A Study on the Association between Body Mass Index and Diabetes Mellitus Incidence according to the Gamma-Glutamyl Transferase Level

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ABSTRACT

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(Directed by Prefessor Sun Ha Jee, MPH, Ph.D.)

Background: Gamma-Glutamyl Transferase (GGT) has been widely used as a marker for excessive alcohol intake and various hepatobiliary diseases such as alcoholic hepatitis, active chronic infection, fatty liver, and liver cancer. Accordingly, a number of studies are being conducted on the rise of GGT levels and incidence of chronic diseases. However, studies analyzing the association between body mass index (obesity) and diabetes according to GGT levels remain limited. This study sought to analyze how the association between body mass index (BMI) and diabetes prevalence changes according to serum GGT levels within the normal range among the Korean people.

Methods: This study was conducted on participants of the Korean Cancer Prevention Study-II. As a general population cohort developed by the Seoul Metabolic Syndrome Research Project in 2005, 121,053 participants were included in the final analysis among the total 160,407 participants whose blood samples had been obtained. Those with prediabetes at the time of registration and those with missing values on blood tests or questionnaires were excluded. Among 121,053 participants, there were 18,116 cases of diabetes, which were analyzed by using a control group of 102,937 persons. After extracting SNPs having causality with GGT

using the Genome Wide Association Study (GWAS) method, the weighted Genetic Risk Score (GRS) was calculated as follows.

Results: A total of 121,053 participants were studied, consisting of 77,312 men and 43,741 women. By age, 13,305 persons were 20-30 years old, 55,515 persons 30-40 years old, 40,972 persons 40-50 years old, 20,007 persons 50-60 years old, 6,544 persons 60-70 years old, and 1,309 persons were 70 years or older, indicating that the persons in their 30s made up the majority. BMI levels were 21.9 ±3.36(kg/m^2) for those aged 20-30 years, 23.38±3.35(kg/m^2) for those aged 30-40 years, 23.90±2.90(kg/m^2) for those aged 40-50 years, 24.23±2.73(kg/m^2) for those aged 50-60 years, 24.45±2.75(kg/m^2) for those aged 60-70 years, 24.11± 2.83(kg/m^2) for those aged 70-80 years, and 24.68±3.72(kg/m^2) for those aged 80 year or older. The BMI level increased with age. The BMI levels were 24.41± 2.90(kg/m^2) for men and 22.15±3.09(kg/m^2) for women, showing that the BMI level was higher in men than in women. The GGT levels were 24.85±24.88(mg/dl) for those aged 20-30 years, 35.32±42.79(mg/dl) for those aged 30-40 years, 39.83± 55.55(mg/dl) for those aged 40-50 years, 41.76±67.98(mg/dl) for those aged 50-60 years, 37.11±72.37(mg/dl) for those aged 60-70 years, 31.59±34.41(mg/dl) for

those aged 70-80 years, and 27.87±23.21(mg/dl) for those aged 80 years or older. BMI levels increase until the age of 50 but tend to decrease from the age of 60. The GGT levels were 47.14±60.93(mg/dl) for men and 18.80±19.8(mg/dl) for women.

In both men and women, when the BMI level increased, the risk ratio for diabetes significantly increased (HR:1.97; 95% CI:1.69-2.31), and this tendency was stronger in the group with the higher GGT level (HR:2.45; 95% CI:2.02-2.98). However, no difference was observed in the association according to the GGT genetic risk score (GRS). For both men and women, the association between BMI level and diabetes tended to increase as the GGT level increased.

Conclusion: In Korean adult men and women, the association between BMI and the risk of diabetes tended to increase in the group with higher GGT levels. However, the association according to the GGT genetic risk is unclear. This seems to suggest that an increase in GGT caused by factors influences the association between obesity and diabetes.

Keywords: Body Mass Index(BMI), Gamma-Glutamyl Transferase(GGT), Diabetes, Hazard ratio, Genetic Risk Score(GRS)

Ⅰ. INTRODIUCTION

According to the International Diabetes Federation, 1/10 of 537 million adults (20-79 years old) in 2021 have diabetes, and this number is expected to grow up to 643 million by 2030, and 783 million in 2045 (Saeedi et al., 2019). A similar trend of rapid increase in the number of diabetic patients is observed in Korea, due to Western diet, lack of exercise and increased mental stress. According to the 2020 report by Korean Diabetes Association, 1 out of 7 adults aged 30 or above has diabetes (Grønbæk et al., 2008). In addition, according to the 2020 data by Health Insurance Review & Assessment Service, there was a 27.8% increase in the number of Type 2 diabetes patients in Korea during the last 5 years, and especially, the prevalence of diabetes is steadily increasing in young patients in their twenties and thirties (Thamer et al., 2005). Diabetes is one of the most common chronic diseases, which presents a massive socioeconomic burden on the patients and the medical system. Therefore, the studies to determine the risk factors of diabetes is crucial for screening and preventing diabetes (D.-H. Lee, Ha, et al., 2003; Saeedi et al., 2019).

Glucose is the most basic energy source utilized by human body, and insulin is necessary for the utilization of absorbed glucose by the cells (Poznyak et al., 2020). Insulin is secreted by beta cells of the pancreas, and lowers postprandial blood glucose level (Kenny & Abel, 2019). If insufficient amount of insulin is secreted or if insulin function is impaired by high insulin resistance, absorbed glucose accumulates in the blood and is excreted through urine, and this pathologic state is termed diabetes (Liu et al., 2021; Verma & Hussain, 2017). Therefore, measurement of blood glucose level crucial in the diagnosis of diabetes. Although the cause of diabetes is not yet determined, the main risk factors are defined as genetic and environmental factors (Hossain et al., 2007; Liu et al., 2021; Verma & Hussain, 2017). When individuals with genetic risk factors of diabetes are exposed to environmental risk factors of diabetes, they tend to be affected with diabetes. In addition, it is known that individuals who are overweight or obese need to be cautious of diabetes (Arnott et al., 2020).

Obesity, which is one of the environmental risk factors, is a well-known cause of type 2 diabetes, and the increase in the obese population is reported to play a key role in the increase of diabetes prevalence rate along with the genetic factors

(Astrup & Finer, 2000; Hossain et al., 2007; Verma & Hussain, 2017). However, the recent epidemiologic studies explain that, although obesity influences the onset of diabetes, it is not an essential factor (Al-Goblan et al., 2014; Sonmez et al., 2019). It has been reported that obesity showed a strong relationship with type 2 diabetes only in the normal group with high serum GGT level, and only a weak relationship or no relationship in the normal group with low serum GGT level (Fraser et al., 2009; Kilkkinen et al., 2007; D.-H. Lee, Ha, et al., 2003). Although most studies failed to confirm statistical significance, if there is verity in these results, it signifies that obesity by itself is not sufficient to cause diabetes, and that if intensive management is provided to obese individuals with high serum GGT levels, it will be an effective method of prevention against type 2 diabetes.

Gamma Glutamyl Transferase (GGT), Alanine Aminotransferase (ALT), and Aspartate Transaminase (AST) are used as the main biomarkers of liver function. In particular, GGT is used as a marker for excessive alcohol intake or hepatobiliary disease, and because it is located on the extracellular surface, it mediates the uptake of glutathione which is an important component of intracellular antioxidation defense (Liu et al., 2021). In addition, GGT is known to act as a risk factor of

cardiovascular and cerebrovascular diseases, and is also related to diabetes, aging process, obesity and hypertension (Astrup & Finer, 2000; D.-H. Lee, Ha, et al., 2003; D.-H. Lee, Jacobs Jr, et al., 2003; MEISINGER et al., 2005; Verma & Hussain, 2017). Among various diseases, it has a particularly strong dose-dependent relationship with risk of future type 2 diabetes, which implies that certain factors related to increase in serum GGT level within physiologic range may also be closely related to the pathogenesis of type 2 diabetes (Fraser et al., 2009; MEISINGER et al., 2005; Nannipieri et al., 2005). The environmental factor by itself is limited in the prediction of type 2 diabetes, therefore including the genetic factor into the study process is also necessary. Generic risk score (GRS), which converts the risk of disease-related single-nucleotide polymorphisms (SNPs) into scores using genome wide association analysis (GWAS) is a typical method. Through this approach, the limitations of analysis using environmental factors can be compensated.

Currently, many studies have been conducted on obesity and diabetes, however there are insufficient number of studies that analyze the relationship between BMI according to GGT level and diabetes. This study aims to investigate the relationship

between BMI according to GGT level and the risk of diabetes, and to compare the difference in the risk of diabetes for genetic and environmental factors through GWAS and MR analysis, distinct from previous studies.

Ⅱ. MATERIALS AND METHODS

1. Study population and Data Sources

This study was conducted from 2004 to 2013 in 18 Korean health screening institutions using Korean cancer prevention study-II which includes 160,407 subjects who participated in the study after giving written consent. Mean follow-up period was 12.6 years. Factors which influence the risk of diabetes are age, gender, alcohol, smoking, physical exercise, oral medications (MDM), family history (FDM), body mass index (BMI), alanine transaminase (ALT), aspartate transaminase (AST), Gamma Glutamyl Transferase (GGT), Triglyceride (TG), low density lipoprotein (LDL), high density lipoprotein (HDL), and fasting blood glucose (FBS), which have been investigated in previous studies (Kunutsor et al., 2014; D.-H. Lee, Steffen, et al., 2004; Thamer et al., 2005). Data was collected based on these grounds..

Data collection was standardized, and utilized medical examination data and health screening data which was performed every 2 years in local institutions. As for the medical examination data, the subject directly supplied information for the age,

gender, smoking, alcohol intake, physical exercise, past medical history and medication history, and body mass index was calculated by dividing body weight (kg) by meter square of height (m). Blood sampling was performed in the morning following overnight fasting, and automatic analysis devices (Hitachi 737) were used for the laboratory tests. Smoking history was divided into non-smoker, past smoker and present smoker. Alcohol intake was divided into drinker or non-drinker, and in case of drinkers, amount of intake in a single drinking episode and the number of drinking episodes were investigated, using glasses of soju (Korean spirits) as the unit, converting the results into total amount of alcohol. Physical exercise was divided into exercising and non-exercising. Each medical institution that performed the tests were accredited for internal and external quality assessment by the Korean Association of External Quality Assessment Service, as to maintain the accuracy of the laboratory tests.

Subjects who have diabetes, are unable to utilize genetic test results, or have missing values of variables were excluded from the study, and 121,053 subjects were included in the final analysis. There were 77,312 males (63.87%) and 43,741 females (36.13%).

The definition of diabetic subjects was those with history of outpatient clinic visit or hospitalization due to diabetes. The definition of fatty liver was cases that exceeded 40(mg/dl) for both AST and ALT levels.

2. SNPs selection and genotyping

Genetic analysis was performed using Affymetrix Genome-Wide Human SNP array 5.0 (Affymetrix, Santa Clara, CA, USA). For quality control, monomorphic variants were excluded by the following criteria: (1) call rate<0.95 (2) Hardy-Weinberg equilibrium (HWE) ($p<1\times10^{-4}$) and (3) minor allele frequencies<0.01. GWAS method was used to extract 143 SNPs related to serum GGT, and these SNPs were coded as 0, 1 and 2 according to the presence or absence of a risk allele. Finally, using the weighted method, Genetic Risk Score (GRS) was calculated. Weighted GRS is calculated by giving a different weighting to each SNPs genotype before summing up. For example, if there is allele A and B of a SNP and B is the risky allele, the number of risky alleles for genetic polymorphism AA, AB, and BB will be 0, 1, and 2, respectively. Then, using additive model assumption, regression coefficient for each increased allele was determined and multiplied to the number

of risky alleles (0, 1, 2) to give weighting before summing up.

$$\text{Weighted GRS} = \sum_{i=1}^{n} \textit{Number of risky allele in SNPi} \times \textit{Weighti}$$

3. Statistical analysis

For the comparison of general characteristics, analysis was performed according to the presence of diabetes, gender, oral diabetic medication history and AST/ALT level. For the confirmation of potential confounders and comparison between groups, subjects were divided, according to GGT, BMI and GGT level converted to genetic risk score, into 4 quartiles of 25% or lower, higher than 25% and 50% or lower, higher than 50% and 75% or lower, and higher than 75%. In comparing general characteristics of subjects, Chi-squared test and ANOVA were performed according to the type of the variable for confirmation of statistical difference. Continuous data such as distribution of general characteristics is presented as Mean±SD, and categorical data as N(%). Cox proportional model regression was used to analyze BMI according to serum GGT and development of type 2 diabetes, and calculated by controlling covariates.

For genetic analysis, logistic regression analysis was performed on the presence or absence of diabetes according to the GGT level, with age and gender as control variables. The statistical program is PLINK ver. 1.09 (Free Software Foundation, Inc. Boston, USA) and SAS 9.1 were used, a confidence interval of 95% was presented, and a case where the P-value was less than 0.05 was considered statistically significant.

Ⅲ. RESULTS

1. General Characteristics

The subjects of this study were a total of 121,053, 77,312 (63.87%) men and 43,741 (36.13%) women. The age distribution was 20 to 88 years old, and the average age of men was 41.59±9.36 years old and 40.86±10.72 years old for women. There were statistically significant differences in all the characteristics of the subjects according to the presence or absence of diabetes and the presence or absence of oral medicine. However, there was no significant difference in family history (p=0.089) when classified by gender, and both AST and ALT levels were not significant in smoking history (p=0.073) and LDL (p=0.1946) in the characteristics of subjects exceeding 40 (mg/dl).

Table 1. General characteristics according to T2DM status

		Non_T2DM group (N=102,937)	T2DM group (N=18,116)	*P-value*
		N(%)	N(%)	
Sex	Male	64,376 (83.27)	12,936 (16.73)	<0.0001
	Female	38,561 (88.16)	5,180 (11.84)	
Alcohol status (g/day)	0	29,503 (83.68)	5,756 (16.32)	<0.0001
	0.1-25	53,728 (86.92)	8,087 (13.08)	
	25.1-50	13,321 (83.67)	2,599 (16.33)	
	50.1-100	4,821 (80.28)	1,184 (19.72)	
	>100	1,564 (76.14)	490 (23.86)	
Smoking status	Never smoker	54,885 (87.18)	8,071 (12.82)	<0.0001
	Former smoker	17,917 (81.78)	993 (18.22)	
	Current smoker	30,135 (83.28)	6,052 (16.72)	
Exercise status	No	60,457 (83.53)	11,919 (16.47)	<0.0001
	Yes	42,480 (87.27)	6,097 (12.73)	
Medication use	No	102,746 (87.05)	15,289 (12.95)	<0.0001
	Yes	191 (6.33)	2,827 (96.67)	
Family history of DM	No	87,742 (86.86)	13,274 (13.14)	<0.0001
	Yes	15,195 (75.83)	4,842 (24.17)	
		Mean ± S.D.	Mean ± S.D.	
Age (years)		40.18 ± 9.28	47.86 ± 10.62	<0.0001
BMI (kg/m^2)		23.32 ± 3.06	25.19 ± 3.22	<0.0001
AST (mg/dl)		22.77 ± 14.58	27.00 ± 24.12	<0.0001
ALT (mg/dl)		24.45 ± 24.21	33.04 ± 26.34	<0.0001
GGT (mg/dl)		34.51 ± 45.76	52.16 ± 73.76	<0.0001
TG (mg/dl)		130.2 ± 83.96	179.40 ± 115.6	<0.0001
LDL (mg/dl)		112.00 ± 30.88	118.10 ± 34.61	<0.0001
HDL (mg/dl)		52.43 ± 10.62	49.01 ± 11.55	<0.0001
FBS (mg/dl)		87.71 ± 10.50	111.40 ± 35.37	<0.0001

Values are n(%) or Mean ± S.D.
T2DM=type 2 diabetes mellitus, BMI=body mass index, AST=aspartate transaminase, ALT=alanine transaminase, GGT=gammaglutamyl transferase, TG=triglyceride, LDL-C=low density lipoprotein cholesterol, HDL-C=high density lipoprotein cholesterol, FBS=fasting blood glucose

Table 2. General characteristics according to sex

		Male (N=77,312)	Female (N=43,741)	*P-value*
		N(%)	N(%)	
T2DM	No	64,376 (62.54)	38,561 (37.46)	<0.0001
	Yes	12,936 (71.41)	5,180 (28.59)	
Alcohol status (g/day)	0	10,659 (30.23)	24,600 (69.77)	<0.0001
	0.1-25	44,086 (71.32)	17,729 (28.68)	
	25.1-50	14,892 (93.54)	1,028 (6.46)	
	50.1-100	5,704 (94.99)	301 (5.01)	
	>100	1,971 (95.96)	83 (4.04)	
Smoking status	Never smoker	22,580 (35.87)	40,376 (64.13)	<0.0001
	Former smoker	20,202 (92.20)	1,708 (7.80)	
	Current smoker	34,530 (95.42)	1,657 (4.58)	
Exercise status	No	51,582 (71.27)	20,794 (28.73)	<0.0001
	Yes	25,730 (52.86)	22,947 (47.14)	
Medication use	No	75,000 (63.54)	43,035 (36.46)	<0.0001
	Yes	2,312 (76.61)	706 (23.39)	
Family history of DM	No	64,621 (63.97)	36,395 (36.03)	0.089
	Yes	12,691 (63.64)	7,346 (36.66)	
		Mean ± S.D.	Mean ± S.D.	
Age (years)		41.59 ± 9.36	40.86 ± 10.72	<0.0001
BMI (kg/m^2)		24.42 ± 2.90	22.16 ± 3.09	<0.0001
AST (mg/dl)		25.37 ± 18.67	19.94 ± 10.62	<0.0001
ALT (mg/dl)		30.57 ± 27.04	17.20 ± 16.90	<0.0001
GGT (mg/dl)		47.48 ± 59.98	18.89 ± 20.23	<0.0001
TG (mg/dl)		158.90± 98.95	99.73 ± 58.57	<0.0001
LDL (mg/dl)		115.6 ± 31.79	108.1 ± 30.53	<0.0001
HDL (mg/dl)		48.83 ± 9.30	57.37± 11.19	<0.0001
FBS (mg/dl)		93.10 ± 20.22	88.00 ± 15.38	<0.0001

Values are n(%) or Mean ± S.D.
T2DM=type 2 diabetes mellitus, BMI=body mass index, AST=aspartate transaminase, ALT=alanine transaminase, GGT=gammaglutamyl transferase, TG=triglyceride, LDL-C=low density lipoprotein cholesterol, HDL-C=high density lipoprotein cholesterol, FBS=fasting blood glucose

Table 3. General characteristics according to drug use

		Non-DM medication use (N=118,035)	DM Medication use (N=3,018)	*P-value*
		N(%)	N(%)	
T2DM	No	102,746 (99.81)	191 (0.19)	<0.0001
	Yes	15,289 (84.40)	2,827 (15.60)	
Alcohol status (g/day)	0	34,270 (97.20)	989 (2.80)	<0.0001
	0.1-25	60,500 (97.87)	1,315 (2.13)	
	25.1-50	15,499 (97.36)	421 (2.64)	
	50.1-100	5,787 (96.37)	218 (3.63)	
	>100	1,979 (96.35)	75 (3.65)	
Smoking status	Never smoker	61,708 (98.02)	1,248 (1.98)	<0.0001
	Former smoker	21,098 (96.29)	812 (3.71)	
	Current smoker	35,229 (97.35)	958 (2.65)	
Exercise status	No	70,161 (96.94)	2,215 (3.06)	<0.0001
	Yes	47,874 (98.35)	803 (1.65)	
FDM	No	99,292 (98.29)	1,724 (1.71)	<0.0001
	Yes	18,743 (93.54)	1,294 (6.46)	
		Mean ± S.D.	Mean ± S.D.	
Age (years)		51.79 ± 10.63	41.06 ± 9.72	<0.0001
BMI (kg/m^2)		25.39 ± 3.26	23.56 ± 3.14	<0.0001
AST (mg/dl)		28.49 ± 48.14	23.28 ± 14.74	<0.0001
ALT (mg/dl)		33.90 ± 25.24	25.53 ± 24.68	<0.0001
GGT (mg/dl)		55.39 ± 99.96	36.68 ± 49.37	<0.0001
TG (mg/dl)		184.80 ± 122.00	136.30 ± 89.86	<0.0001
LDL (mg/dl)		111.00 ± 35.00	112.90 ± 31.45	<0.0001
HDL (mg/dl)		47.98 ± 12.79	52.02 ± 10.76	<0.0001
FBS (mg/dl)		141.20 ± 46.71	89.98 ± 15.50	<0.0001

Values are n(%) or Mean ± S.D.
T2DM=type 2 diabetes mellitus, BMI=body mass index, AST=aspartate transaminase, ALT=alanine transaminase, GGT=gammaglutamyl transferase, TG=triglyceride,
LDL-C=low density lipoprotein cholesterol, HDL-C=high density lipoprotein cholesterol,
FBS=fasting blood glucose

Table 4. General characteristics according to AST/ ALT levels

		AST and ALT 40(mg/dl) or less (N=105,476)			AST and ALT levels over 40(mg/dl) (N=15,577)		
T2DM		No	Yes	*P-value*	No	Yes	*P-value*
FDM	No	78,280 (88.46)	10,208 (11.54)	<0.0001	9,462 (75.53)	3,066 (24.47)	<0.0001
	Yes	13,368 (78.69)	3,620 (21.31)		1,827 (59.92)	1,222 (40.08)	
MDM	No	91497 (88.64)	11731(11.36)	<0.0001	11,249 (75.97)	3,558 (24.03)	<0.0001
	Yes	151 (6.72)	2097 (93.28)		40 (5.19)	730 (94.81)	
Alcohol status	0	27,462 (85.00)	4,846 (15.00)	<0.0001	2,041 (69.16)	910 (30.84)	<0.0001
	0.1-25	47,812 (88.77)	6,046 (11.23)		5,916 (74.35)	2,041 (25.65)	
	25.1-50	11,178 (86.16)	1,796 (13.84)		2,143 (72.74)	803 (27.26)	
	50.1-100	3,974 (83.14)	806 (16.86)		847 (69.14)	378 (30.86)	
	>100	1,222 (78.53)	334 (21.47)		342 (68.67)	156 (31.33)	
Smoking status	Never smoker	51,183 (88.37)	6,737 (11.63)	<0.0001	3,702 (73.51)	1,334 (26.49)	0.073
	Former smoker	15,433 (83.76)	2,993 (16.24)		2,484 (71.30)	1,000 (28.70)	
	Current smoker	25,032 (85.93)	4,098 (14.07)		5,103 (72.31)	1,954 (27.69)	
Exercise status	No	53,570 (85.32)	9,246 (14.68)	<0.0001	6,707 (71.50)	2,673 (28.50)	<0.0001
	Yes	37,898 (89.21)	4,582 (10.79)		4,582 (73.94)	1,615 (26.06)	
		Mean ± S.D.	Mean ± S.D.		Mean ± S.D.	Mean ± S.D.	
Age (years)		40.25±9.39	48.94±10.68	<0.0001	39.62±8.31	44.41±9.67	<0.0001
BMI (kg/m^2)		23.02±2.92	24.66±3.00	<0.0001	25.76±3.15	26.91±3.31	<0.0001
AST (mg/dl)		20.46±4.85	21.78±5.20	<0.0001	41.59±36.74	43.84±44.72	0.0014
ALT (mg/dl)		19.48±8.06	22.65±8.14	<0.0001	64.84±54.62	66.53±35.31	0.0594
GGT (mg/dl)		28.74±28.03	38.85±33.56	<0.0001	81.33±101.2	95.07±130.2	<0.0001
TG (mg/dl)		122.6±75.00	164.6±104.5	<0.0001	191.2±114.9	227.1±135.0	<0.0001
LDL (mg/dl)		110.8±30.17	116.9±33.59	<0.0001	121.3±34.81	122.1±37.41	0.1946
HDL (mg/dl)		53.02±10.59	49.94±11.92	<0.0001	47.58±9.56	46.01±9.68	<0.0001
FBS (mg/dl)		87.33±10.23	110.2±35.43	<0.0001	90.73±12.05	115.5±34.86	<0.0001

Values are n(%) or Mean ± S.D.

T2DM=type 2 diabetes mellitus, BMI=body mass index, AST=aspartate transaminase, ALT=alanine transaminase, GGT=gammaglutamyl transferase, TG=triglyceride, LDL-C=low density lipoprotein cholesterol, HDL-C=high density lipoprotein cholesterol, FBS=fasting blood glucose

Table 5. General characteristics according to AST/ ALT levels

		AST and ALT 40(mg/dl) or less (N=105,476)			AST and ALT levels over 40(mg/dl) (N=15,577)		
T2DM		No	Yes	*P-value*	No	Yes	*P-value*
FDM	No	78,280 (88.46)	10,208 (11.54)	<0.0001	9,462 (75.53)	3,066 (24.47)	<0.0001
	Yes	13,368 (78.69)	3,620 (21.31)		1,827 (59.92)	1,222 (40.08)	
MDM	No	91497 (88.64)	11731(11.36)	<0.0001	11,249 (75.97)	3,558 (24.03)	<0.0001
	Yes	151 (6.72)	2097 (93.28)		40 (5.19)	730 (94.81)	
Alcohol status	0	27,462 (85.00)	4,846 (15.00)	<0.0001	2,041 (69.16)	910 (30.84)	<0.0001
	0.1-25	47,812 (88.77)	6,046 (11.23)		5,916 (74.35)	2,041 (25.65)	
	25.1-50	11,178 (86.16)	1,796 (13.84)		2,143 (72.74)	803 (27.26)	
	50.1-100	3,974 (83.14)	806 (16.86)		847 (69.14)	378 (30.86)	
	>100	1,222 (78.53)	334 (21.47)		342 (68.67)	156 (31.33)	
Smoking status	Never smoker	51,183 (88.37)	6,737 (11.63)	<0.0001	3,702 (73.51)	1,334 (26.49)	0.073
	Former smoker	15,433 (83.76)	2,993 (16.24)		2,484 (71.30)	1,000 (28.70)	
	Current smoker	25,032 (85.93)	4,098 (14.07)		5,103 (72.31)	1,954 (27.69)	
Exercise status	No	53,570 (85.32)	9,246 (14.68)	<0.0001	6,707 (71.50)	2,673 (28.50)	<0.0001
	Yes	37,898 (89.21)	4,582 (10.79)		4,582 (73.94)	1,615 (26.06)	
		Mean ± S.D.	Mean ± S.D.		Mean ± S.D.	Mean ± S.D.	
Age (years)		40.25±9.39	48.94±10.68	<0.0001	39.62±8.31	44.41±9.67	<0.0001
BMI (kg/m^2)		23.02±2.92	24.66±3.00	<0.0001	25.76±3.15	26.91±3.31	<0.0001
AST (mg/dl)		20.46±4.85	21.78±5.20	<0.0001	41.59±36.74	43.84±44.72	0.0014
ALT (mg/dl)		19.48±8.06	22.65±8.14	<0.0001	64.84±54.62	66.53±35.31	0.0594
GGT (mg/dl)		28.74±28.03	38.85±33.56	<0.0001	81.33±101.2	95.07±130.2	<0.0001
TG (mg/dl)		122.6±75.00	164.6±104.5	<0.0001	191.2±114.9	227.1±135.0	<0.0001
LDL (mg/dl)		110.8±30.17	116.9±33.59	<0.0001	121.3±34.81	122.1±37.41	0.1946
HDL (mg/dl)		53.02±10.59	49.94±11.92	<0.0001	47.58±9.56	46.01±9.68	<0.0001
FBS (mg/dl)		87.33±10.23	110.2±35.43	<0.0001	90.73±12.05	115.5±34.86	<0.0001

Values are n(%) or Mean ± S.D.

T2DM=type 2 diabetes mellitus, BMI=body mass index, AST=aspartate transaminase, ALT=alanine transaminase, GGT=gammaglutamyl transferase, TG=triglyceride, LDL-C=low density lipoprotein cholesterol, HDL-C=high density lipoprotein cholesterol, FBS=fasting blood glucose

2. BMI, GGT, and GGT_GRS distributions by the presence of Diabetes Mellitus

The distribution of BMI, GGT, and GGT_GRS was compared according to gender. In male subjects without diabetes, 3rd BMI quartile had the largest proportion with 30.7%, and in subjects with diabetes, the distribution increased with each quartile (Q1:14.0%-Q4: 45.4%). However, in female subjects without diabetes, 1st BMI quartile had the largest proportion with 47.21%, and in subjects with diabetes, there was an opposite tendency with the distribution increasing gradually with each quartile (Q1:18.4%-Q4: 34.1%).

In male subjects without diabetes, 4th GGT quartile had the largest proportion with 35.2%, and in subjects with diabetes, the distribution showed a tendency to increase with each quartile (Q1:2.9%-Q4: 55.6%). However, in female subjects without diabetes, 1st GGT quartile had the largest proportion with 57.1%, and in subjects with diabetes, the distribution showed a tendency to decrease with each quartile (Q1:33.5%-Q4: 12.0%).

In male subjects without diabetes, 4th GGT_GRS quartile had the largest

proportion with 26.6%, and in subjects with diabetes, the distribution showed a tendency to increase with each quartile (Q1:22.9%-Q4: 26.7%). In female subjects without diabetes, 1st BMI quartile had the largest proportion with 25.9%, and subjects without diabetes showed a tendency of decrease in distribution with increase in quartile (Q1: 26.9-Q4: 23.7%). In contrast to the distribution of BMI and GGT, there was almost no variation in the distribution of GGT_GRS.

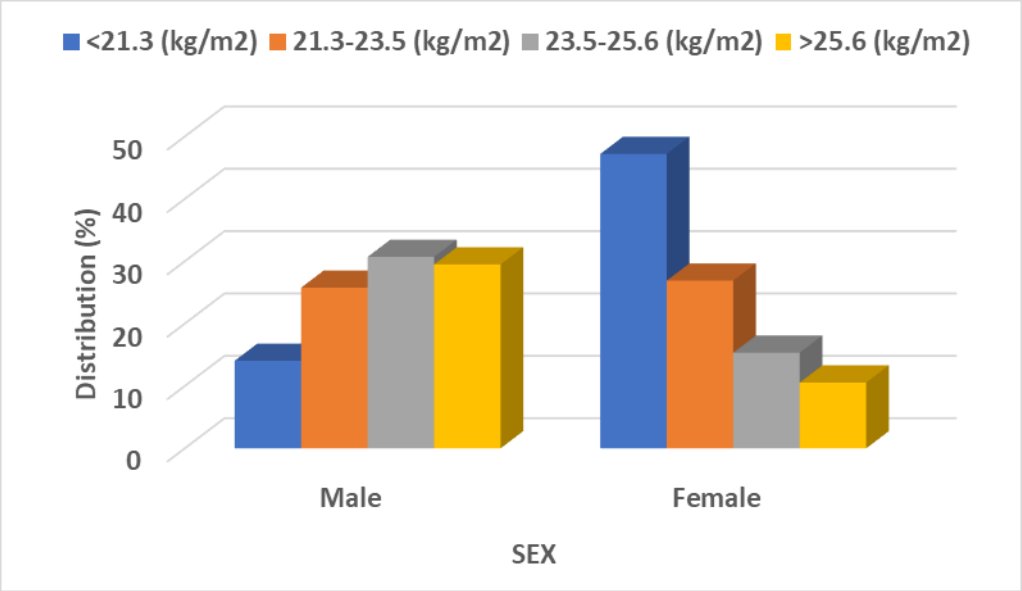


Figure 1. Distribution of BMI by sex in non-diabetics

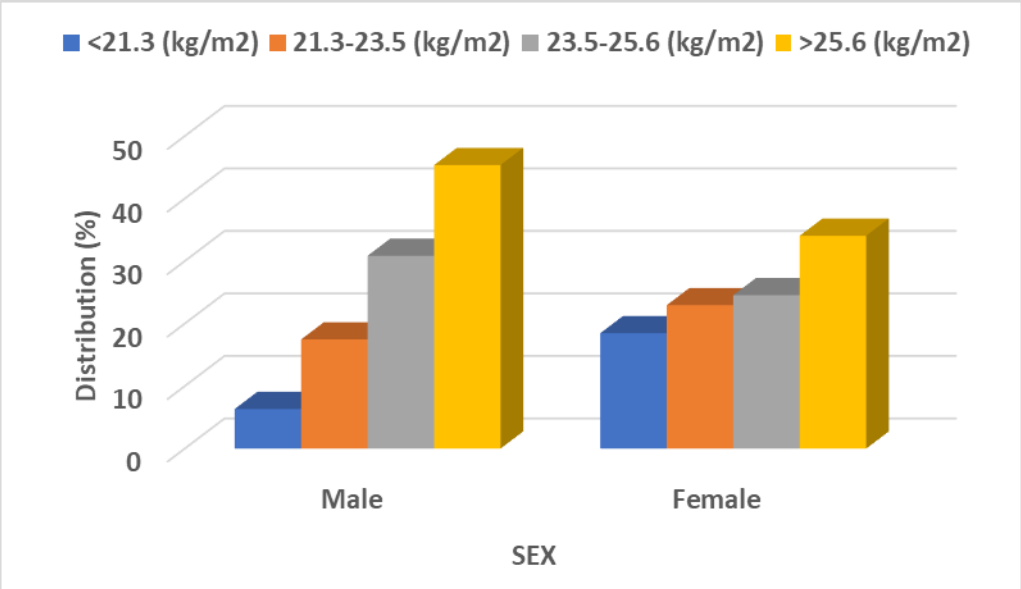


Figure 2. Distribution of BMI by sex in diabetics

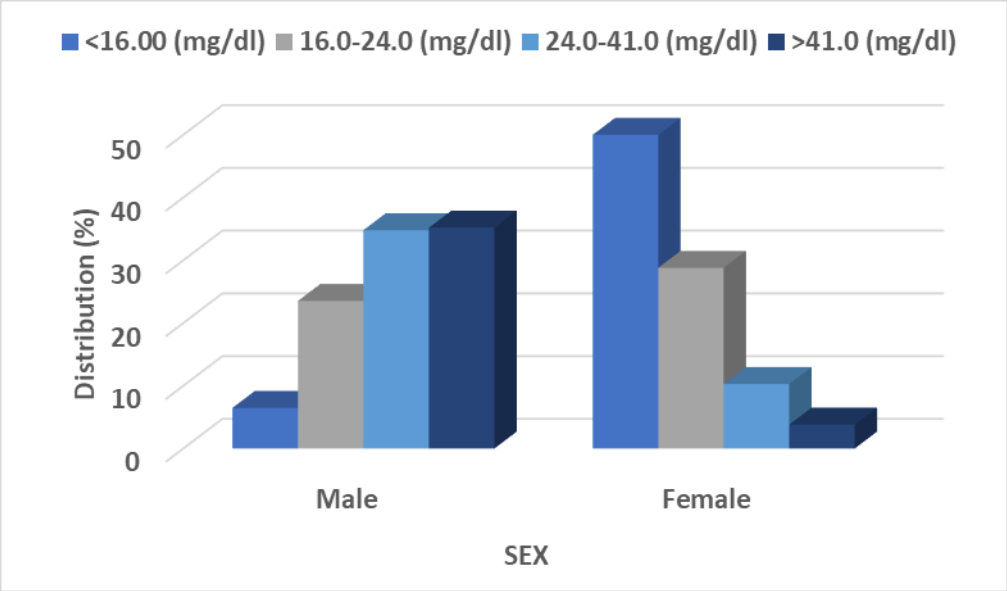


Figure 3. Distribution of GGT by sex in non-diabetics

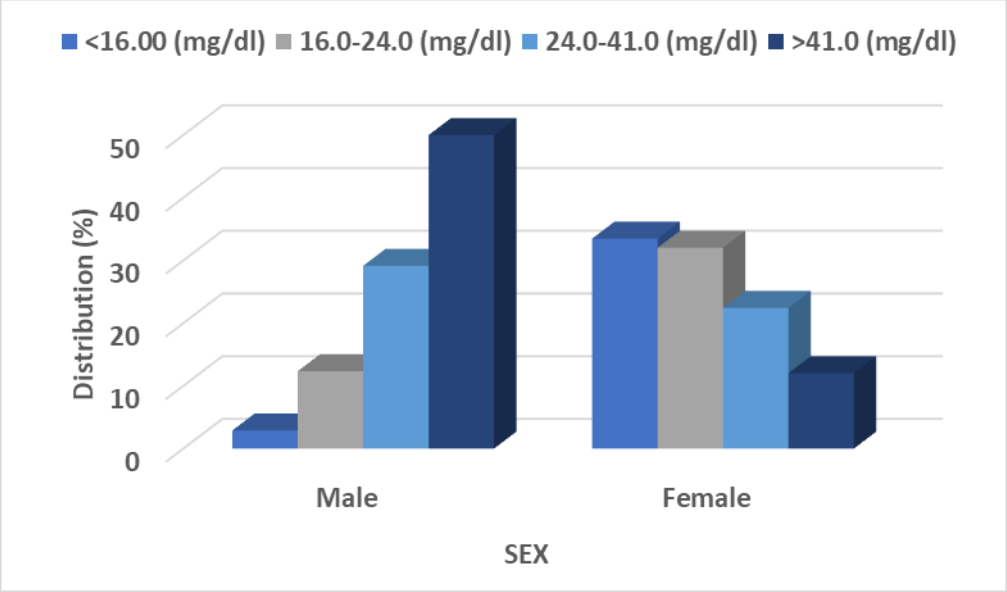


Figure 4. Distribution of GGT by sex in diabetic

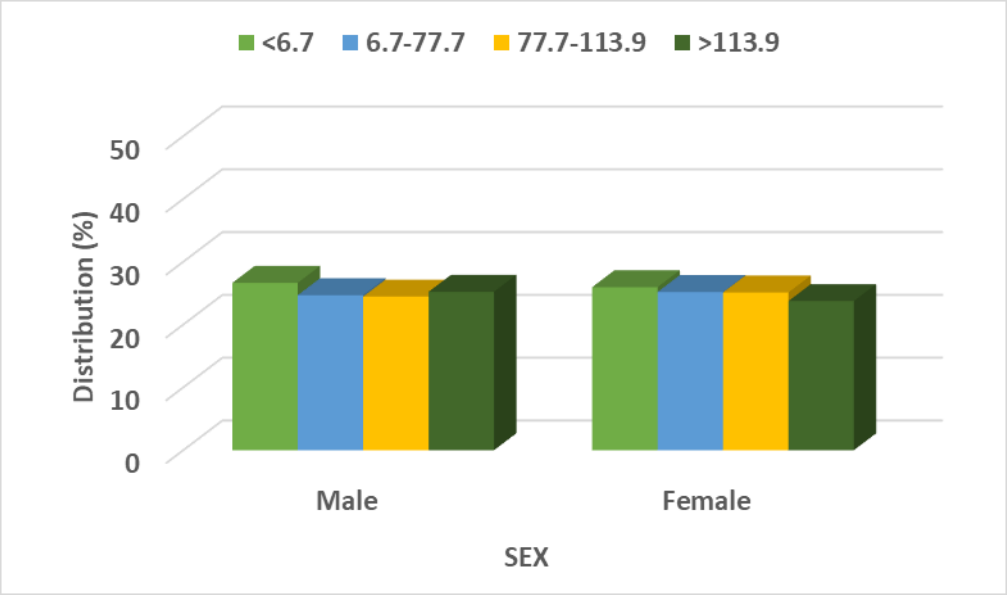


Figure 5. Distribution of GGT_GRS by sex in non-diabetics

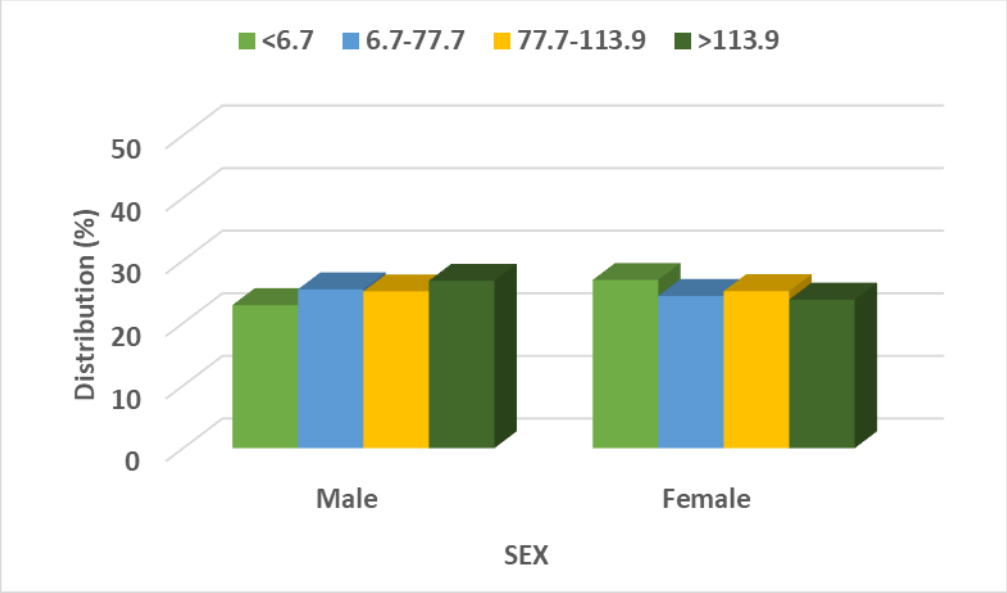


Figure 6. Distribution of GGT_GRS by sex in diabetics

GGT and GGT_GRS levels were compared between gender groups. In male subjects without diabetes, 1st GGT_GRS quartile decreased (14.89%) with the increase of GGT level, and the proportion of 4th GGT_GRS quartile increased (33.2%). In subjects with diabetes, 1st GGT_GRS quartile decreased (15.87%) with the increase of GGT level, and the proportion of 4th GGT_GRS quartile increased (32.27%). Tendencies were similar between groups with or without diabetes.

In female subjects without diabetes, 1st GGT_GRS quartile decreased (19.95%) with the increase of GGT level, and the proportion of 4th GGT_GRS quartile increased (29.85%). In subjects with diabetes, 1st GGT_GRS quartile decreased (24.24%) with the increase of GGT level, and the proportion of 4th GGT_GRS quartile increased (28.73%). Both males and females showed a similar tendency, however the female subjects showed a distribution that was almost uninfluenced by the GGT and GGT_GRS levels.

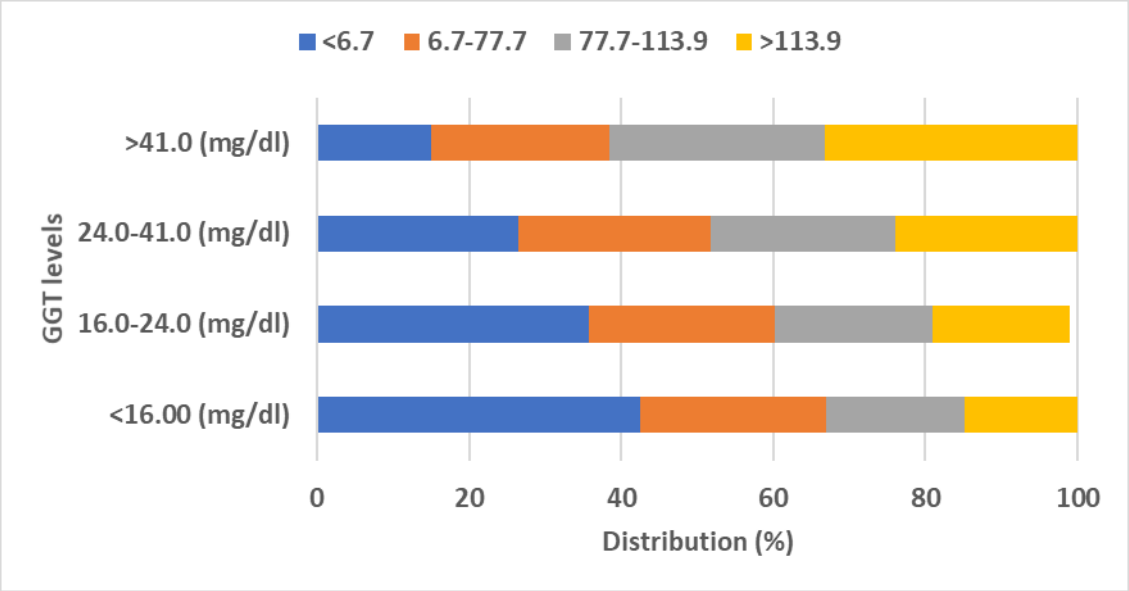


Figure 7. Distribution of GGT_GRS by GGT in non-diabetics (Male)

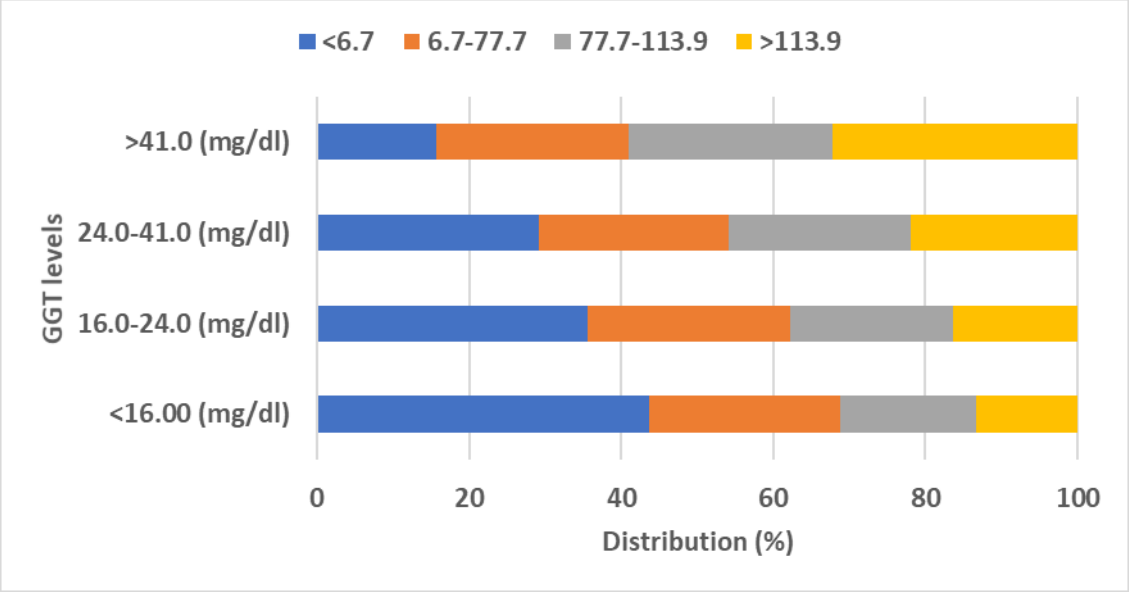


Figure 8. Distribution of GGT_GRS by GGT in diabetics (Male)

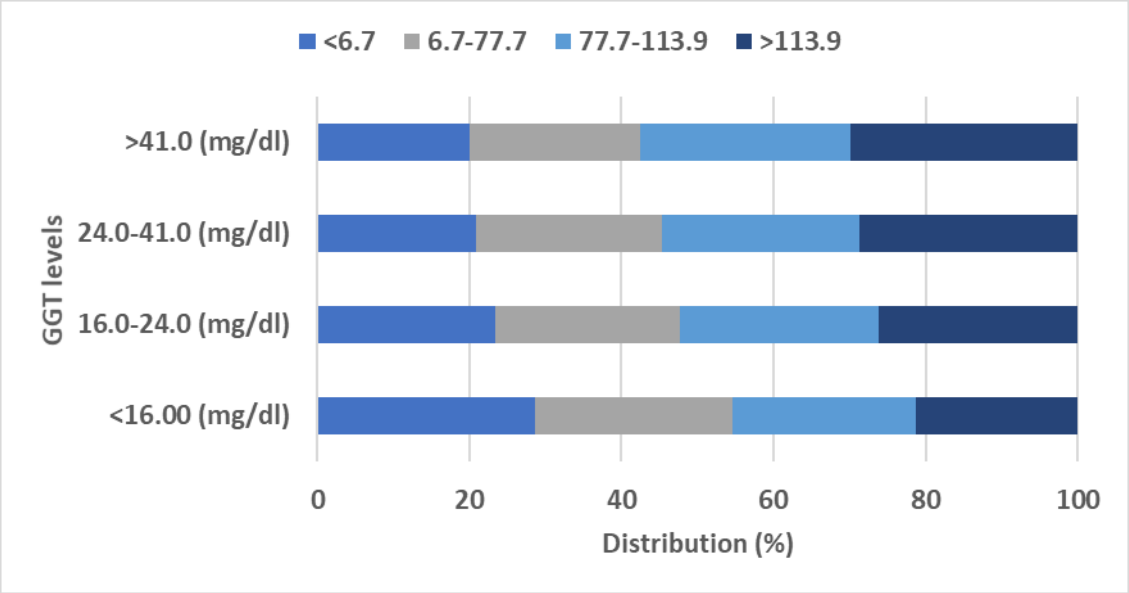


Figure 9. Distribution of GGT_GRS by GGT in non-diabetics (Female)

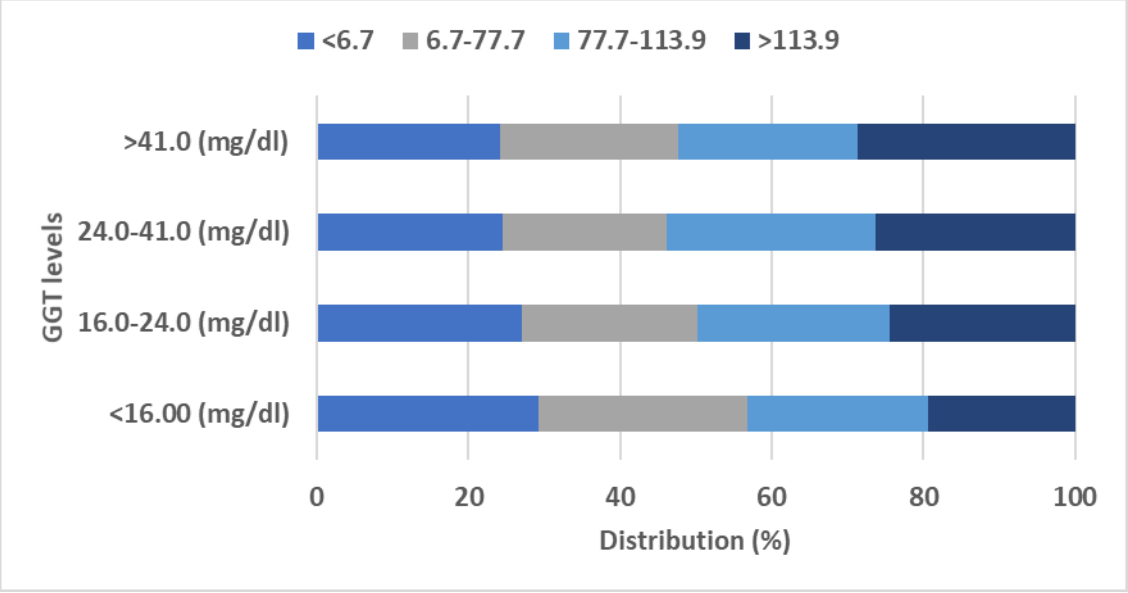


Figure 10. Distribution of GGT_GRS by GGT in non-diabetics (Female)

The distribution of BMI, GGT, and GGT_GRS were compared between age groups. 1st quartile, without diabetes and with the lowest BMI, had the highest proportion of subjects aged 20~39. The proportion of elderly subjects, compared to younger subjects, increased with the increase in BMI quartile. In subjects with diabetes, the distribution increased with BMI and the age of the subjects.

In subjects without diabetes, 1st quartile with the lowest GGT level showed the highest proportion of subjects aged 20~39 with 38.14%. With the increase in GGT quartile, the proportion of elderly subjects increased compared to the younger subjects. In subjects with diabetes, the proportion increased with GGT level and the age of the subjects. In particular, 4th quartile with the highest GGT level showed the highest proportion of subjects aged 30~49 with 50.74%, and the proportion decreased with aging.

On the other hand, when GGT_GRS levels were investigated according to each age group, similar proportion was observed in all age groups without any particular tendency.

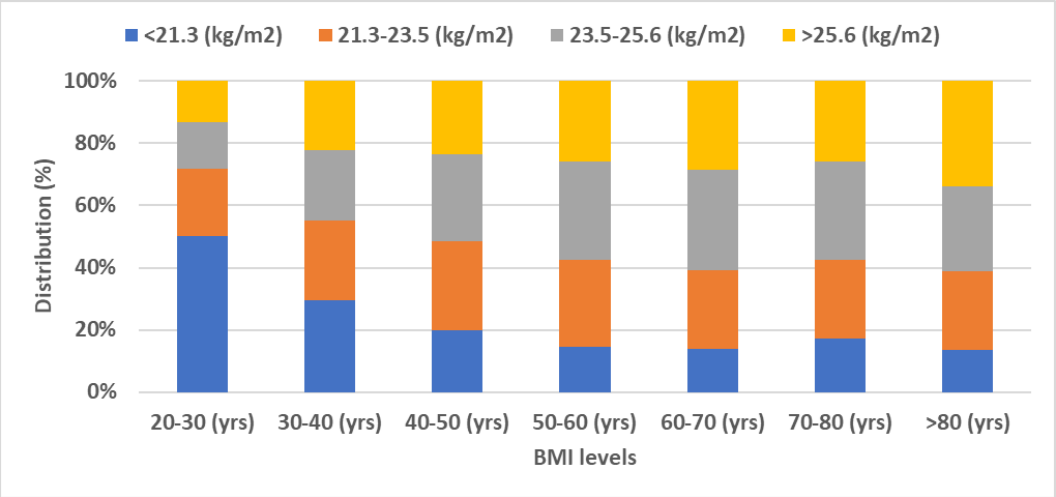


Figure 11. Distribution of BMI by age in non-diabetics

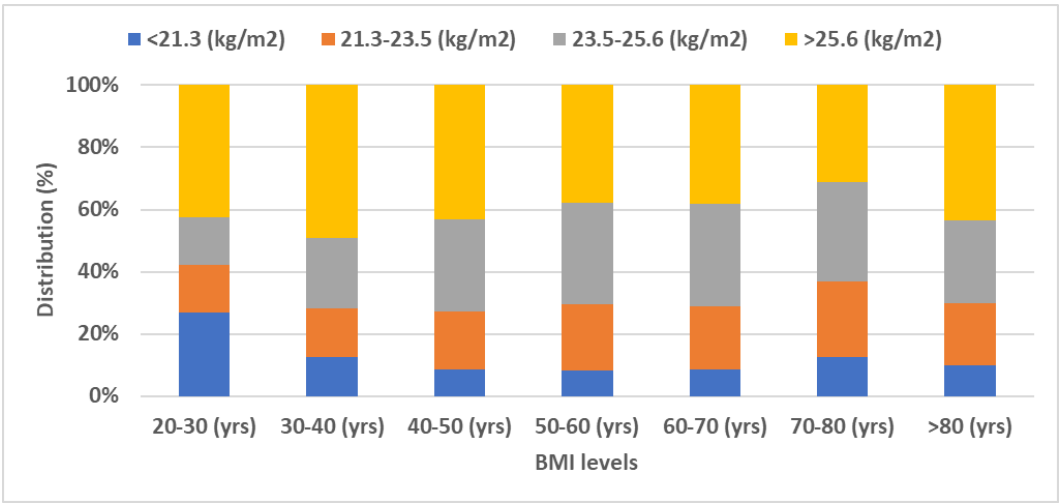


Figure 12. Distribution of BMI by age in diabetics

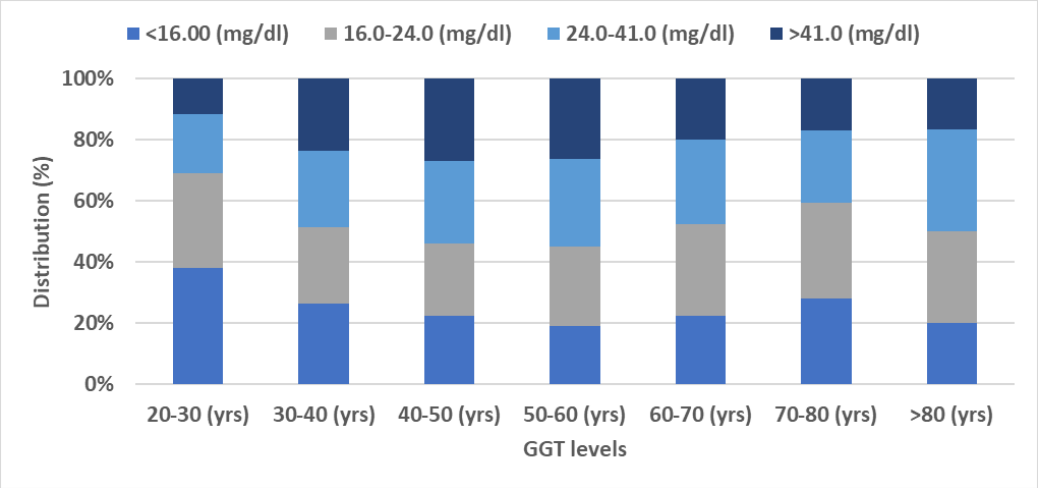


Figure 13. Distribution of GGT by age in non-diabetics

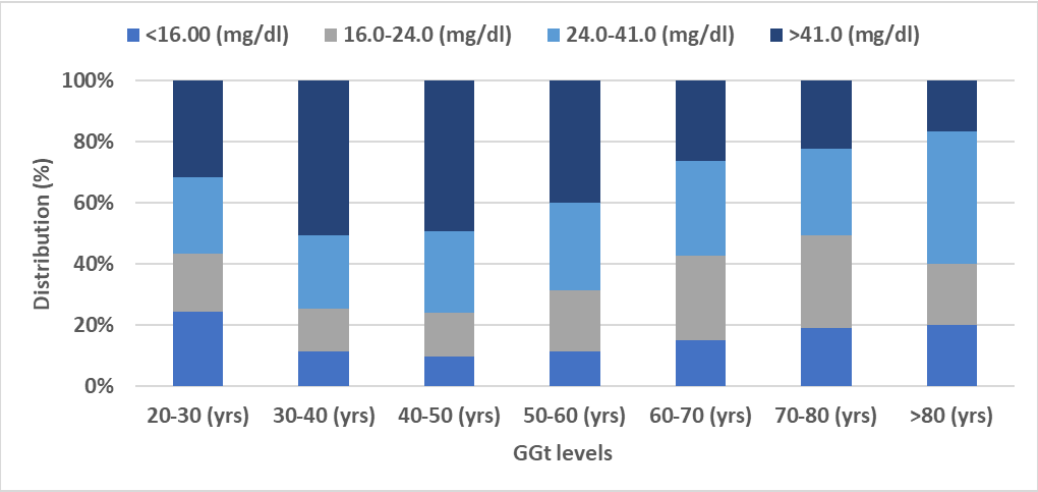


Figure 14. Distribution of GGT by age in diabetics

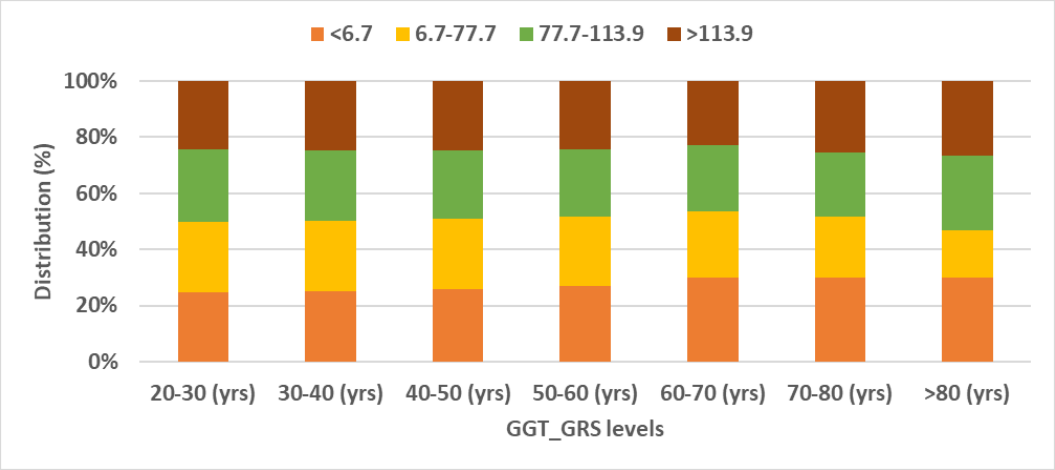


Figure 15. Distribution of GGT_GRS by age in non-diabetics

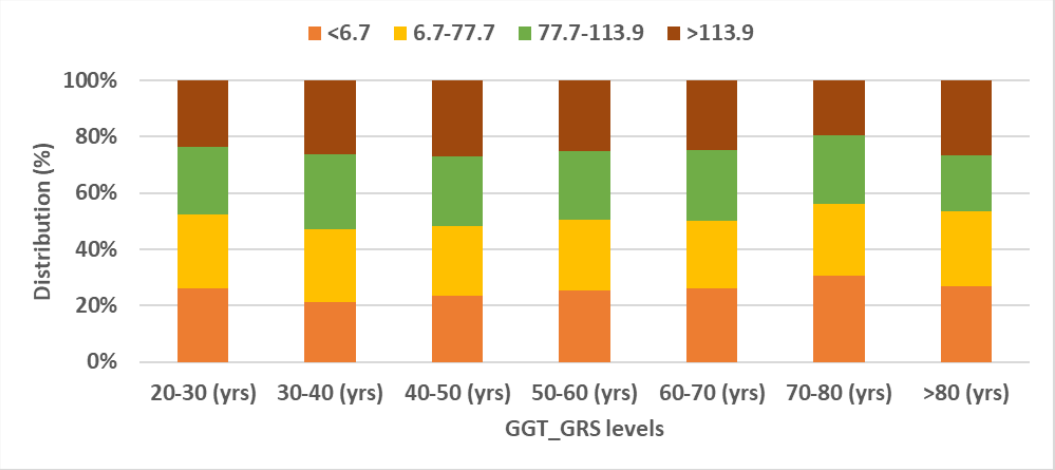


Figure 16. Distribution of GGT_GRS by age in diabetics

3. Hazard Risks (HR) for incidence of Diabetes Mellitus (DM) by BMI and GGT concentraions

BMI was classified into 4 groups of lower than 21.3(kg/m^2), 21.3-23.5(kg/ m^2), 23.5-25.6(kg/ m^2), and higher than 25.6(kg/ m^2), and GGT was classified into 4 groups of lower than 16.0(mg/dl), 16.0-24.0(mg/dl), 24.0-41.0(mg/dl), and higher than 41.0 (mg/dl). When the risk ratio for diabetes in the group with BMI lower than 21.3 (kg/ m^2) was 1.00, the risk for male subjects in the group with BMI higher than 25.6(kg/ m^2) was significantly increased by 1.05, and in the group with GGT higher than 41.0(mg/dl), by 1.98. GGT converted to genetic score was classified into 4 groups of lower than 6.7, 6.3-77.7, 77.7-113.9, and higher than 113.9. When the risk ratio for diabetes in the group with BMI lower than 21.3(kg/ m^2) was 1.00, the risk for the group with BMI higher than 25.6(kg/ m^2) was increased significantly by 2.40, and in the group with GGT_GRS >113.9, by 2.45 [Table 5]. The risk for female subjects increased significantly by 1.60 in the group with BMI higher than 25.6(kg/m2), and by 3.30 in the group with GGT higher than 41.0 (mg/dl). When converted to genetic score, the risk increased significantly by 3.02 in the group with BMI higher than 25.6(kg/ m^2), and by 2.83 in the group with GGT_GRS higher

than 113.9 [Table 6]. In both male and female subjects, the risk ratio for diabetes increased significantly with the increase of BMI and GGT level.

Subjects with both AST and ALT levels higher than 40(mg/dl) were excluded from the study because they were considered to have fatty liver, and HR was calculated. When the risk ratio for diabetes in the group with BMI lower than 21.3 (kg/ m^2) was 1.00, the risk for male subjects in the group with BMI higher than 25.6(kg/ m^2) was significantly increased by 0.95, and for the group with GGT higher than 41.0(mg/dl), by 1.61. In case of GGT converted to genetic score, when the risk ratio for diabetes in the group with BMI lower than 21.3(kg/ m^2) was 1, the risk was significantly increased by 1.89 in the group with BMI higher than 25.6(kg/ m^2), and by 1.75 in the group with GGT_GRS >113.9 [Table 7]. The risk for female subjects was significantly increased by 1.58 in the group with BMI higher than 25.6(kg/ m^2), and by 2.93 in the group with GGT higher than 41.0 (mg/dl). In case of GGT converted to genetic score, the risk was significantly increased by 2.37 in the group with BMI higher than 25.6(kg/m2), and by 2.42 in the group with GGT_GRS higher than 113.9 [Table 8].

4. Incidence of Diabetes Mellitus (DM) by BMI and GGT concentraions

BMI was classified into 4 groups of lower than 21.3(kg/ m^2), 21.3-23.5(kg/ m^2), 23.5-25.6(kg/ m^2), and higher than 25.6(kg/ m^2), GGT was classified into 4 groups of lower than 16.0(mg/dl), 16.0-24.0(mg/dl), 24.0-41.0(mg/dl), and higher than 41.0 (mg/dl), and the prevalence rate of diabetes was compared between the gender groups. In all groups, the prevalence rate of diabetes increased with GGT [Figure 17 & 18]. In particular, the highest prevalence rate of diabetes was observed in BMI(Q4) and GGT(Q4) (male: 13.19%, female: 15.78%) [Figure 17 & 18].

Subjects with both AST and ALT levels higher than 40(mg/dl) were excluded from the study because they were considered to have fatty liver, and HR was calculated. In all groups, the prevalence rate of diabetes increased with GGT [Figure 19 & 20]. In particular, the highest prevalence rate of diabetes was observed in BMI(Q4) and GGT(Q4) (male: 9.59%, female: 9.01%) [Figure 19 & 20]

Table 6. Hazard Risks (HR) for incidence of diabetes mellitus by BMI and GGT concentrations (Male)

Male		BMI levels								
		<21.3		21.3-23.5		23.5-25.6		>25.6		TOT
		Events	HR	Events	HR (95% CI)	Events	HR (95% CI)	Events	HR (95% CI)	HR (95% CI)
GGT_levels	<16.0 (n=375)	96	1.00	127	0.90 (0.62-1.34)	101	0.94 (0.63-1.40)	51	1.04 (0.63-1.72)	1.01 (0.87-1.78)
	16.0-24.0 (n=1,597)	229	1.00	479	1.31 (1.05-1.64)	493	1.60 (1.28-2.00)	396	1.93 (1.53-2.44)	1.24 (1.15-1.32)
	24.0-41.0 (n=3,771)	237	1.00	731	1.26 (1.04-1.53)	1,319	1.60 (1.33-1.92)	1,484	1.95 (1.62-2.34)	1.24 (1.19-1.30)
	>41.0 (n=7,183)	257	1.00	921	1.23 (1.04-1.46)	2,078	1.48 (1.26-1.74)	3,937	1.97 (1.69-2.31)	1.27 (1.23-1.32)
GGT_GRS levels	<6.7 (n=2,956)	219	1.00	554	1.29 (1.05-1.58)	912	1.73 (1.42-2.10)	1,271	2.40 (1.98-2.91)	1.35 (1.29-1.42)
	6.7-77.7 (n=3,251)	210	1.00	554	1.55 (1.24-1.93)	970	1.94 (1.57-2.40)	1,547	3.19 (2.59-3.92)	1.47 (1.40-1.55)
	77.7-113.9 (n=3,240)	197	1.00	538	1.21 (1.98-1.50)	1,056	1.74 (1.43-2.13)	1,449	2.04 (1.67-2.49)	1.27 (1.21-1.34)
	>113.9 (n=3,459)	193	1.00	612	1.43 (1.16-1.76)	1,053	1.76 (1.44-2.15)	1,601	2.45 (2.02-2.98)	1.33 (1.27-1.40)

*Adjusted for age, alcohol status, smoking status, exercise status, FM, MDM, LDL, HDL, TG, FBS, AST, and ALT
*GGT; Gamma-glutamyl Transferase, GRS; Genetic risk score, BMI; Body mass index, HR; Hazard ratio; CI; Confidence interval

Table 7. Hazard Risks (HR) for incidence of diabetes mellitus by BMI and GGT concentrations (Female)

Male		BMI levels								
		<21.3		21.3-23.5		23.5-25.6		>25.6		TOT
		Events	HR	Events	HR (95% CI)	Events	HR (95% CI)	Events	HR (95% CI)	HR (95% CI)
GGT_levels	<16.0 (n=1,735)	536	1.00	489	1.06 (0.90-1.24)	376	1.22 (1.02-1.46)	334	1.60 (1.32-1.94)	1.16 (1.09-1.24)
	16.0-24.0 (n=1,659)	286	1.00	359	1.45 (1.18-1.79)	443	2.13 (1.73-2.62)	571	2.46 (2.00-3.02)	1.34 (1.26-1.43)
	24.0-41.0 (n=1,163)	93	1.00	238	2.05 (1.52-2.77)	304	2.23 (1.66-3.01)	528	3.11 (2.33-4.15)	1.35 (1.26-1.46)
	>41.0 (n=623)	41	1.00	103	1.69 (1.08-2.65)	148	1.94 (1.25-3.01)	331	3.30 (2.19-4.99)	1.46 (1.31-1.63)
GGT_GRS levels	<6.73 (n=1,392)	265	1.00	321	1.54 (1.24-2.12)	340	1.93 (1.55-2.41)	466	3.02 (2.44-3.74)	1.43 (1.34-1.52)
	6.7-77.7 (n=1,260)	238	1.00	303	1.29 (1.03-1.62)	315	1.80 (1.43-2.41)	404	2.30 (1.82-2.90)	1.33 (1.24-1.43)
	77.7-113.9 (n=1,299)	235	1.00	300	1.54 (1.24-1.92)	313	1.70 (1.35-2.14)	451	2.59 (2.08-3.22)	1.35 (1.26-1.44)
	>113.9 (n=1,229)	218	1.00	265	1.37 (1.08-1.74)	303	2.09 (1.65-2.64)	443	2.83 (2.23-3.58)	1.42 (1.32-1.53)

*Adjusted for age, alcohol status, smoking status, exercise status, FM, MDM, LDL, HDL, TG, FBS, AST, and ALT
*GGT; Gamma-glutamyl Transferase, GRS; Genetic risk score, BMI; Body mass index, HR; Hazard ratio; CI; Confidence interval

Table 8. Hazard Risks (HR) for incidence of diabetes mellitus by BMI and GGT concentrations (Male)

Male		BMI levels								
		<21.3		21.3-23.5		23.5-25.6		>25.6		TOT
		Events	HR	Events	HR (95% CI)	Events	HR (95% CI)	Events	HR (95% CI)	HR (95% CI)
GGT_levels	<16.0 (n=367)	94	1.00	124	0.89 (0.60-1.31)	100	0.90 (0.60-1.36)	49	0.95 (0.57-1.59)	0.98 (0.84-1.15)
	16.0-24.0 (n=1,528)	223	1.00	466	1.30 (1.04-1.63)	475	1.59 (1.27-1.99)	364	1.85 (1.46-2.35)	1.22 (1.14-1.31)
	24.0-41.0 (n=3,232)	223	1.00	682	1.28 (1.05-1.56)	1,168	1.54 (1.27-1.87)	1,159	1.83 (1.50-2.22)	1.21 (1.15-1.27)
	>41.0 (n=3,991)	181	1.00	648	1.22 (0.99-1.50)	1,342	1.36 (1.11-1.66)	1,820	1.61 (1.32-1.97)	1.16 (1.11-1.22)
GGT_GRS levels	<6.7 (n=2,170)	207	1.00	488	1.19 (0.96-1.47)	716	1.41 (1.14-1.73)	759	1.89 (1.53-2.33)	1.25 (1.18-1.32)
	6.7-77.7 (n=2,318)	183	1.00	471	1.53 (1.20-1.95)	755	1.87 (1.47-2.36)	909	2.60 (2.05-3.29)	1.34 (1.26-1.42)
	77.7-113.9 (n=2,281)	172	1.00	459	1.21 (0.96-1.53)	800	1.48 (1.18-1.84)	850	1.55 (1.24-1.94)	1.14 (1.08-1.21)
	>113.9 (n=2,349)	159	1.00	502	1.31 (1.04-1.66)	814	1.48 (1.18-1.86)	874	1.75 (1.39-2.19)	1.18 (1.11-1.25)

*Excluding AST and ALT level over 40
*Adjusted for age, alcohol status, smoking status, exercise status, FM, MDM, LDL, HDL, TG, and FBS
*GGT; Gamma-glutamyl Transferase, GRS; Genetic risk score, BMI; Body mass index, HR; Hazard ratio; CI; Confidence interval

Table 9. Hazard Risks (HR) for incidence of diabetes mellitus by BMI and GGT concentrations (Female)

Male		BMI levels								
		<21.3		21.3-23.5		23.5-25.6		>25.6		TOT
		Events	HR	Events	HR (95% CI)	Events	HR (95% CI)	Events	HR (95% CI)	HR (95% CI)
GGT_levels	<16.0 (n=1,717)	532	1.00	485	1.05 (0.90-1.24)	370	1.20 (1.00-1.44)	330	1.58 (1.30-1.92)	1.16 (1.09-.23)
	16.0-24.0 (n=1,598)	281	1.00	348	1.42 (1.15-1.76)	419	2.04 (1.65-2.51)	550	2.41 (1.95-2.97)	1.33 (1.25-1.42)
	24.0-41.0 (n=1,002)	86	1.00	221	1.96 (1.43-2.68)	265	1.95 (1.42-2.68)	430	2.65 (1.94-3.62)	1.28 (1.18-1.39)
	>41.0 (n=393)	35	1.00	79	1.89 (1.15-3.10)	90	1.70 (1.03-2.83)	189	2.93 (1.82-4.72)	1.36 (1.19-1.55)
GGT_GRS levels	<6.7 (n=1,268)	260	1.00	311	1.48 (1.19-1.84)	302	1.59 (1.26-2.01)	395	2.37 (1.88-2.98)	1.30 (1.21-1.40)
	6.7-77.7 (n=1,159)	230	1.00	293	1.30 (1.03-1.63)	287	1.68 (1.33-2.13)	349	2.04 (1.59-2.61)	1.27 (1.18-1.37)
	77.7-113.9 (n=1,165)	230	1.00	279	1.42 (1.13-1.78)	283	1.51 (1.19-1.91)	373	2.03 (1.61-2.57)	1.24 (1.16-1.34)
	>113.9 (n=1,118)	214	1.00	250	1.26 (0.99-1.61)	272	1.84 (1.44-2.35)	382	2.42 (1.88-3.10)	1.36 (1.25-1.47)

*Excluding AST and ALT level over 40
*Adjusted for age, alcohol status, smoking status, exercise status, FM, MDM, LDL, HDL, TG, and FBS
*GGT; Gamma-glutamyl Transferase, GRS; Genetic risk score, BMI; Body mass index, HR; Hazard ratio; CI; Confidence interval

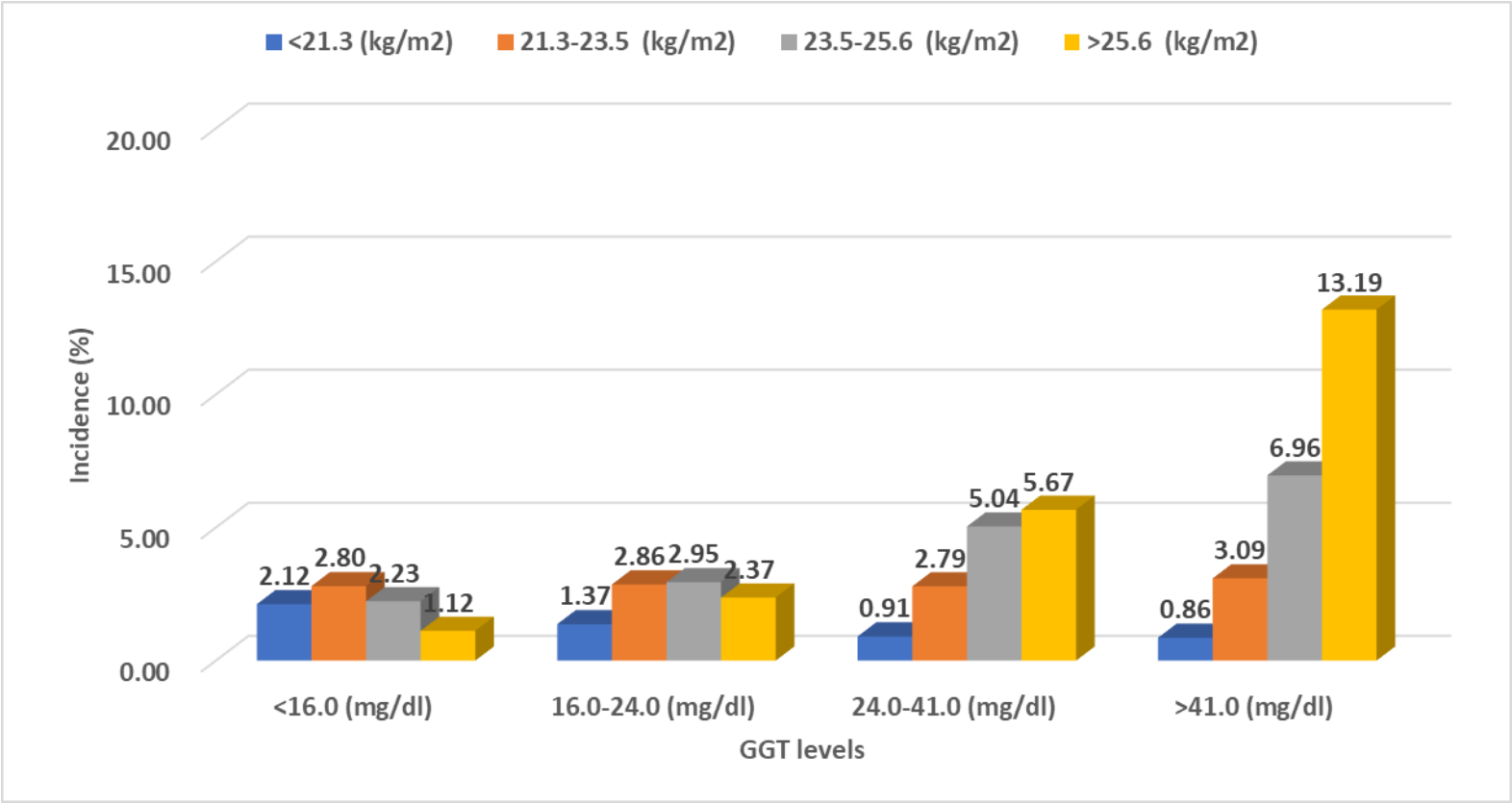


Figure 17. Incidence of diabetes by BMI and baseline GGT concentration (Male)

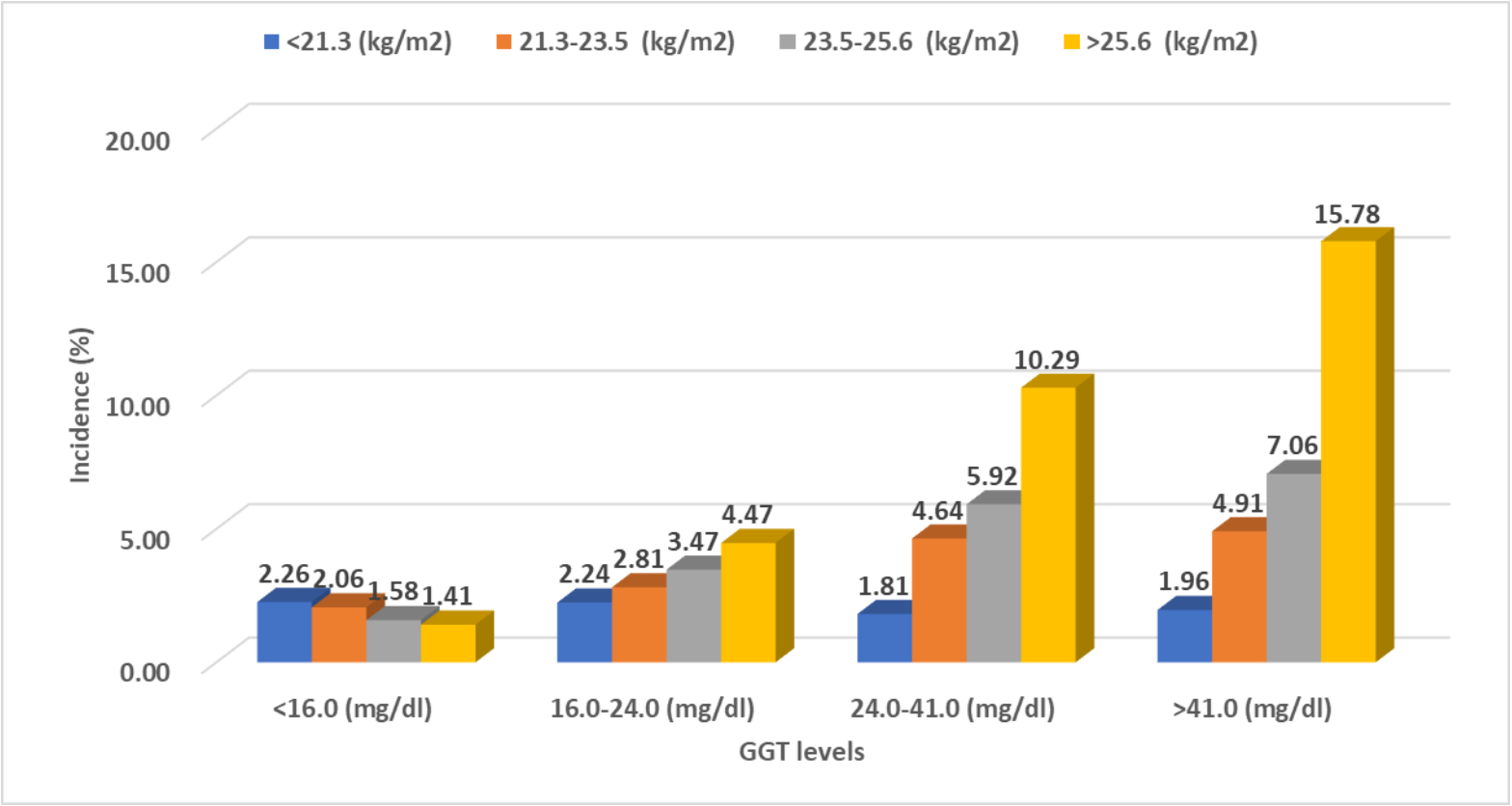


Figure 18. Incidence of diabetes by BMI and baseline GGT concentration (Female)

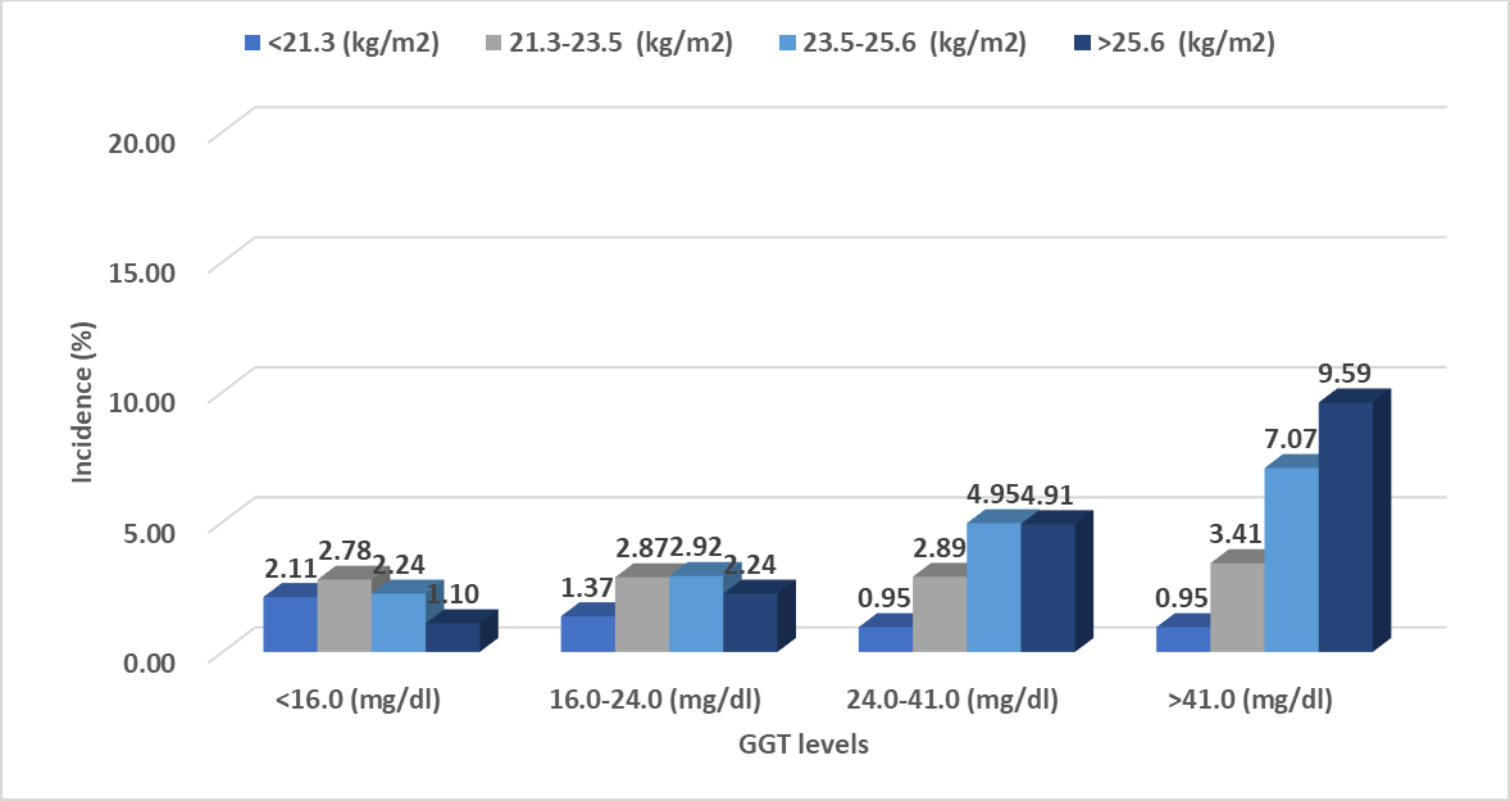


Figure 19. Incidence of diabetes by BMI and baseline GGT concentration (Male) excluding AST and ALT level over 40(mg/dl)

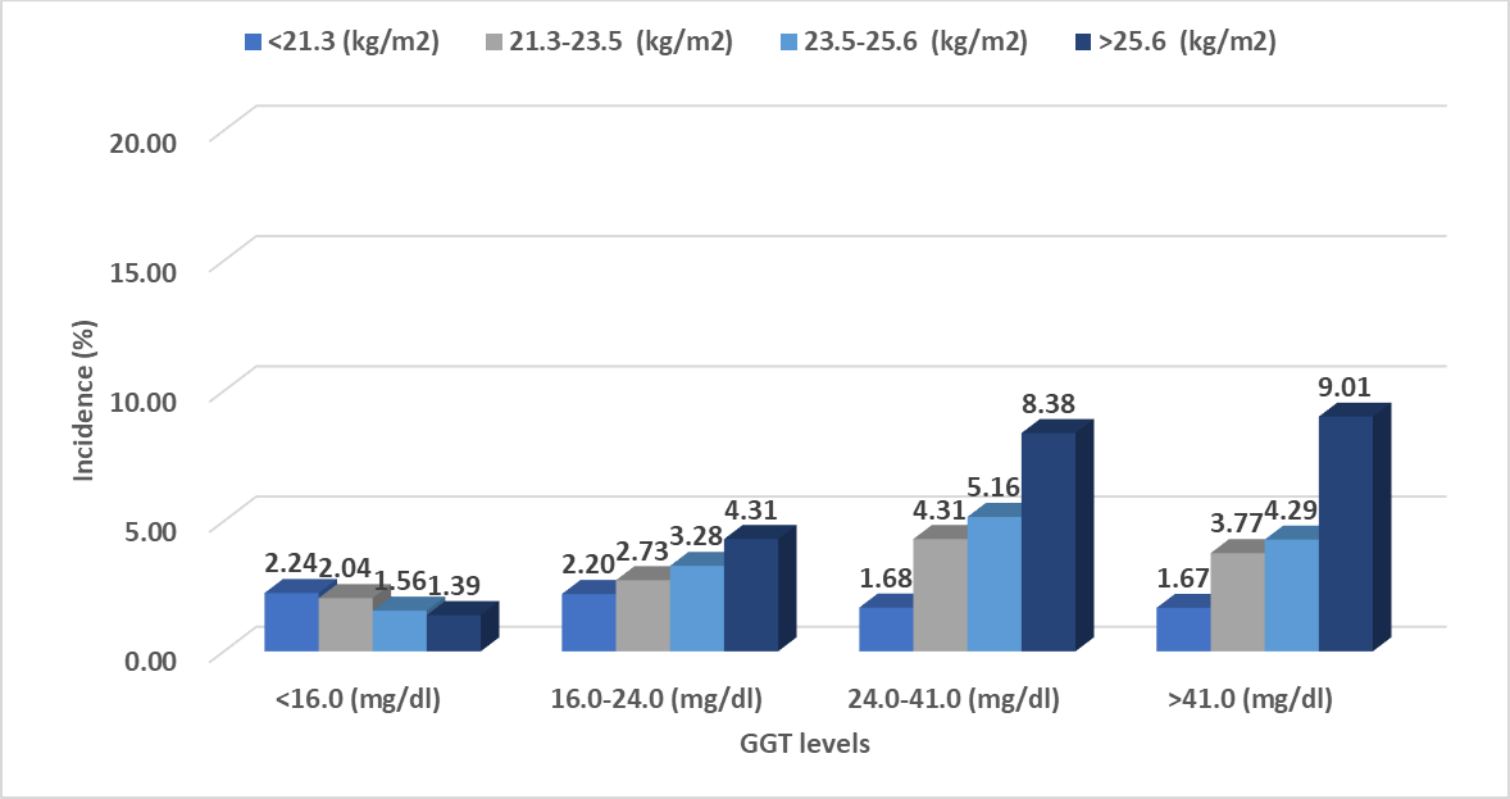


Figure 20. Incidence of diabetes by BMI and baseline GGT concentration (Female) excluding AST and ALT level over 40(mg/dl)

Ⅳ. DISCUSSION

1. Key findings

A significant relationship was confirmed in this study between BMI and the risk of diabetes with GGT level elevation in Korean adults. After controlling potential confounders, the group with the highest serum GGT showed 2~4 times higher risk of diabetes than the group with the lowest serum GGT level in both male and female groups. Similar results were achieved when the GGT level was converted to genetic score, and no remarkable tendency was observed. These results showed a similar tendency to previous studies, and can be interpreted that the relationship between BMI and the onset of diabetes is modified by GGT levels elevated by environmental factors, rather than by congenital factors such as genetic factors.

2. Previous studies

Previous studies reported the relationship between GGT levels and the risk of diabetes (André et al., 2006; D.-H. Lee, Ha, et al., 2003; D.-H. Lee, Jacobs Jr, et al., 2003; MEISINGER et al., 2005; Zhao et al., 2020). According to a prospective study, the influence of age and BMI on the risk of diabetes differed by GGT levels. In subjects with low GGT levels (68% of participants), age and BMI showed a low relevancy to the risk of diabetes, however in the group with high GGT (11% of participants), age and BMI showed a high relevancy to the risk of diabetes (D.-H. Lee, Ha, et al., 2003a). Another study reported a graded relationship between GGT levels and the risk of type 2 diabetes (Perry et al., 1998). According to a Japanese cross-sectional study, GGT levels showed a relationship with increase in the risk of diabetes, regardless of age, gender, smoking, alcohol intake, BMI, SBP, ALT, AST, TG and FBS (Zhao et al., 2020). In addition, a non-linear relationship between the GGT level and the risk of diabetes was reported. When the GGT level was lower than 24IU/L, the risk of diabetes increased with GGT level, and when the GGT level was higher than 24IU/L, the risk level was constant.

As for meta-analysis, there was a difference between the results from before

and after 2009(Kunutsor et al., 2014). Results from meta-analysis before 2009 were focused on dose-dependent relationship, however the results thereafter used a non-linear model to explain the relationship between GGT levels and type 2 diabetes. The risk of diabetes was strong when the GGT level was 9~35U/L, however no increase or decrease was observed at levels higher than 35U/L (Kunutsor et al., 2014). In a gender stratification analysis, male subjects showed a tendency of sharp increase at GGT levels of 4.5~23U/L and gradual increase thereafter, and female subjects showed an increase of diabetes risk at the GGT level of GGT 7U/L (Kunutsor et al., 2014; Logue et al., 2011).

Although the observation studies prove the relationship between GGT levels and risk of diabetes, it is unclear whether there is a confounder between GGT levels and diabetes. During the recent years, genetic information was used to deduce causal relationship in diseases with complicated pathogenesis. These deductions are based on the fact of randomization. Therefore, genetic modifications are inherited regardless of potential confounders (Emdin et al., 2017). Based on these facts, a study was conducted using Mendelian Randomization (MR) method to reveal the relationship between GGT and diabetes. According to the MR study results,

although the relationship between genetic modifications and GGT levels was observed, there was no relevancy to the onset of diabetes (Nano et al., 2017). According to the study results using Two- Sample MR analysis, there was no relevancy between GGT and the onset of diabetes (Bi et al., 2022). According to a study conducted in Korea, the result from a single genetic modification showed a 11% higher risk of type 2 diabetes for per unit (1(IU/L)) increase in the GGT level, and when 7 previously proved genetic modifications were used in the analysis, the risk ratio increased by 2.6% (Y. S. Lee et al., 2016). This result implies the possibility that the genetic modification of GGT may be a risk factor of type 2 diabetes..

3. Mechanisms of GGT and Diabetes

The main biologic mechanism that supports the relationship between GGT levels and the onset on type 2 diabetes can be explained by oxidative stress and inflammation. GGT is an enzyme that is located on the outer surface of the cell membrane in many organs of the human body, and plays a key role in intracellular antioxidation. It is mainly expressed in the liver, and is known to increase by factors that cause hepatocellular damage (Kaneko et al., 2019; D.-H. Lee, Ha, et al., 2003). Although the causes of GGT level elevation are known as alcohol intake and hepatocellular damage, there are studies reporting that other complex factors also contribute to the elevation of GGT level, and based on these reports, GGT elevation should be considered as an index of oxidative stress to the human body, rather than simply the result of alcohol intake and hepatocellular damage. (André et al., 2006; Bi et al., 2022; D.-H. Lee, Gross, et al., 2004; Logue et al., 2011).

Serum GGT levels increase to maintain glutathione level, which is an intracellular antioxidant. Therefore, it can be deduced that GGT is closely related to oxidative stress. According to an observative study, when excessive stress depletes intracellular glutathione, GGT synthesis is induced to supply intracellular

glutathione (D.-H. Lee, Gross, et al., 2004; D.-H. Lee, Steffen, et al., 2004). . In order to compensate for external oxidative stress, GGT located on the hepatocellular membrane is involved in the breakdown of extracellular glutathione to meet the intracellular demand of amino acids (André et al., 2006; D.-H. Lee, Gross, et al., 2004; D.-H. Lee, Steffen, et al., 2004). However, liver diseases, alcohol and external factors increase free radicals and depletes glutathione, which leads to the elevation of GGT level (D.-H. Lee, Blomhoff, et al., 2004; Whitfield, 2001). Therefore, when interpreting GGT level elevations, multiple causes other than alcohol intake or hepatocellular damage should be considered even if the level is within normal range.

Non-alcoholic fatty liver disease can be another factor that explains the relationship between GGT and the onset of diabetes. Non-alcoholic fatty liver disease is known as a metabolic syndrome that is connected to insulin resistance, hypertension, central obesity, dyslipidemia and diabetes (Balkau et al., 2010; Finelli & Tarantino, 2013; Islam et al., 2020; Lebovitz, 2006). In addition, it is related to obesity and accumulation of visceral fat, and is a common finding of insulin resistance

syndrome (Ahn et al., 2014). GGT can thus be related to diabetes through non-alcoholic fatty liver disease, and cause problems concerning insulin resistance (Grønbæk et al., 2008; J.-H. Lee et al., 2020; Thamer et al., 2005). Insulin resistance refers to a state in which there is a dysfunction of insulin in lowering blood sugar, which results in ineffective control of cellular and metabolic glucose balance, and leads to the overload of beta cells (Fernandez-Real & Pickup, 2012). A large-scale cohort study conducted in Korea observed the relationship between GGT and the onset of diabetes by controlling hsCRP and HOMA-IR. The risk ratio of male subjects in the model without calibration at GGT level 4(>51U/L) was 3.75(CI: 2.96-4.75), and in the model with hsCRP and HOMA-IR controlled, 2.55 (CI: 1.86-3.51). The risk ratio of female subjects at GGT level 4(>19U/L) was 3.33(CI: 2.66-4.17), and in the model with hsCRP and HOMA-IR controlled, 1.90 (CI: 1.40-2.58) (J.-H. Lee et al., 2020). This implies that liver enzymes are related to insulin resistance in diabetic patients. On the other hand, a Chinese study analyzed and evaluated the relationship between insulin resistance and liver enzymes according to body weight in adults without diabetes. Insulin resistance was related to the risk of ALT, AST and GGT elevation even in individuals without

diabetes (Liu et al., 2021). Therefore, insulin resistance may be an important predictive factor for abnormal liver enzyme levels in individuals without diabetes, and this relationship can be a stronger predictive factor in overweight and obese population.

Another possible mechanism can be explained by congenital immunity. Although many genetic loci related to diabetes have been revealed recently through GWAS analysis, the genetic locus definitely involved in inflammation and macrophage function was not related to insulin resistance (Ioannidis et al., 2009; Prasad & Groop, 2015). Furthermore, the possibility of genetic modification in diabetes influencing insulin resistance is only 0.01% (Palmer et al., 2008; Ruchat et al., 2009). Most of the confirmed genetic loci appear to influence the production of insulin by pancreatic beta cells (Ioannidis et al., 2009; Prasad & Groop, 2015). Physiological causes and investigation is more complicated for insulin resistance than the sensitivity of diabetes due to the dysfunction of pancreatic beta cells, presenting issues that hinder related studies.

Therefore, further studies are necessary to investigate the relationship between GGT levels and onset of diabetes, and the continuously increasing prevalence rate of diabetes should be focused through the interaction between genetic factors and rapidly changing environmental factors.

4. Strengths and limitations

The advantages of this study are the large scale and the accuracy. The number of subjects participating in the study are approximately 160,000, and the documentation of medical examination, physical examination, and blood samples are well established. Because all participants were assigned with an identification number at birth, follow-up observation is convenient, and diagnosis of cancer shows a high accuracy because it is based on histological type. These reasons guarantee sufficient statistical power in investigating the relationship between serum GGT levels and diabetes. The second advantage of this study is the young mean age of the subjects, allowing long-term assessment of health promoting behaviors and habits and their influence in the early stages of middle age. The third advantage is the comparison of risk ratio between GGT levels in blood and converted genetic risk scores. Obviously, confounders can be included, however

the difference in risk ratio when blood GGT levels and GGT_GRS are controlled can present many possibilities regarding future studies, providing new hypothesis. However, there are limitations to this study as well. First, the collected data are concentrated on the participants from Seoul and Gyung-gi area, and cannot represent the entire Korean population. Therefore, the generalized approximation of diabetes prevalence is limited. Second, the criteria for fatty liver is controlled by AST or ALT levels, leading to imprecision in the discrimination between GGT level elevation and the presence of liver disease, and this can be a confounder in the analysis of relationship between GGT and type 2 diabetes. Third, the mechanism of the relationship between GGT levels and the risk of type 2 diabetes is unclear. Oxidative stress, insulin resistance, liver disease and congenital factors are suggested as the cause, however definite results are yet to be confirmed.

Ⅴ. CONCLUSIONS

This study confirmed a significant relationship between BMI and the risk of diabetes in cases with elevated GGT levels in Korean adults. However, when GGT levels were converted by genetic scores, no remarkable tendency was observed. These results can be interpreted that the relationship between BMI and the onset of diabetes is dependent on the elevated GGT level due to external factors such as environmental factor, rather than internal factors such as genetic factor. Therefore, if external factors that elevate GGT level can be controlled and GGT level can be maintained within normal range, it could provide a basis for the prediction and prevention of diabetes and many other degenerative diseases, opening a new prospect in the field of preventive medicine..

References

Ahn, H. R., Shin, M. H., Nam, H. S., Park, K. S., Lee, Y. H., Jeong, S. K., Choi, J. S., & Kweon, S. S. (2014). *The association between liver enzymes and risk of type 2 diabetes: the Namwon study. Diabetol Metab Syndr 6 (1): 14*.

Al-Goblan, A. S., Al-Alfi, M. A., & Khan, M. Z. (2014). Mechanism linking diabetes mellitus and obesity. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*, *7*, 587.

André, P., Balkau, B., Born, C., Charles, M.-A., & Eschwège, E. (2006). Three-year increase of gamma-glutamyltransferase level and development of type 2 diabetes in middle-aged men and women: the DESIR cohort. *Diabetologia*, *49*(11), 2599–2603.

Arnott, C., Li, Q., Kang, A., Neuen, B. L., Bompoint, S., Lam, C. S. P., Rodgers, A., Mahaffey, K. W., Cannon, C. P., & Perkovic, V. (2020). Sodium-glucose cotransporter 2 inhibition for the prevention of cardiovascular events in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. *Journal of the American Heart Association*, *9*(3), e014908.

Astrup, A., & Finer, N. (2000a). Redefining Type 2 diabetes: 'Diabesity' or 'Obesity Dependent Diabetes Mellitus'? *Obesity Reviews*, *1*(2), 57–59. https://doi.org/https://doi.org/10.1046/j.1467-789x.2000.00013.x

Balkau, B., Lange, C., Fumeron, F., & Bonnet, F. (2010). Nine-year incident diabetes is predicted by fatty liver indices: the French DESIR study. *BMC Gastroenterology*, *10*(1), 1–9.

Bi, Y., Yang, S., Liu, Y., Cao, L., Gao, M., Liu, W., Li, Y., Tian, S., & Sun, C. (2022). To explore association between gamma-glutamyl transferase and type 2 diabetes using a real-world study and mendelian randomization analysis. *Frontiers in Endocrinology*, *13*.

Emdin, C. A., Khera, A. v, & Kathiresan, S. (2017). Mendelian randomization. *Jama*, *318*(19), 1925–1926.

Fernandez-Real, J. M., & Pickup, J. C. (2012). Innate immunity, insulin resistance and type 2 diabetes. *Diabetologia*, *55*(2), 273–278.

Finelli, C., & Tarantino, G. (2013). What is the role of adiponectin in obesity related non-alcoholic fatty liver disease? *World Journal of Gastroenterology: WJG*,

19(6), 802.

Fraser, A., Harris, R., Sattar, N., Ebrahim, S., Davey Smith, G., & Lawlor, D. A. (2009). Alanine Aminotransferase, γ-Glutamyltransferase, and Incident Diabetes: The British Women's Heart and Health Study and meta-analysis. *Diabetes Care*, *32*(4), 741–750. https://doi.org/10.2337/dc08-1870

Grønbæk, H., Thomsen, K. L., Rungby, J., Schmitz, O., & Vilstrup, H. (2008). Role of nonalcoholic fatty liver disease in the development of insulin resistance and diabetes. *Expert Review of Gastroenterology & Hepatology*, *2*(5), 705–711.

Hossain, P., Kawar, B., & el Nahas, M. (2007). Obesity and Diabetes in the Developing World — A Growing Challenge. *New England Journal of Medicine*, *356*(3), 213–215. https://doi.org/10.1056/NEJMp068177

Ioannidis, J., Thomas, G., & Daly, M. J. (2009). Validating, augmenting and refining genome-wide association signals. *Nature Reviews Genetics*, *10*(5), 318–329.

Islam, S., Rahman, S., Haque, T., Sumon, A. H., Ahmed, A. Z. M., & Ali, N. (2020). Prevalence of elevated liver enzymes and its association with type 2 diabetes: A cross-sectional study in Bangladeshi adults. *Endocrinology, Diabetes & Metabolism*, *3*(2), e00116.

Kaneko, K., Yatsuya, H., Li, Y., Uemura, M., Chiang, C., Hirakawa, Y., Ota, A., Tamakoshi, K., & Aoyama, A. (2019). Association of gamma-glutamyl transferase and alanine aminotransferase with type 2 diabetes mellitus incidence in middle-aged Japanese men: 12-year follow up. *Journal of Diabetes Investigation*, *10*(3), 837–845.

Kenny, H. C., & Abel, E. D. (2019). Heart failure in type 2 diabetes mellitus: impact of glucose-lowering agents, heart failure therapies, and novel therapeutic strategies. *Circulation Research*, *124*(1), 121–141.

Kilkkinen, A., Heistaro, S., Laatikainen, T., Janus, E., Chapman, A., Absetz, P., & Dunbar, J. (2007). Prevention of type 2 diabetes in a primary health care setting: Interim results from the Greater Green Triangle (GGT) Diabetes Prevention Project. *Diabetes Research and Clinical Practice*, *76*(3), 460–462. https://doi.org/10.1016/J.DIABRES.2006.09.027

Kunutsor, S. K., Abbasi, A., & Adler, A. I. (2014). Gamma-glutamyl transferase and risk of type II diabetes: an updated systematic review and dose-response meta-analysis. *Annals of Epidemiology*, *24*(11), 809–816.

Lebovitz, H. E. (2006). Insulin resistance–a common link between type 2 diabetes

and cardiovascular disease. *Diabetes, Obesity and Metabolism*, *8*(3), 237–249.

Lee, D.-H., Blomhoff, R., & Jacobs, D. R. (2004). Review is serum gamma glutamyltransferase a marker of oxidative stress? *Free Radical Research*, *38*(6), 535–539.

Lee, D.-H., Gross, M. D., & Jacobs Jr, D. R. (2004). Association of serum carotenoids and tocopherols with ɣ-glutamyltransferase: the Cardiovascular Risk Development in Young Adults (CARDIA) study. *Clinical Chemistry*, *50*(3), 582–588.

Lee, D.-H., Ha, M.-H., Kim, J.-H., Christiani, D. C., Gross, M. D., Steffes, M., Blomhoff, R., & Jacobs, D. R. (2003). Gamma-glutamyltransferase and diabetes-a 4 year follow-up study. *Diabetologia*, *46*, 359–364. https://doi.org/10.1007/s00125-003-1036-5

Lee, D.-H., Jacobs Jr, D. R., Gross, M., Kiefe, C. I., Roseman, J., Lewis, C. E., & Steffes, M. (2003). ɣ-glutamyltransferase is a predictor of incident diabetes and hypertension: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Clinical Chemistry*, *49*(8), 1358–1366.

Lee, D.-H., Steffen, L. M., & Jacobs Jr, D. R. (2004). Association between serum ɣ-glutamyltransferase and dietary factors: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. *The American Journal of Clinical Nutrition*, *79*(4), 600–605.

Lee, J.-H., Lee, H. S., & Lee, Y.-J. (2020). Serum ɣ-glutamyltransferase as an independent predictor for incident type 2 diabetes in middle-aged and older adults: Findings from the KoGES over 12 years of follow-up. *Nutrition, Metabolism and Cardiovascular Diseases*, *30*(9), 1484–1491.

Lee, Y. S., Cho, Y., Burgess, S., Davey Smith, G., Relton, C. L., Shin, S.-Y., & Shin, M.-J. (2016). Serum gamma-glutamyl transferase and risk of type 2 diabetes in the general Korean population: a Mendelian randomization study. *Human Molecular Genetics*, *25*(17), 3877–3886.

Liu, C., Shao, M., Lu, L., Zhao, C., Qiu, L., & Liuid, Z. (2021). *Obesity, insulin resistance and their interaction on liver enzymes*. https://doi.org/10.1371/journal.pone.0249299

Logue, J., Walker, J. J., Colhoun, H. M., Leese, G. P., Lindsay, R. S., McKnight, J. A., Morris, A. D., Pearson, D. W., Petrie, J. R., & Philip, S. (2011). Do men develop type 2 diabetes at lower body mass indices than women? *Diabetologia*, *54*(12), 3003–3006.

MEISINGER, C., LÖWEL, H., HEIER, M., SCHNEIDER, A., THORAND, B., & GROUP, F. O. R. T. H. E. K. S. (2005). Serum γ-glutamyltransferase and risk of type 2 diabetes mellitus in men and women from the general population. *Journal of Internal Medicine*, *258*(6), 527–535. https://doi.org/https://doi.org/10.1111/j.1365-2796.2005.01572.x

Nannipieri, M., Gonzales, C., Baldi, S., Posadas, R., Williams, K., Haffner, S. M., Stern, M. P., & Ferrannini, E. (2005). Liver Enzymes, the Metabolic Syndrome, and Incident Diabetes : The Mexico City Diabetes Study. *Diabetes Care*, *28*(7), 1757–1762. https://doi.org/10.2337/diacare.28.7.1757

Nano, J., Muka, T., Ligthart, S., Hofman, A., Darwish Murad, S., Janssen, H. L. A., Franco, O. H., & Dehghan, A. (2017). Gamma-glutamyltransferase levels, prediabetes and type 2 diabetes: a Mendelian randomization study. *International Journal of Epidemiology*, *46*(5), 1400–1409.

Palmer, N. D., Goodarzi, M. O., Langefeld, C. D., Ziegler, J., Norris, J. M., Haffner, S. M., Bryer-Ash, M., Bergman, R. N., Wagenknecht, L. E., & Taylor, K. D. (2008). Quantitative trait analysis of type 2 diabetes susceptibility loci identified from whole genome association studies in the Insulin Resistance Atherosclerosis Family Study. *Diabetes*, *57*(4), 1093–1100.

Perry, I. J., Wannamethee, S. G., & Shaper, A. G. (1998). Prospective study of serum γ-glutamyltransferase and risk of NIDDM. *Diabetes Care*, *21*(5), 732–737.

Poznyak, A., Grechko, A. v, Poggio, P., Myasoedova, V. A., Alfieri, V., & Orekhov, A. N. (2020). The diabetes mellitus–atherosclerosis connection: The role of lipid and glucose metabolism and chronic inflammation. *International Journal of Molecular Sciences*, *21*(5), 1835.

Prasad, R. B., & Groop, L. (2015). Genetics of type 2 diabetes—pitfalls and possibilities. *Genes*, *6*(1), 87–123.

Ruchat, S.-M., Elks, C. E., Loos, R. J. F., Vohl, M.-C., Weisnagel, S. J., Rankinen, T., Bouchard, C., & Pérusse, L. (2009). Association between insulin secretion, insulin sensitivity and type 2 diabetes susceptibility variants identified in genome-wide association studies. *Acta Diabetologica*, *46*(3), 217–226.

Saeedi, P., Petersohn, I., Salpea, P., Malanda, B., Karuranga, S., Unwin, N., Colagiuri, S., Guariguata, L., Motala, A. A., Ogurtsova, K., Shaw, J. E., Bright, D., & Williams, R. (2019). Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. *Diabetes Research and*

Clinical Practice, *157*, 107843. https://doi.org/10.1016/J.DIABRES.2019.107843

Sonmez, A., Yumuk, V., Haymana, C., Demirci, I., Barcin, C., Kıyıcı, S., Güldiken, S., Örük, G., Saydam, B. O., & Baldane, S. (2019). Impact of obesity on the metabolic control of type 2 diabetes: results of the Turkish nationwide survey of glycemic and other metabolic parameters of patients with diabetes mellitus (TEMD obesity study). *Obesity Facts*, *12*(2), 167–178.

Thamer, C., Tschritter, O., Haap, M., Shirkavand, F., Machann, J., Fritsche, A., Schick, F., Häring, H., & Stumvoll, M. (2005). Elevated serum GGT concentrations predict reduced insulin sensitivity and increased intrahepatic lipids. *Hormone and Metabolic Research*, *37*(04), 246–251.

Verma, S., & Hussain, M. E. (2017a). Obesity and diabetes: An update. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*, *11*(1), 73–79. https://doi.org/10.1016/J.DSX.2016.06.017

Whitfield, J. B. (2001). Gamma glutamyl transferase. *Critical Reviews in Clinical Laboratory Sciences*, *38*(4), 263–355.

Zhao, W., Tong, J., Liu, J., Liu, J., Li, J., & Cao, Y. (2020). *The Dose-Response Relationship between Gamma-Glutamyl Transferase and Risk of Diabetes Mellitus Using Publicly Available Data: A Longitudinal Study in Japan*. https://doi.org/10.5061/dryad.8q0p192

APPENDICES

Appendix Table 1. Hazard Risks (HR) for incidence of diabetes mellitus by BMI and GGT concentrations (Male)

Male		BMI levels							
		<21.4		21.4-23.5		23.5-25.6		>25.6	
		Events	HR	Events	HR (95% CI)	Events	HR (95% CI)	Events	HR (95% CI)
GGT_levels	<16.0 (n=375)	94	1.00	124	1.10 (0.75-1.59)	101	1.28 (0.87-1.87)	51	1.46 (0.91-2.33)
	16.0-24.0 (n=1,597)	229	0.88 (0.63-1.24)	479	1.19 (0.87-1.63)	493	1.48 (1.09-2.01)	396	1.89 (1.38-2.58)
	24.0-42.0 (n=3,771)	237	1.26 (0.90-1.76)	731	1.66 (1.23-2.24)	1,319	2.19 (1.63-2.94)	1,484	2.77 (2.06-3.71)
	>42.0 (n=7,193)	257	2.16 (1.56-2.99)	921	2.63 (1.95-3.54)	2,078	3.17 (2.37-4.24)	3,937	4.25 (3.18-5.68)
GGT_GRS levels	<6.7 (n=2,956)	219	1.00	554	1.35 (1.10-1.66)	912	1.88 (1.56-2.28)	1,271	2.76 (2.29-3.33)
	6.7-77.7 (n=3,281)	210	1.02 (0.78-1.32)	554	1.48 (1.21-1.82)	970	1.86 (1.54-2.26)	1,547	3.14 (2.61-3.78)
	77.7-113.9 (n=3,240)	197	1.24 (0.96-1.60)	538	1.51 (1.23-1.85)	1,056	2.19 (1.81-2.65)	1,449	2.53 (2.10-3.05)
	>113.9 (n=3,459)	193	1.17 (0.91-1.51)	612	1.66 (1.36-2.03)	1,053	2.03 (1.68-2.46)	1,601	2.76 (2.29-3.33)

*Adjusted for age, alcohol status, smoking status, exercise status, family history of DM, Medication use of DM, LDL, HDL, TG, FBS, AST, and ALT
*GGT; Gamma-glutamyl Transferase, GRS; Genetic risk score, BMI; Body mass index, HR; Hazard ratio; CI; Confidence interval

Appendix Table 2. Hazard Risks (HR) for incidence of diabetes mellitus by BMI and GGT concentrations (Female)

Female		BMI levles							
		<21.4		21.4-23.5		23.5-25.6		>25.6	
		Events	HR	Events	HR (95% CI)	Events	HR (95% CI)	Events	HR (95% CI)
GGT_levels	<16.0 (n=1,735)	536	1.00	489	1.19 (1.02-1.39)	376	1.49 (1.26-1.77)	334	2.14 (1.79-2.56)
	16.0-24.0 (n=1,659)	286	1.04 (0.86-1.25)	359	1.56 (1.31-1.86)	443	2.37 (2.01-2.79)	571	2.84 (2.42-3.33)
	24.0-41.0 (n=1,163)	93	1.26 (0.96-1.66)	238	2.50 (2.06-3.04)	304	2.70 (2.24-3.24)	528	3.83 (3.26-4.51)
	>41.0 (n=623)	41	1.63 (1.11-2.40)	103	2.19 (1.66-2.90)	148	2.51 (1.96-3.21)	331	3.45 (2.84-4.19)
GGT_GRS levels	<6.7 (n=1,392)	265	1.00	321	1.51 (1.22-1.86)	340	1.87 (1.52-2.31)	466	2.98 (2.44-3.63)
	6.7-77.7 (n=1,260)	238	1.00 (0.80-1.26)	303	1.32 (1.07-1.63)	315	1.92 (1.55-2.38)	404	2.32 (1.89-2.85)
	77.7-113.9 (n=1,299)	235	1.02 (0.82-1.28)	300	1.52 (1.22-1.88)	313	1.79 (1.44-2.21)	451	2.74 (2.24-3.35)
	>113.9 (n=1,229)	218	0.95 (0.75-1.20)	265	1.26 (1.01-1.57)	303	1.92 (1.55-2.38)	443	2.43 (1.98-3.00)

*Adjusted for age, alcohol status, smoking status, exercise status, family history of DM, Medication use of DM, LDL, HDL, TG, FBS, AST, and ALT
*GGT; Gamma-glutamyl Transferase, GRS; Genetic risk score, BMI; Body mass index, HR; Hazard ratio; CI; Confidence interval

Appendix Table 3 . Hazard Risks (HR) for incidence of diabetes mellitus by BMI and GGT concentrations (Male)

Male		BMI levels							
		<21.4		21.4-23.5		23.5-25.6		>25.6	
		Events	HR	Events	HR (95% CI)	Events	HR (95% CI)	Events	HR (95% CI)
GGT_levels	<16.0 (n=367)	94	1.00	124	1.08 (0.74-1.58)	100	1.23 (0.84-1.81)	49	1.30 (0.80-2.11)
	16.0-24.0 (n=1,528)	223	0.86 (0.61-1.21)	466	1.11 (0.81-1.53)	475	1.35 (0.99-1.85)	364	1.64 (1.19-2.25)
	24.0-41.0 (n=3,232)	223	1.16 (0.83-1.62)	682	1.49 (1.10-2.02)	1,168	1.80 (1.34-2.44)	1,159	2.10 (1.56-2.84)
	>41.0 (n=3,991)	181	1.71 (1.21-2.42)	648	2.07 (1.52-2.82)	1,342	2.28 (1.68-3.08)	1,820	2.72 (2.01-3.67)
GGT_GRS levels	<6.7 (n=2,170)	207	1.00	488	1.23 (0.99-1.52)	716	1.51 (1.23-1.86)	759	1.97 (1.61-2.41)
	6.7-77.7 (n=2,318)	183	0.86 (0.85-1.14)	471	1.28 (1.03-1.59)	755	1.51 (1.23-1.86)	909	2.10 (1.72-2.57)
	77.7-113.9 (n=2,281)	172	1.18 (0.90-1.54)	459	1.42 (1.14-1.76)	800	1.72 (1.41-2.11)	850	1.73 (1.41-2.11)
	>113.9 (n=2,349)	159	1.12 (0.85-1.46)	502	1.44 (1.16-1.78)	814	1.64 (1.33-2.00)	874	1.89 (1.54-2.31)

*Excluding AST and ALT levels over 40(mg/dl)
*Adjusted for age, alcohol status, smoking status, exercise status, family history of DM, Medication use of DM, LDL, HDL, TG, FBS, AST, and ALT
*GGT; Gamma-glutamyl Transferase, GRS; Genetic risk score, BMI; Body mass index, HR; Hazard ratio; CI; Confidence interval

Appendix Table 4 . Hazard Risks (HR) for incidence of diabetes mellitus by BMI and GGT concentrations (Female)

Female		BMI levels							
		<21.4		21.4-23.5		23.5-25.6		>25.6	
		Events	HR	Events	HR (95% CI)	Events	HR (95% CI)	Events	HR (95% CI)
GGT_levels	<16.0 (n=1,717)	532	1.00	485	1.15 (0.98-1.35)	370	1.40 (1.18-1.66)	330	1.98 (1.65-2.37)
	16.0-24.0 (n=1,598)	281	1.01 (0.84-1.22)	348	1.42 (1.19-1.70)	419	2.07 (1.75-2.45)	550	2.47 (2.09-2.91)
	24.0-41.0 (n=1,002)	86	1.14 (0.86-1.52)	221	2.16 (1.76-2.64)	265	2.12 (1.74-2.59)	430	2.88 (2.40-3.44)
	>41.0 (n=393)	35	1.30 (0.85-1.99)	79	1.97 (1.46-2.67)	90	1.79 (1.31-2.43)	189	2.07 (1.62-2.66)
GGT_GRS levels	<6.7 (n=1,268)	260	1.00	311	1.46 (1.18-1.80)	302	1.59 (1.28-1.98)	395	2.41 (1.96-2.97)
	6.7-77.7 (n=1,159)	230	0.96 (0.76-1.22)	293	1.25 (1.01-1.56)	287	1.70 (1.37-2.12)	349	1.93 (1.55-2.39)
	77.7-113.9 (n=1,165)	230	1.01 (0.80-1.27)	279	1.41 (1.13-1.75)	283	1.58 (1.26-1.97)	373	2.17 (1.75-2.68)
	>113.9 (n=1,118)	214	0.95 (0.75-1.20)	250	1.16 (0.92-1.46)	272	1.67 (1.33-2.08)	382	2.03 (1.63-2.53)

*Excluding AST and ALT levels over 40(mg/dl)
*Adjusted for age, alcohol status, smoking status, exercise status, family history of DM, Medication use of DM, LDL, HDL, TG, FBS, AST, and ALT
*GGT; Gamma-glutamyl Transferase, GRS; Genetic risk score, BMI; Body mass index, HR; Hazard ratio; CI; Confidence interval

Appendix Table 5. Hazard Risks (HR) for incidence of diabetes mellitus by BMI and GGT concentrations (Model)

Total	BMI levels			
	<21.4	21.4-23.5	23.5-25.6	>25.6
	HR	HR (95% CI)	HR (95% CI)	HR (95% CI)
Model1	1.00	1.39 (1.29-1.50)	1.84 (1.71-1.97)	2.59 (2.41-2.78)
Model2	1.00	1.29 (1.19-1.39)	1.61 (1.49-1.73)	2.16 (2.01-2.32)
Model3	1.00	1.39 (1.29-1.50)	1.84 (1.71-1.97)	2.59 (2.41-2.78)

*Model1: Adjusted for age, sex, alcohol status, smoking status, exercise status, family history of DM, medication use of DM, LDL, HDL, TG, FBS, AST, and ALT
*Model2: Adjusted for age, sex, alcohol status, smoking status, exercise status, family history of DM, medication use of DM, LDL, HDL, TG, FBS, AST, and ALT and GGT_levels
*Model3: Adjusted for age, sex, alcohol status, smoking status, exercise status, family history of DM, medication use of DM, LDL, HDL, TG, FBS, AST, and ALT and GGT_GRS levels
*GGT; Gamma-glutamyl Transferase, BMI; Body mass index, HR; Hazard ratio; CI; Confidence interval

Appendix Table 6. Hazard Risks (HR) for incidence of diabetes mellitus by BMI and GGT concentration (GGT_level(Q1))

Total		BMI levels			
		<21.4	21.4-23.5	23.5-25.6	>25.6
		HR	HR (95% CI)	HR (95% CI)	HR (95% CI)
GGT_GRS levels	<6.7	1.00	1.08 (0.83-1.39)	1.05 (0.79-1.41)	1.27 (0.91-1.76)
	6.73-77.7	1.00	0.89 (0.67-1.19)	1.00 (0.72-1.38)	1.45 (1.03-2.04)
	77.7-113.9	1.00	1.06 (0.78-1.43)	1.14 (0.82-1.60)	1.28 (0.88-1.86)
	>113.9	1.00	1.11 (0.77-1.60)	1.47 (1.00-2.18)	2.57 (1.70-3.88)

*Adjusted for age, sex, alcohol status, smoking status, exercise status, family history of DM, medication use of DM, LDL, HDL, TG, FBS, AST, and ALT

*GGT; Gamma-glutamyl Transferase, GRS; Genetic risk score, BMI; Body mass index, HR; Hazard ratio; CI; Confidence interval

Appendix Table 7. Hazard Risks (HR) for incidence of diabetes mellitus by BMI and GGT concentration (GGT_level(Q2))

Total		BMI levels			
		<21.4	21.4-23.5	23.5-25.6	>25.6
		HR	HR (95% CI)	HR (95% CI)	HR (95% CI)
GGT_GRS levels	<6.7	1.00	1.37 (1.04-1.81)	2.00 (1.53-2.63)	2.40 (1.82-3.17)
	6.73-77.7	1.00	1.33 (0.97-1.81)	1.91 (1.40-2.60)	2.52 (1.69-3.18)
	77.7-113.9	1.00	1.43 (1.03-1.99)	1.95 (1.41-2.69)	2.52 (1.82-3.50)
	>113.9	1.00	1.30 (0.95-1.78)	1.25 (0.90-1.73)	1.67 (0.20-2.33)

*Adjusted for age, sex, alcohol status, smoking status, exercise status, family history of DM, medication use of DM, LDL, HDL, TG, FBS, AST, and ALT

*GGT; Gamma-glutamyl Transferase, GRS; Genetic risk score, BMI; Body mass index, HR; Hazard ratio; CI; Confidence interval

Appendix Table 8. Hazard Risks (HR) for incidence of diabetes mellitus by BMI and GGT concentration (GGT_level(Q3))

	Total	BMI levels			
		<21.4	21.4-23.5	23.5-25.6	>25.6
		HR	HR (95% CI)	HR (95% CI)	HR (95% CI)
GGT_GRS levels	<6.7	1.00	1.15 (0.85-1.56)	1.41 (1.06-1.89)	1.90 (1.43-2.52)
	6.73-77.7	1.00	2.17 (1.44-3.27)	2.90 (1.95-4.31)	3.90 (2.63-5.78)
	77.7-113.9	1.00	1.25 (0.94-1.68)	1.33 (1.00-1.77)	1.68 (1.27-2.21)
	>113.9	1.00	1.39 (1.00-1.93)	1.66 (1.21-2.29)	1.91 (1.39-2.64)

*Adjusted for age, sex, alcohol status, smoking status, exercise status, family history of DM, medication use of DM, LDL, HDL, TG, FBS, AST, and ALT

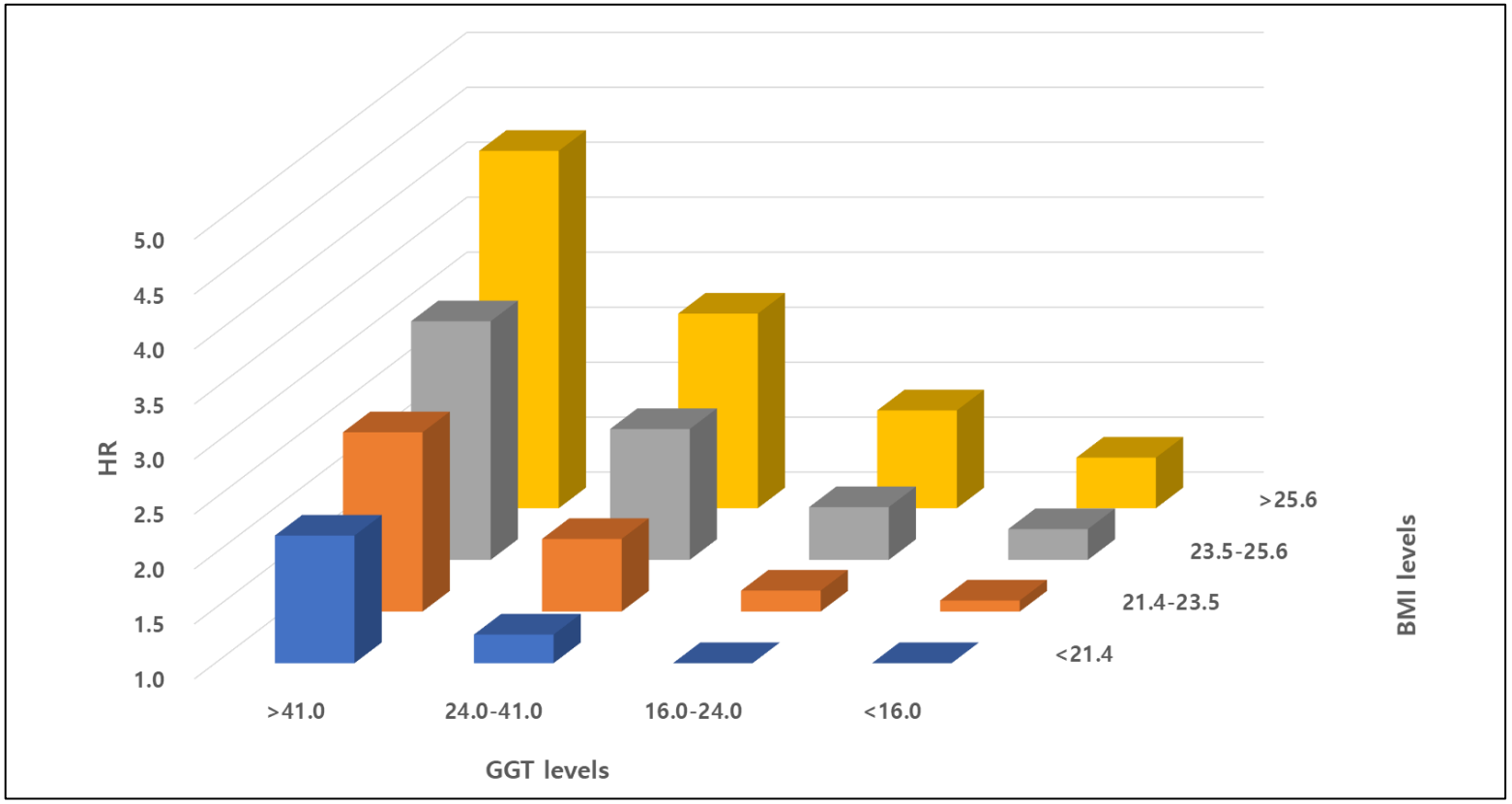
*GGT; Gamma-glutamyl Transferase, GRS; Genetic risk score, BMI; Body mass index, HR; Hazard ratio; CI; Confidence interval

Appendix Table 9. Hazard Risks (HR) for incidence of diabetes mellitus by BMI and GGT concentration (GGT_level(Q4))

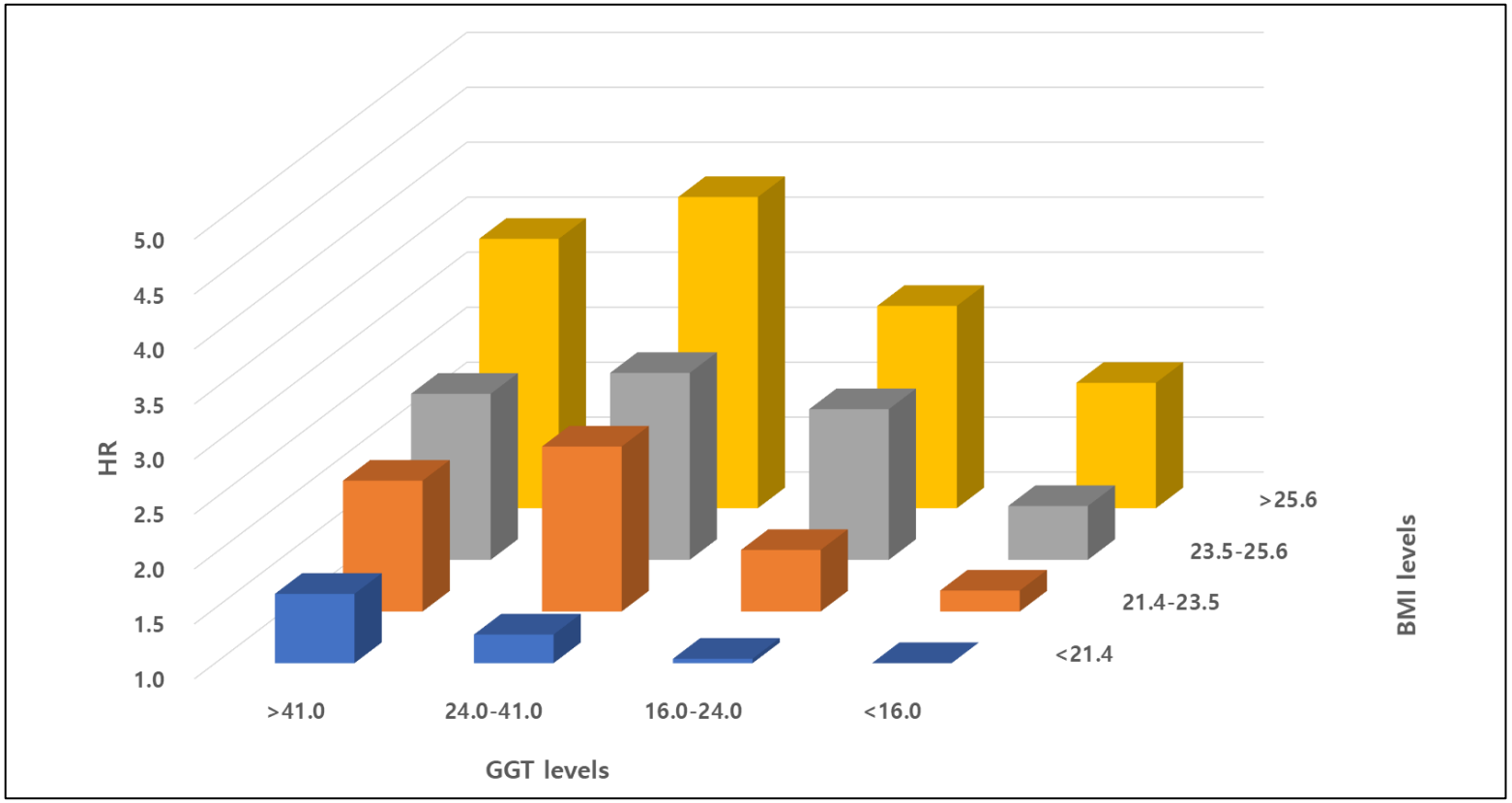
Total		BMI levels			
		<21.4	21.4-23.5	23.5-25.6	>25.6
		HR	HR (95% CI)	HR (95% CI)	HR (95% CI)
GGT_GRS levels	<6.7	1.00	2.08 (1.26-3.43)	2.20 (1.36-3.57)	3.25 (2.02-5.22)
	6.73-77.7	1.00	1.17 (0.86-1.60)	1.28 (0.95-1.71)	1.98 (1.49-2.63)
	77.7-113.9	1.00	1.78 (0.86-1.62)	1.68 (1.25-2.26)	1.95 (1.46-2.61)
	>113.9	1.00	1.23 (0.94-1.61)	1.47 (1.14-1.89)	1.96 (1.53-2.50)

*Adjusted for age, sex, alcohol status, smoking status, exercise status, family history of DM, medication use of DM, LDL, HDL, TG, FBS, AST, and ALT

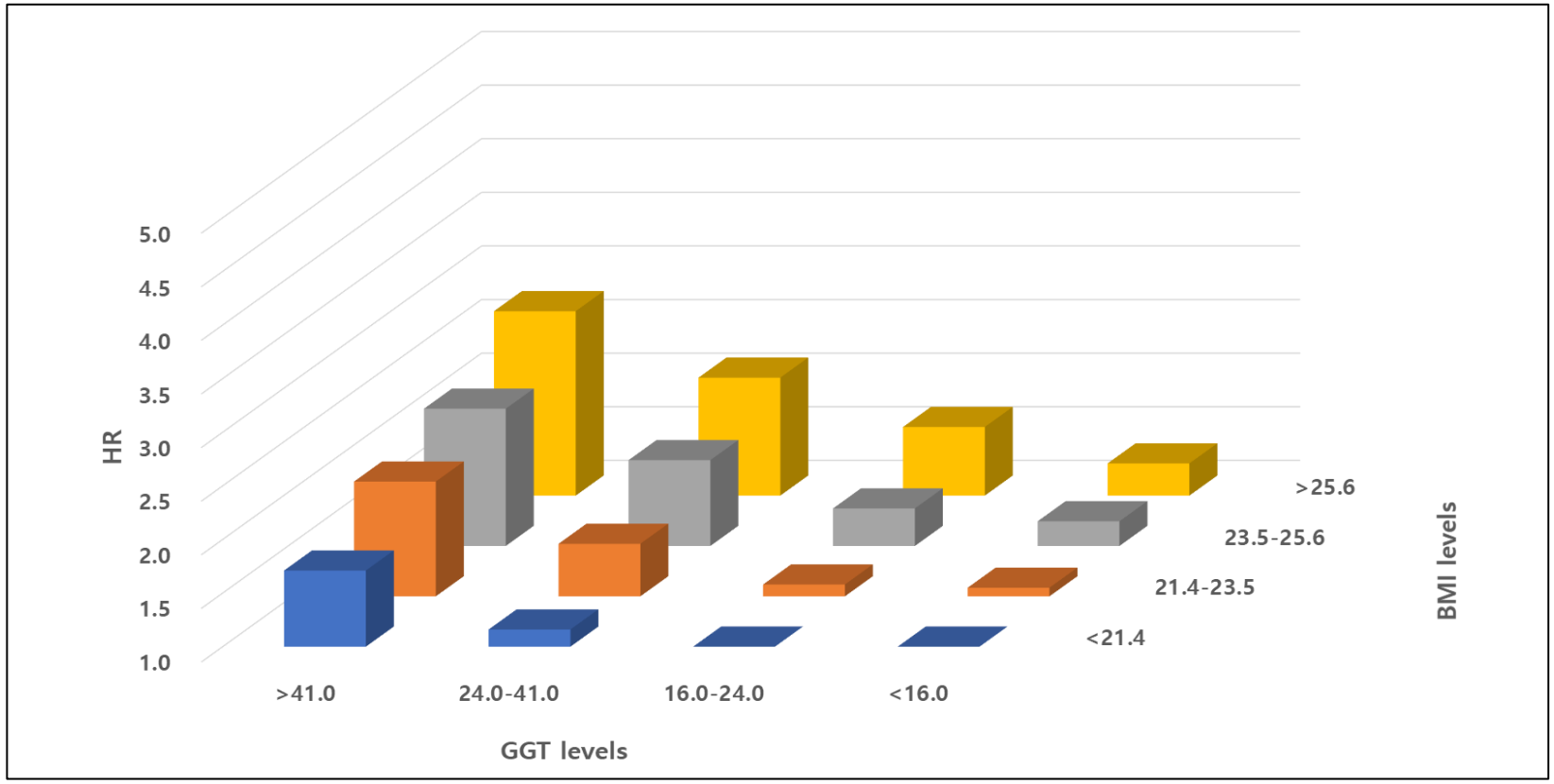
*GGT; Gamma-glutamyl Transferase, GRS; Genetic risk score, BMI; Body mass index, HR; Hazard ratio; CI; Confidence interval



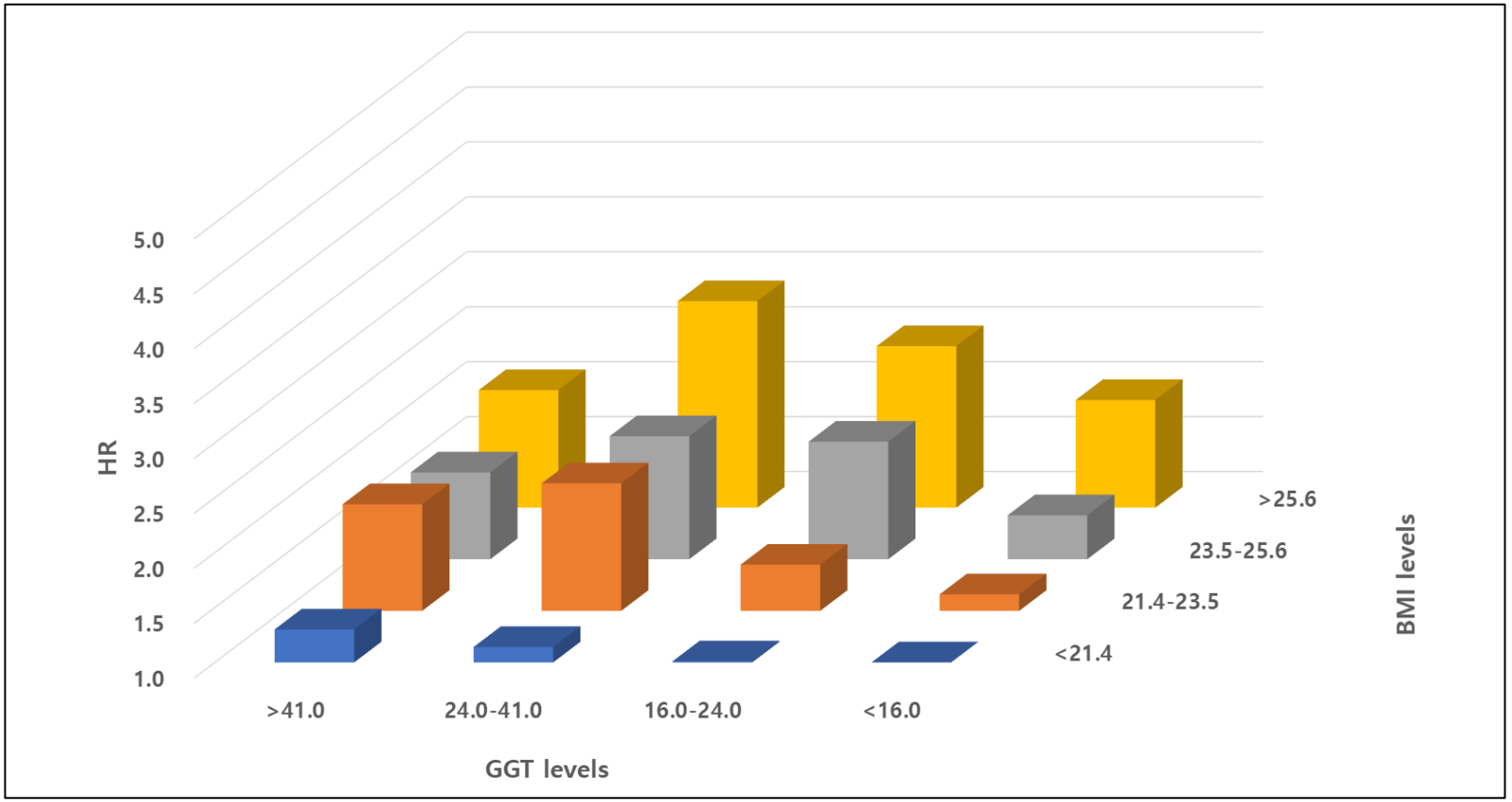
Appendix Figure 1. Incidence of diabetes by BMI and GGT concentration (Male)



Appendix Figure 2. Incidence of diabetes by BMI and GGT concentration (Female)



Appendix Figure 3. Incidence of diabetes by BMI and GGT concentration (Male) excluding AST and ALT level over 40(mg/dl)



Appendix Figure 4. Incidence of diabetes by BMI and GGT concentration (Female) excluding AST and ALT level over 40(mg/dl)

ABSTRACT (KOREAN)

감마글루타밀전이효소 수준에 따른 체질량지수와 당뇨병 발생과의 관련성 연구

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배경 및 목적:

글루타민전이효소(GGT)는 과도한 알코올 섭취, 알코올성 간염, 간경변증, 지방간, 간암 등의 각종 간담도계 질환의 표지자로 널리 사용되어져 왔다. 이에 GGT 상승과 당뇨병에 대한 다수의 연구가 진행되어 왔지만, GGT에 따라 체질량지수와 당뇨병의 연관성에 대해 분석한 연구는 아직 부족한 실정이다. 본 연구에서는 정상 범위내의

GGT 수준에 따라 체질량지수와 당뇨병 발생위험과의 관련성에 대해 알아보고자 하였다.

연구 방법:

연구는 2004-2013 전국 18개 종합검진센터에서 서면동의와 함께 연구에 참여한 160,407명으로 구축된 한국인 암 예방연구-Ⅱ를 대상으로 하였다. 대상자 중 당뇨병 유병자, 유전검사 결과를 이용할 수 없는 대상자, 주요 변수의 결측지를 가진 대상자를 제외한 121,053명을 최종 분석 대상자로 하였다. 체질량지수, GGT, 유전위험점수(Genetic Risk Score, GRS)로 환산한 GGT_GRS수치를 사분위수로 층화하여 분석하였다. GGT에 따른 체질량지수와 당뇨병 발생은 콕스 비례모형 회귀분석을 사용하였다.

연구 결과:

연구 대상자는 총 121,053명으로 남성 77,312명(63.87%), 여성 43,741명(36.13%)이었다. 이들 중 추적기간 동안 당뇨병 발생자는 20,701명(15%)이었다. 남성의 체질량지수는 24.41 kg/m2(표준편차: 2.90)이며, 여성은 22.15 kg/m2(표준편차: 3.09)로 남성이 여성보다 높았다. GGT 수치는 남성은 47.14 mg/dl이며, 여자는 18.80 mg/dl이었다. 남성과 여성 모두 체질량지수가 증가할수록 당뇨병에 대한 위험비가 유의하

게 증가하는 경향을 보였다. 특히, 이러한 관련성은 GGT 수치가 높은 군에서 강해지는 경향을 보였다. 그러나 이러한 관련성은 GGT_GRS 수준에 따라서 차이를 보이지 않았다.

결론 및 고찰:

한국 성인에서 체질량 지수와 당뇨병 발생과 관련성은 GGT 수치가 높은 군에서 증가하는 경향을 보였지만, GGT_GRS 수준에 따라서는 뚜렷한 경향성은 관찰되지 않았다. 따라서 체질량 지수와 당뇨병 발생과 관련성은 유전요인과 같은 내부적인 요인보다는 환경 등 외부요인에 의해 증가된 GGT 수준에 의해서 modify 되는 것으로 해석될 수 있다.

핵심어: 체질량지수, 감마글루타밀전인효소(GGT), 당뇨병, 위험비, 유전위험점수