4.23)	23 / 572 (4.0)	1.73 (0.79 – 3.77)	25 / 503 (5.0)	1.48 (0.66 – 3.29)
Q3 (24.2-<26.4 kg/m^2)	12 / 407 (3.0)	2.72 (0.93 – 7.99)	25 / 558 (4.5)	1.38 (0.63 – 3.04)	49 / 656 (7.5)	2.31 (1.11 – 4.82)
Q4 (≥26.4 kg/m^2)	11 / 272 (4.0)	2.14 (0.68 – 6.72)	37 / 518 (7.1)	2.45 (1.14 – 5.24)	82 / 831 (9.9)	3.00 (1.48 – 6.07)
p-trend		0.096		0.038		<0.001
per 1 kg/m^2		1.11 (0.97 – 1.26)		1.09 (1.01 – 1.19)		1.14 (1.07 – 1.20)
p-interaction			0.977			
	Lower AST < 21 U/L (n=1,746)		**21 ≤ Middle AST < 27 U/L (n=2,554)**		**Upper AST ≥ 27 U/L (n=2,184)**	
Q1 (<22.4 kg/m^2)	8 / 450 (1.8)	reference	9 / 670 (1.3)	reference	14 / 502 (2.8)	reference
Q2 (22.4-<24.2 kg/m^2)	9 / 464 (1.9)	0.97 (0.31 – 3.04)	20 / 678 (3.0)	2.19 (0.91 – 5.24)	28 / 478 (5.9)	1.89 (0.92 – 3.88)
Q3 (24.2-<26.4 kg/m^2)	15 / 442 (3.4)	1.46 (0.50 – 4.23)	41 / 626 (6.6)	3.68 (1.63 – 8.30)	30 / 553 (5.4)	1.61 (0.79 – 3.27)
Q4 (≥26.4 kg/m^2)	21 / 390 (5.4)	2.00 (0.71 – 5.62)	45 / 580 (7.8)	3.81 (1.69 – 8.57)	64 / 651 (9.8)	3.07 (1.59 – 5.94)
p-trend		0.097		<0.001		<0.001
per 1 kg/m^2		1.07 (0.96 – 1.19)		1.15 (1.07 – 1.24)		1.14 (1.07 – 1.21)
p-interaction			0.194			

*Adjusted for age, sex, study year, residential area, hypertension, family history of diabetes, smoking status, alcohol intake, exercise, fasting glucose, and ALT or AST.

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Table 13. Odds ratio for incident diabetes according to baseline waist circumference after stratification into the three groups of liver enzymes

Waist circumference*	Case/no. of participants (%)	OR (95% CI)†	Case/no. of participants (%)	OR (95% CI)†	Case/no. of participants (%)	OR (95% CI)†
	Lower ALT < 17 U/L (n=1,860)		**17 ≤ Middle ALT < 24 U/L (n=2,241)**		**Upper ALT ≥ 24 U/L (n=2,383)**	
Q1	5 / 607 (0.8)	reference	13 / 559 (2.3)	reference	5 / 373 (1.3)	reference
Q2	12 / 538 (2.2)	2.39 (0.75 – 7.60)	16 / 572 (2.8)	1.25 (0.55 – 2.82)	31 / 532 (5.8)	3.27 (1.17 – 9.13)
Q3	11 / 425 (2.6)	1.81 (0.55 – 5.94)	36 / 620 (5.8)	1.26 (0.60 – 2.66)	42 / 632 (6.7)	3.36 (1.23 – 9.18)
Q4	11 / 290 (3.8)	2.31 (0.67 – 7.92)	33 / 490 (6.7)	1.56 (0.72 – 3.36)	89 / 846 (10.5)	5.32 (2.00 – 14.17)
p-trend		0.309		0.269		<0.001
per 1 cm		1.03 (0.99 – 1.08)		1.02 (0.99 – 1.05)		1.05 (1.03 – 1.08)
p-interaction			0.395			
	Lower AST < 21 U/L (n=1,746)		**21 ≤ Middle AST < 27 U/L (n=2,554)**		**Upper AST ≥ 27 U/L (n=2,184)**	
Q1	5 / 420 (1.2)	reference	10 / 648 (1.5)	reference	8 / 471 (1.7)	reference
Q2	11 / 472 (2.3)	1.62 (0.48 – 5.46)	21 / 659 (3.2)	1.66 (0.73 – 3.77)	27 / 511 (5.3)	2.46 (1.04 – 5.84)
Q3	17 / 454 (3.7)	1.86 (0.57 – 6.08)	45 / 685 (6.6)	2.06 (0.96 – 4.41)	27 / 538 (5.0)	1.96 (0.83 – 4.63)
Q4	20 / 400 (5.0)	1.85 (0.56 – 6.20)	39 / 562 (6.9)	2.08 (0.95 – 4.54)	74 / 664 (11.1)	4.79 (2.15 – 10.69)
p-trend		0.360		0.071		<0.001
per 1 cm		1.03 (0.99 – 1.07)		1.03 (1.00 – 1.06)		1.06 (1.03 – 1.08)
p-interaction			0.267			

* Waist circumference was classified into sex-specific quartile groups (Men, < 81.5, 81.5 -< 87.0, 87.0 -< 91.4, ≥ 91.4 cm; Women, < 76.0, 76.0 -< 82.0, 82.0 -< 88.2, ≥ 88.2 cm).

† Adjusted for age, sex, study year, residential area, hypertension, family history of diabetes, smoking status, alcohol intake, exercise, fasting glucose, and ALT or AST.

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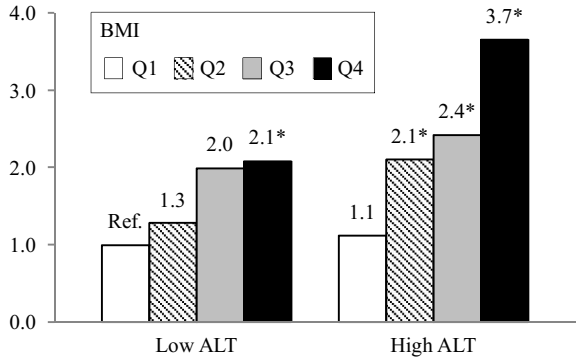
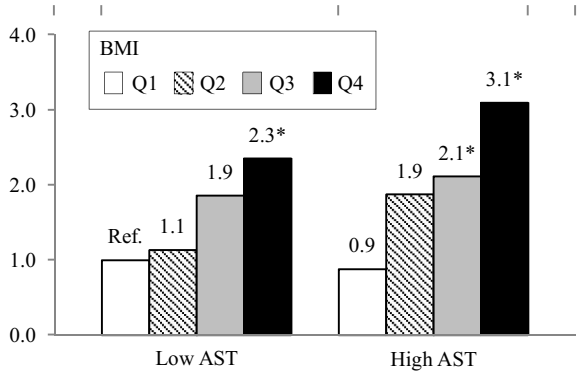
A. Adjusted odds ratio for incident diabetes according to baseline ALT level and BMI



B. Adjusted odds ratio for incident diabetes according to baseline AST level and BMI



C. Adjusted odds ratio for incident diabetes according to baseline ALT and AST levels and BMI

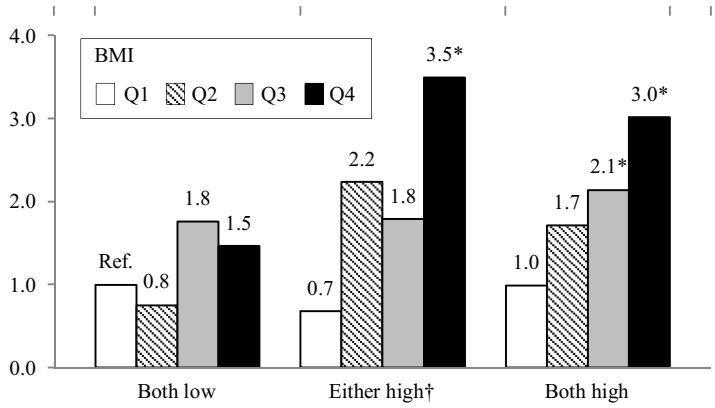


Figure 2. Odds ratio for incident diabetes according to baseline liver enzymes and BMI

Adjusted for age, sex, study year, residential area, hypertension, family history of diabetes, smoking status, alcohol intake, exercise, and fasting glucose
*, p <0.05
†, 'High ALT and low AST' or 'low ALT and high AST'

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Ⅳ. DISCUSSION

A. Summary of Findings

The current study investigated whether the relationship between BMI and incident diabetes is modified by serum ALT or AST levels in the general Korean population. I observed the different associations between BMI and the incident diabetes according to serum ALT or AST levels. In people belonging to the low liver enzyme levels, BMI showed weak associations with the risk of diabetes. However, in people within the high liver enzyme levels, the risk of diabetes was 3-4 times higher among people with highest quartile of BMI than among those with the lowest quartile of BMI. Interestingly, the findings persisted with adjustment for baseline glucose levels, a strong predictor for the development of diabetes. These findings were still significant in several sensitivity analyses. When the analyses were performed after stratification for sex, in women, high BMI was associated with the incident diabetes in the high liver enzyme groups but not associated in the low liver enzyme groups. Meanwhile, in men, the associations between high BMI and the incident diabetes were significant in the high liver enzyme groups and also significant in the highest BMI quartile of the low liver enzyme groups. It is probably since the liver enzyme levels of men are higher than that of women (median ALT, 24 versus 18 U/L; median AST, 26 versus 23 U/L). Among men classified to the low liver enzyme groups, some obese people with relatively high liver enzyme levels showed the significant association with the incident diabetes.

B. Comparison with Previous Studies

These data are in agreement with results of previous studies (Hong et al. 2014, 57, Lee et al. 2003, 359-64, Lee et al. 2003, 1358-66, Lee et al. 2004, 5410-4, Lim et al. 2007, 1092-8),

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which reported that obesity was weakly or not associated with diabetes in people with low liver enzymes but strongly associated in those with high liver enzymes. In Framingham Offspring Heart Study, combined effects of BMI and ALT levels on the development of diabetes were assessed (Goessling et al. 2008, 1935-1944. e1). In age and sex-adjusted models, the association between ALT and the incident diabetes were investigated after stratification into normal, overweight, and obese groups based on BMI. Compared with normal-weight individuals in the lowest third of ALT levels, the risk of diabetes was 14- and 30-fold for overweight and obese participants, respectively. The interaction between the BMI category and ALT levels for the development of diabetes was significant (p for interaction = 0.01). However, only two factors, age and sex were used as confounders in this study. I sufficiently adjusted for potential confounders affecting the development of diabetes and could observe a close to the actual results considering the effect of the confounders.

In most studies, the interaction with BMI on diabetes was assessed only with γ-GTP not ALT or AST since the association of ALT with diabetes was weaker than that of γ-GTP with diabetes (Lee et al. 2003, 359-64, Lee et al. 2003, 1358-66) or ALT and AST itself were not measured (Lee et al. 2004, 5410-4, Lim et al. 2007, 1092-8). The studies shown that the significant interaction between γ-GTP and BMI on diabetes explained that γ-GTP might be a marker of serum persistent organic pollutants concentrations, which is related to diabetes (Lee, and Jacobs 2006, 1825-7, Lim et al. 2007, 1092-8). However, I investigated ALT and AST not γ-GTP to assess the roles of liver in the association between obesity and diabetes. Since ALT and AST are more sensitive and specific markers of fatty liver and less influenced by external factor such as alcohol consumption than γ-GTP (Westerbacka et al. 2004, 1360-1369, Yu, and Keeffe 2003, 955-6).

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C. Possible Explanations

Obesity, particularly visceral fat accumulation, decreases secretion of adiponectin, which is one of the circulating hormones secreted from adipose tissue (Cnop et al. 2003, 459-69). Adiponectin stimulates glucose utilization by modulating insulin sensitivity and fatty acid oxidation by activating AMP-activated protein kinase in the liver (Yamauchi et al. 2002, 1288-95). Thus, low levels of adiponectin may play a role in the pathogenesis of nonalcoholic fatty liver disease (NAFLD). In previous studies, adiponectin levels have been found to be significantly lower in subjects with NAFLD, and adiponectin levels have also been found to correlate negatively with hepatic fat and positively with hepatic and peripheral insulin sensitivity (Bajaj et al. 2004, 783-9, Bugianesi et al. 2005, 3498-504). In turn, the hepatic insulin resistance leads to whole-body insulin resistance, and develops the type 2 diabetes. Meanwhile, NAFLD causes asymptomatic elevation of the level of liver enzymes. Of these liver enzymes, ALT and AST are most closely related to liver fat accumulation, and consequently ALT and AST has been used as surrogate markers of NAFLD (Clark, Brancati, and Diehl 2003, 960-7, Karmen, Wroblewski, and Ladue 1955, 126, Westerbacka et al. 2004, 1360-1369). Also, elevated ALT or AST levels may impair insulin signaling in the liver (Vozarova et al. 2002, 1889-95)

Second, there are studies reported that elevated ALT or AST levels may reflect chronic subclinical inflammation, which may induce oxidative stress (Kim et al. 2009, 64-9). Several epidemiologic studies have demonstrated that elevated ALT or AST levels are significantly and positively related to the development of diabetes even after adjusting for classical risk factors of diabetes (Hanley et al. 2004, 2623-32, Sattar et al. 2004, 2855-60).

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Synthetically, obesity with high liver enzyme levels indicates metabolically unhealthy obese but obesity with low liver enzyme levels indicates metabolically healthy obese. Therefore, for obese people with high liver enzyme levels, the risk of metabolic derangement is high, and then the risk of diabetes increases, while obese people with low liver enzyme levels have the low risk of metabolic derangement, and then the risk of diabetes decreases.

D. Strengths and Limitations

This study is unique in that participants were recruited from similar rural communities and they were relatively homogeneous. Above all, I firstly reported that the different association between obesity and the development of diabetes according to ALT or AST levels in Korean men and women to the best my knowledge. It could be to present the robust results using the some sensitivity analyses.

The present study has several limitations. First, participants were enrolled from the three rural communities. Consequently, these findings may not be generalized to the entire Korean people. Second, follow-up period of 4.5 years was relatively short. Also, among the 10,615 participants who enrolled the baseline survey, only 7,445 completed all follow-up examinations until 2014 and were analyzed in the current study. There were different in the several baseline characteristics between respondents and non-respondents to follow-up evaluation and this might cause the selection bias. However, serum ALT, AST, and fasting glucose levels, the major variables, were similar between respondents and non-respondents. Third, high BMI could not distinguish whether due to increased lean mass or to increased fat mass. I used waist circumference, which reflects abdominal fat mass, instead of BMI. However, waist circumference could not distinguish visceral fat accumulation which is the

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primary cause of metabolic impairment from subcutaneous fat accumulation. Fourth, glycated hemoglobin and two-hour post-load glucose levels were not measured for the participants, which might have included participants with undiagnosed diabetes at baseline. Fifth, repeated fasting blood glucose measurements were unavailable in this community-based study. Nevertheless, most community-based cohort studies collect blood samples only once because it is difficult for participants to repeatedly visit research clinics (Goessling et al. 2008, 1935-44, 1944.e1, Hanley et al. 2004, 2623-32, Hong et al. 2014, 57, Lim et al. 2007, 1092-8). Sixth, information on the usage of diabetic medications by participants was only obtained from the questionnaires; this method of collection may have possibly resulted in the underestimation of diabetes. Such a non-differential misclassification of outcomes would tend to attenuate the strength of the association. Lastly, since the information of the time of diagnosis of diabetes was incomplete, I could not use Cox proportional hazard regression models in spite of longitudinal data.

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Ⅴ. CONCLUSIONS

In summary, there was a strong association between BMI and incident diabetes among people with high liver enzyme levels, but the association was only modest among those with low liver enzyme levels. These findings suggest that serum ALT and AST tests may improve identification of individuals at high-risk of developing diabetes. For people with higher BMI and elevated liver enzyme levels, intensive lifestyle intervention is recommended to prevent development of diabetes. For those with higher BMI but low liver enzyme levels, further studies are required to know how we can improve their risk stratification.

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ABSTRACT (KOREAN)

혈청 간 효소, 체질량지수와 당뇨병 발생

지도교수 김현창

연세대학교 대학원 보건학과

송보미

배경 및 목적

당뇨병의 유병률 및 발생률은 모든 연령, 성별, 인종에서 전세계적으로 증가하고 있고, 비만은 당뇨병의 잘 알려진 원인이다. 한편, 간 효소와 당뇨병간의 관련성에 대한 연구들도 보고되고 있는데, 간 효소, 비만, 당뇨병 발생에 대한 연구는 미비한 실정이다. 따라서, 본 연구에서는 간 효소인 ALT와 AST 수치에 따른 체질량지수와 당뇨병 발생간의 관련성을 검토하고자 한다.

연구 방법

본 연구는 2005년부터 강화, 평창, 원주에서 진행된 지역사회 기반 코호트 자료를 이용하였다. 기반조사에 입적된 40세 이상의 10,615명 중에서 추적조사에 참여한 6,484명이 최종 연구 대상자로 선정되었다. 체질량지수는 연속형 변수와 범주형 변수로 분석되었고, 당뇨병은 공복혈당이 126 mg/dL 이상이거나 현재 치료 중인 사람으로 정의하였다. ALT와 AST 수치에 따른 체질량지수와 당뇨병 발생간의 관련성을 평가하기 위해서 ALT와 AST의 중위수를 기준으로 두 그룹으로 층화한

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후 연령, 성별, 기반조사 연도, 거주 지역, 고혈압, 당뇨병 가족력, 흡연, 음주, 운동, 공복혈당을 보정한 다변량 로지스틱 회귀분석을 시행하였다.

연구 결과

평균 4.5년의 추적조사 기간 동안 304건(4.7%)의 당뇨병이 발생하였다. ALT가 높은 그룹에서는, 체질량지수의 첫 번째 사분위수 대비, 두 번째, 세 번째, 네 번째 사분위수의 오즈비가 각각 1.88 (95% 신뢰구간, 0.98-3.62), 2.24 (1.21-4.13), 3.32 (1.84-5.99) 이었다. 반면, ALT가 낮은 그룹은 체질량지수와 당뇨병간의 유의한 관련성이 관찰되지 않았다. 비슷하게, AST가 높은 그룹에서는 체질량지수의 첫 번째 사분위수 대비, 두 번째, 세 번째, 네 번째 사분위수의 오즈비가 각각 2.14 (1.13-4.08), 2.44 (1.32-4.53), 3.65 (2.02-6.60)이었고, AST가 낮은 그룹에서는 범주형의 체질량지수와 당뇨병간의 유의한 관련성을 관찰할 수 없었으나, 체질량지수를 연속형으로 분석했을 때 오즈비가 1.10 (1.02-1.19)로 약한 관련성을 보였다.

연구 결론

결론적으로, 혈청 간 효소가 낮은 그룹에서는 비만과 당뇨병 발생간의 약한 관련성이 관찰되었으나, 혈청 간 효소가 높은 그룹에서는 비만과 당뇨병 발생간의 독립적이고 강한 관련성이 관찰되었다.