The relation between weight changes and alanine aminotransferase levels in a nonalcoholic population

Ji Eun Yun

Department of Public Health

The Graduate School

Yonsei University

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Ji Eun Yun

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This certifies that the dissertation of Ji Eun Yun is approved.

Thesis Supervisor: Sun Ha Jee

Chung Mo Nam: Thesis Committee Member

Soon Young Lee: Thesis Committee Member

Hyeon Chang Kim: Thesis Committee Member

Justin Jeon: Thesis Committee Member

The Graduate School

Yonsei University

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Abstract

Nonalcoholic fatty liver disease (NAFLD) is one of the most common forms of chronic liver disease. Obesity is the single most common condition found in association with NAFLD. Obesity is also a risk factor for elevation of serum liver enzymes, reflecting hepatic injury. Of these liver enzymes, alanine aminotransferase (ALT) has been used as a marker of NAFLD.

A few studies have shown an association between weight change and serum ALT levels. However, weight change (gain or loss) was assessed at only one or two points of time, and this may be partly explained by the benefit of fewer observations. This has led to a question as whether weight change in several repeated data is associated with a risk of ALT abnormality. In the present study, which utilized selected data from a prospective cohort, the Korean Cancer Prevention Study (KCPS), I attempted to determine association between changes in weight and the risk of abnormal ALT levels in a nonalcoholic population.

The cohort study was performed on participants among 1,329,525 Koreans between the ages of 30 and 95 years who had at least one routine medical examination through the National Health Insurance Corporation (NHIC) between 1992 and 1995. Of the study participants, 241,334 nonalcoholic healthy subjects aged 30 to 44 years who had completed an examination in 1992, and who had body weight measurement data for at least four of the seven visits up to 2004 were included.

Abnormal ALT level was defined as ALT $\geq$40 IU/L. Three dimensions of weight changes were used in these analyses; these were the slope, initial value (intercept), and fluctuation of weight. The slope of weight was classified into five group based on quintiles in order to assess the associations between weight changes and ALT levels. The odds ratios (OR) and 95% confidence intervals (CI) were assessed using the generalized estimating equation (GEE) model to determine the risk of ALT abnormality.

The mean age of study subjects was 36.5 years for men and 35.2 years for women. An increased slope of weight was associated with ALT abnormality. A higher slope of weight was associated with substantially increased risk for abnormal ALT (OR for highest vs. lowest quintiles, 2.58 [95% CI, 2.50 to 2.66] for men; OR for highest vs. lowest quintiles, 2.30 [95% CI, 2.12 to 2.49] for women). Increased ALT abnormality was also strongly associated with increased initial weight and weight fluctuation. Initial weight and weight fluctuation were found to be independent risk factors for ALT abnormality, and modified the association between ALT abnormality and the slope of weight. More specifically, an increase in the slope of weight was significantly associated with a change in abnormal ALT risk among those who had low initial weight and among men with mild weight fluctuation.

In conclusion, these longitudinal data indicate a strong association between weight change and the risk of ALT abnormality. A higher slope of weight was strongly associated with an increased risk of ALT abnormality. The association between the slope of weight and ALT abnormality was modified by initial weight and weight fluctuation.

Keywords: weight change, obesity, ALT, aminotransferase

Ⅰ. Introduction

Obesity is a fast-growing problem that is reaching epidemic proportions worldwide, and is associated with an increased risk of premature death. Obesity is also associated with a variety of health risks, including increased incidence of cardiovascular events and diabetes mellitus (WHO, 2000; Klein et al, 2004; Lean et al, 2000). Weight gain during adult life seems to have a major effect on diabetes and cardiovascular risk, even within the normal body mass index (BMI) range (Hu et al, 2004). Obesity is also a risk factor for elevation of serum liver enzymes, which reflects hepatic injury (Lee et al, 2001; Strauss et al, 2000; Prati et al, 2002; loannou et al, 2005; Lawlor et al, 2005). Obesity has been postulated to contribute to the risk of non-alcoholic steatotic hepatitis (NASH), an increasingly frequent clinical event (Robinson and Whitehead, 1989; Salvaggio et al, 1991; Bizzaro et al, 1992; Burns et al, 1996; Lee et al, 2001; Strauss et al, 2000). Alcohol consumption is both a potential confounder and a modifier of the relationship between obesity and liver enzyme abnormalities. Obesity and alcohol are thought to cause liver enzyme elevations through different mechanisms, and effect modification is plausible (Mukai et al, 2002).

Nonalcoholic fatty liver disease (NAFLD) is one of the most common forms of chronic liver disease. In some patients, it can progress to cirrhosis, liver failure, and hepatocellular carcinoma (McCullough, 2002; Neuschwander-Tetri and Caldwell, 2003). In general, NAFLD in the absence of NASH is an indolent disease with a benign course. However, end-stage liver disease may occur as a consequence of NASH. The seriousness of this condition is demonstrated by the fact that approximately 50% of patients develop fibrosis, 15% develop cirrhosis, and 3% may advance to liver failure, which requires transplantation (Sheth et al, 1997). NASH is now being recognized as the underlying cause of most cases of cryptogenic cirrhosis

(Caldwell et al, 1999; Poonawala et al, 2000). NAFLD constitutes a spectrum of liver injuries associated with obesity and insulin resistance (Marchesini and Forlani, 2002; Kunde et al, 2005). The natural history of NAFLD is poorly understood, and it is not known why some patients progress to cirrhosis while others do not. However, obesity and insulin resistance have been shown to be associated with more histologically advanced disease (Gill et al, 2006). Obesity is the single most common condition found in association with NAFLD. Other features of the metabolic syndrome, such as hyperinsulinemia, hypertriglyceridemia, and hypertension, also play significant pathophysiological roles in its development.

NAFLD causes asymptomatic elevation of the level of liver enzymes, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), and r-glutamyltransferase (GGT) (Clark et al, 2003). Of these liver enzymes, ALT is most closely related to liver fat accumulation (Westerbacka et al, 2004), and ALT has consequently been used as a marker of NAFLD. Several cross-sectional studies have found associations between ALT and several features of metabolic syndrome. At present, ALT is often used as a surrogate marker for NAFLD in epidemiological studies (Schindhelm et al, 2006). Previous studies have reported that liver enzyme levels increase progressively with increasing BMI. Hepatic aminotransaminases, ALT and AST, are both markers for hepatocellular injury, although ALT is considered more specific (Kunde et al, 2005).

The relationships between weight change and health outcomes, as well as body weight, have been of great concern in recent years. Several prospective studies have reported that individuals showing fluctuations in body weight are at increased risk for cardiovascular and all-cause mortality (Hamm et al, 1989; Lissner et al, 1989; Lissner et al, 1991; Blair et al, 1993). In a recent study from the Chicago Western Electric Company, weight loss and weight gain were associated with increased mortality, but weight variability was not associated with mortality when weight loss or weight gain was taken into account (Dyer et al, 2000).

A few studies have shown an association between weight change and ALT

levels. Some clinically-based studies have also shown that the effect of weight loss seemed to be more crucial in normalizing the liver enzyme than reduced alcohol consumption (Fagerberg et al, 1993; Powell et al, 1990). In a longitudinal cohort study, Suzuki *et al.* showed that weight reduction ≥5% and regular exercise were independently associated with a decrease in serum ALT levels (Suzuki et al, 2005). Lee *et al.* (2001) also reported that ALT was strongly associated with BMI at baseline and a change in BMI was strongly associated with an abnormal ALT level on follow-up.

However, most studies about weight change and ALT levels were cross-sectional studies and intervention studies, and no data were presented from large prospective studies. Weight change (gain or loss) was assessed at only one or two points in time, and the observed relationships may be partly explained by the benefit of fewer observations. This has led to a question as to whether weight change in several repeated data (intentional or unintentional) increases the risk of ALT abnormality.

In this study, which utilized selected data from a prospective cohort, the Korean Cancer Prevention Study (KCPS), I attempted to determine the association between changes in weight and the risk of abnormal alanine aminotransferase (ALT) levels among a healthy nonalcoholic population.

Ⅱ. Objectives

The purpose of this study is to explore the relationship between weight change and the risk of abnormal ALT, which were measured repeatedly over 12 years in a nonalcoholic population.

Specifically,

1. To confirm the association between body weight and the risk of abnormal ALT level.
2. To examine the association between the slope of weight and the risk of abnormal ALT level.
3. To examine whether the association is modified by initial weight and weight fluctuation.

Ⅲ. Subjects and Methods

1. Study population

A cohort study was performed on participants among 1,329,525 Koreans between the ages of 30 and 95 years who had undergone one biennial medical evaluation through the National Health Insurance Corporation (NHIC) from 1992 to 1995 (Jee et al, 2005 & 2006). The NHIC provides health insurance to government employees, private school teachers, and staffs, as well as their dependents. For the analyses in this study, subjects were included based on the outlined inclusion criteria (Figure 1).

Participants were confined to 388,146 men and 101,007 women aged 35-44 years because the follow-up rate was not sufficient for those over 45 years of age due to the age-limit system for government employees and private school teachers and staff. The participants were examined at baseline (year 0) and at follow-up examinations in years 2, 4, 6, 8, 10, and 12. Participants were excluded if they had liver disease (including positive hepatitis B surface antigen), atherosclerotic cardiovascular disease, cancer, diabetes, or respiratory disease at or before the baseline visit (n=53,297), and if the mean value of the ALT level was not 40 IU/L or more at baseline. Participants who indicated daily alcohol consumption equal to or more than 20g/day at baseline were also excluded. The nonalcoholic population was defined as participants indicating alcohol consumption less than 20g/day. Of the nonalcoholic population, 245,919 subjects who had completed examination at 1992, and who had body weight measurements for at least four of the seven visits were included (Table 1). In addition, subjects with extremely low body mass index (<16 or >40kg/m^2) or short stature (1.3m or less), and those with extremely high ALT levels (≥100 IU/L) were excluded at baseline. Therefore, the final sample included 241,334 subjects. The study was approved by the Institutional Review Boards of Yonsei University and the Johns Hopkins Bloomberg School of Public Health.

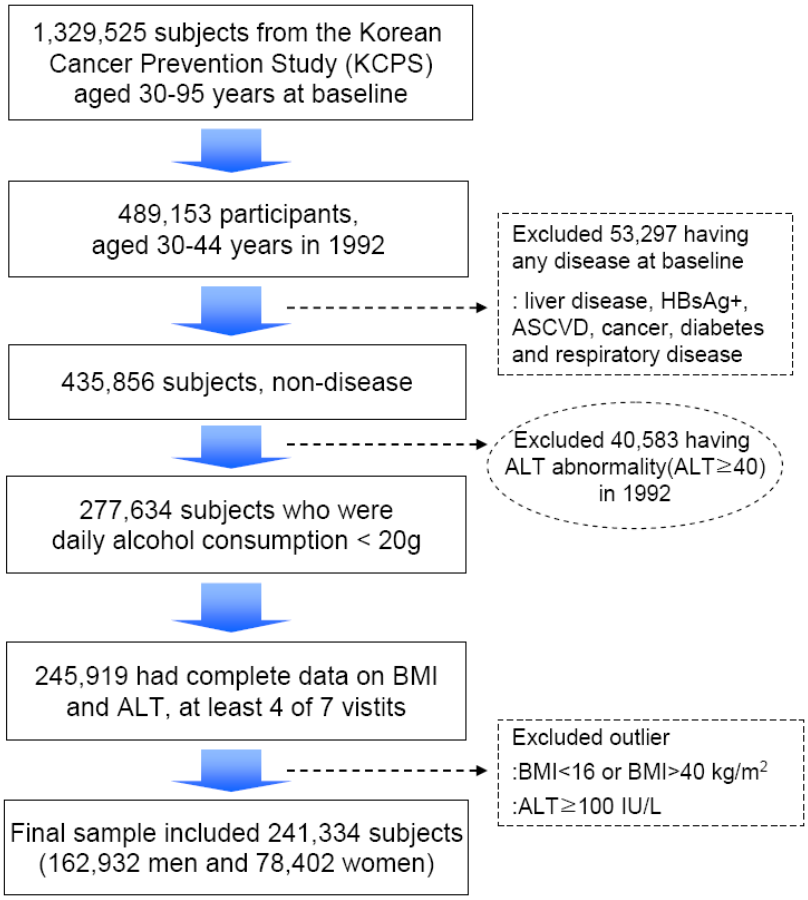


Figure 1. Flow chart of selection of the study population.

2. Data collection

This dataset was collected from participants who had 12 years of follow-up during examination; 82.3 percent subjects had weight measurements for at least six of the seven visits, and 62.2 percent had weight measurements for all seven visits. The KCPS database includes biennial health checkup data with the results of all

subsequent examinations, health-related information including past and family history, and lifestyle-related information such as alcohol consumption, smoking status, and exercise habits. Total daily alcohol consumption was expressed as the number of glasses per week, in relation to the most popular alcoholic beverage in the Republic of Korea, ‘Soju’.

The biennial medical examinations were conducted by medical staff at local hospitals according to a standard procedure. These routine examinations include measurement of weight and height (wearing light clothing), as well as blood pressure (taken while seated). Blood samples, taken after an overnight fast, were used to determine total cholesterol, serum glucose, and ALT. Quality control procedures were performed in accordance with the Korean Association of Laboratory Quality Control.

Hypertension was defined as a systolic blood pressure of at least 140mm Hg or a diastolic blood pressure of at least 90 mm Hg. Using diagnostic criteria from the National Diabetes Data Group (1999), diabetes was defined by a fasting serum glucose level of 126 mg/dL (6.99 mmol/L) or higher.

Table 1. Data collection schedule.

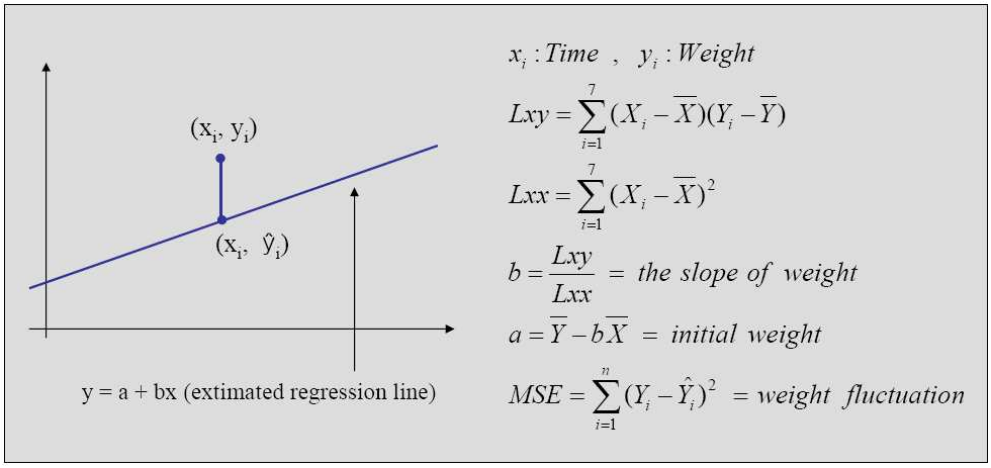
	1992	1994	1996	1998	2000	2002	2004	
Weight	●	◎	◎	◎	◎	◎	◎	at least 4 repeats
ALT	●	◎	◎	◎	◎	◎	◎	″
FSG	●	◎	◎	◎	◎	◎	◎	″
SBP	●	◎	◎	◎	◎	◎	◎	″
Smoking	●	◎	◎	◎	◎	◎	◎	″
Drinking	●	◎	◎	◎	◎	◎	◎	<20g per day only

3. Statistical analysis

The odds ratios and 95% confidence intervals (CI) were assessed using the generalized estimating equation (GEE) model in order to determine the risk of ALT abnormality. Abnormal ALT level was defined as ALT ≥40 IU/L. Based on an upper limit of normal as 40 IU/L for ALT, a recent study has also suggested that some individuals with high "normal" ALT levels may have underlying NAFLD (Prati et al, 2002). All of the GEE models were adjusted for age, height, and fasting serum glucose (FSG).

Obesity was estimated using both weight and body mass index (BMI). BMI was used to determine the degree of obesity, and was calculated as the weight in kilograms divided by the height (in meters) squared.

Three dimensions of weight changes were used in these analyses; these include slope, initial value (intercept), and fluctuation of weight (Figure 2). The slope of weight was calculated as the mean weight at each exam year. The slope of weight was classified into five groups based on quintiles in order to assess the associations of weight changes and ALT levels. Values of initial weight in each tertile were 61.5 kg (tertile 1), 61.5-68.4 kg (tertile 2), and 68.5 kg (tertile 3) for men and 50.0 kg (tertile 1), 50.0-55.1 kg (tertile 2), and 55.2 kg (tertile 3) for women. To measure weight fluctuation, I calculated the root mean square error around the regression line of weight for each subject, using all available measured body weights. This indicated weight fluctuation independent of the overall trend in weight. Both the initial weight and weight fluctuation were separated by tertile groups. The subjects in the lowest tertile for both initial weight and weight fluctuation were the reference group. All statistical analyses were conducted using SAS, version 9.1.3 (SAS Institute Inc, Cary, NC).



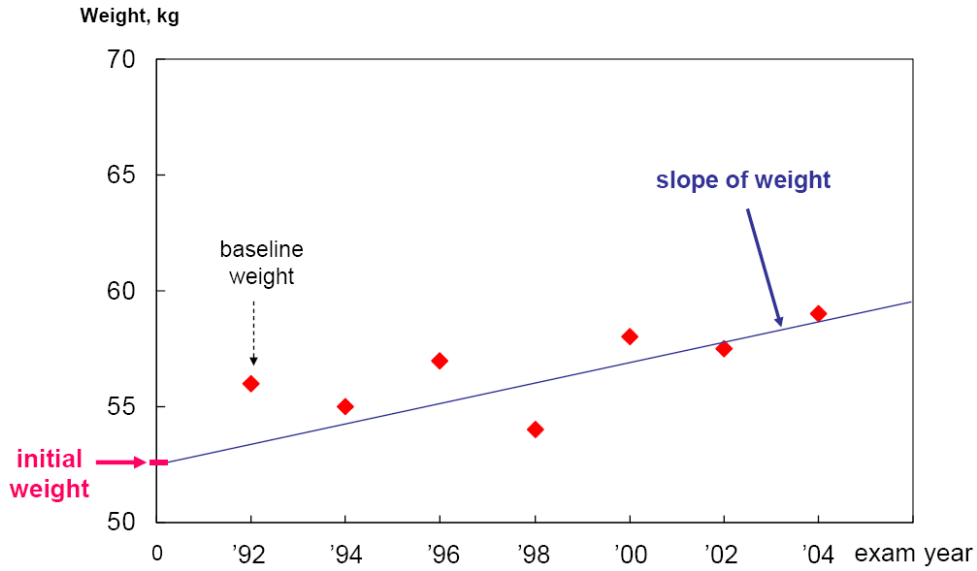


Figure 2. Three dimensions of the means of body weight by each examination year.

Ⅳ. Results

General characteristics of study population

Table 2 and Table 3 show the general characteristics of the study population by sex. The baseline age of study subjects ranged from 30 to 44 years, and the mean baseline age was 35.9 years. During the 12-year follow-up period (1992-2004), a mean increase of approximately 2.8 kg occurred among all subjects. The mean weight was higher among men than women, but the weight status slowly increased among women each year. The mean weight at baseline was 65.5 kg for men and 53.1 kg for women. The mean ALT level in men was higher than that in women. For men, the mean ALT levels were 20.3 IU/L in 1992 and 25.9 IU/L in 2004. For women, the mean ALT levels were 53.1 IU/L in 1992 and 55.4 IU/L in 2004. The systolic blood pressure (SBP) and FSG level were also higher for men than for women. Men were much more likely to be current smokers than women, and were also more likely to exercise. Among the 162,932 men, 89,841 (55.1%) were current smokers and 31.854 (19.6%) were ex-smokers.

To assess the relationship between body weight and ALT abnormality, I divided the cohort from each year into quintiles of body weight. For men, the number of abnormal ALT cases in each quintile in 1994 was 966, 1415, 2727, 3265, and 5209, respectively. For women, the number of abnormal ALT cases in each quintile in 1994 was 109, 166, 199, 167, and 395, respectively. In 1994, the OR for the highest body weight quintile was 9.9 for men and 3.6 for women. These trends were consistent over all of the examination years (Table 4 and Table 5).

Table 2. General characteristics of male study population.

	1992 (n=162,932)	1994 (n=158,819)	1996 (n=155,961)	1998 (n=155,247)	2000 (n=143,787)	2002 (n=129,972)	2004 (n=133,683)
Variable	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Age, y	36.5 (4.2)	38.5 (4.2)	40.5 (4.2)	42.5 (4.2)	44.5 (4.2)	46.4 (4.2)	48.4 (4.2)
Height, cm	169.6 (4.9)	169.4 (5.1)	169.3 (5.2)	169.1 (5.3)	169.1 (5.4)	169.1 (5.4)	169.1 (5.4)
Weight, kg	65.5 (7.9)	65.9 (8.2)	66.6 (8.3)	67.1 (8.5)	68.0 (8.5)	68.7 (8.5)	68.7 (8.4)
BMI, kg/m^2	22.8 (2.4)	22.9 (2.5)	23.2 (2.5)	23.4 (2.6)	23.8 (2.6)	24.0 (2.5)	24.0 (2.5)
ALT, IU/L	20.3 (7.4)	23.4 (11.6)	24.7 (12.2)	26.1 (12.9)	26.2 (12.7)	27.4 (13.8)	25.9 (12.6)
SBP, mmHg	119.5 (12.2)	119.5 (12.8)	119.9(13.5)	120.9 (14.1)	122.9 (15.0)	124.1 (16.2)	124.5 (15.1)
FSG, mg/dL	87.7 (15.2)	88.5 (16.0)	90.0 (17.4)	89.7 (19.0)	91.5 (22.2)	93.1 (28.1)	94.3 (23.4)
	%	%	%	%	%	%	%
Current smoking	55.1	52.8	50.5	49.3	44.7	35.4	32.1
Regular exercise	23.6	29.8	16.5	16.9	19.7	24.9	28.7

Abbreviation: BMI, body mass index; ALT, alanine aminotransferase; SBP, systolic blood pressure; FSG, fasting serum glucose

Table 3. General characteristics of female study population.

	1992 (n=78,402)	1994 (n=75,701)	1996 (n=75,147)	1998 (n=75,212)	2000 (n=67,767)	2002 (n=61,915)	2004 (n=63,804)
Variable	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Age, y	35.2 (4.1)	37.2 (4.1)	39.2 (4.1)	41.2 (4.1)	43.0 (4.0)	45.0 (4.1)	47.0 (4.1)
Height, cm	158.1 (4.3)	157.8 (4.5)	157.5 (4.7)	157.2 (4.8)	157.2 (4.8)	157.3 (4.8)	157.2 (4.8)
Weight, kg	53.1 (6.1)	53.4 (6.4)	53.9 (6.6)	54.4 (6.8)	55.0 (6.9)	55.3 (6.9)	55.4 (6.9)
BMI, kg/m^2	21.2 (2.2)	21.5 (2.3)	21.7 (2.4)	22.0 (2.5)	22.2 (2.5)	22.4 (2.5)	22.4 (2.5)
ALT, IU/L	15.5 (6.2)	15.7 (7.4)	16.1 (7.7)	16.6 (8.1)	16.9 (8.5)	17.3 (9.4)	17.8 (9.4)
SBP, mmHg	111.8 (10.8)	112.3 (11.4)	112.7 (12.4)	113.9 (13.1)	115.5 (14.1)	116.4 (16.4)	116.9 (14.9)
FSG, mg/dL	84.0 (12.3)	84.6 (12.3)	86.0 (12.5)	85.7 (13.7)	86.8 (17.0)	87.7 (23.9)	88.5 (17.4)
	%	%	%	%	%	%	%
Current smoking	0.1	0.1	0.2	0.2	0.3	0.2	0.2
Regular exercise	10.1	14.8	7.9	8.5	12.3	18.0	23.4

Abbreviation: BMI, body mass index; ALT, alanine aminotransferase; SBP, systolic blood pressure; FSG, fasting serum glucose.

Table 4. Odds ratio (OR) of abnormal ALT (≥40 IU/L) by body weight at each examination year in men, using a logistic regression model.

	1994 (n=158,819)		1996 (n=155,961)		1998 (n=155,247)		2000 (n=143,787)		2002 (n=129,972)		2004 (n=133,683)	
Weight, kg*	Case	OR(95% CI)	Case	OR(95% CI)	Case	OR(95% CI)	Case	OR(95% CI)	Case	OR(95% CI)	Case	OR(95% CI)
Quintile 1	966	1.0	1,281	1.0	1,494	1.0	1,523	1.0	1,843	1.0	1,528	1.0
Quintile 2	1,425	1.8(1.7-2.0)	1,779	1.9(1.7-2.0)	2,692	2.0(1.8-2.1)	2,549	1.9(1.8-2.0)	2,264	1.2(1.1-1.2)	1,902	1.1(1.0-1.2)
Quintile 3	2,727	2.7(2.7-3.1)	2,613	2.8(2.6-3.0)	3,426	3.1(3.0-3.3)	3,062	2.9(2.7-3.0)	4,371	1.7(1.6-1.8)	2,696	1.4(1.3-1.5)
Quintile 4	3,265	4.9(4.6-5.3)	4,584	4.5(4.2-4.8)	4,578	4.6(4.3-4.9)	4,273	4.2(3.9-4.4)	4,742	2.2(2.1-2.3)	3,814	1.8(1.7-1.9)
Quintile 5	5,209	9.9(9.1-10.7)	5,818	9.3(8.7-10.0)	7,372	9.2(8.6-9.8)	6,409	7.7(7.2-8.2)	6,736	3.4(3.2-3.6)	6,145	2.7(2.5-2.8)
C statistics	0.687		0.682		0.680		0.667		0.619		0.599	

OR, odds ratio; CI, confidence intervals.

* Year-specific weight quintiles: 1992 (<58, 58-61.9, 62-65.9, 66-70.9, ≥71kg), 1994 (<58, 58-62.9, 63-65.9, 66-70.9, ≥71kg), 1996 (<59, 59-62.9, 63-66.9, 67-71.9, ≥72kg), 1998 (<59, 59-63.9, 64-67.9, 68-72.9, ≥73kg), 2000 (<60, 60-64.9, 65-68.9, 69-73.9, ≥74kg), 2002 (<61, 61-65.9, 66-69.9, 70-74.9, ≥75kg), 2004 (<61, 61-65.9, 66-69.9, 70-74.9, ≥75kg).

†Adjusted for age, height, and smoking status.

Table 5. Odds ratio (OR) of abnormal ALT (≥40 IU/L) by body weight at each examination year in women, using a logistic regression model.

	1994 (n=75,701)		1996 (n=75,147)		1998 (n=75,212)		2000 (n=67,767)		2002 (n=61,915)		2004 (n=63,804)	
Weight, kg*	Case	OR(95% CI)	Case	OR(95% CI)	Case	OR(95% CI)	Case	OR(95% CI)	Case	OR(95% CI)	Case	OR(95% CI)
Quintile 1	109	1.0	132	1.0	142	1.0	140	1.0	197	1.0	211	1.0
Quintile 2	166	1.6(1.3-2.1)	172	1.0(0.8-1.3)	177	1.6(1.3-2.0)	243	1.5(1.2-18)	210	1.4(1.1-1.7)	224	1.3(1.1-1.6)
Quintile 3	199	1.6(1.2-2.0)	168	1.3(1.0-1.6)	186	1.5(1.2-1.9)	230	1.7(1.4-2.1)	256	1.6(1.3-1.9)	323	1.8(1.5-2.2)
Quintile 4	167	2.2(1.7-2.8)	248	1.8(1.5-2.3)	370	2.5(2.0-3.0)	288	2.1(1.7-2.6)	473	2.3(1.9-2.7)	537	2.4(2.0-2.8)
Quintile 5	395	3.6(2.9-4.6)	444	3.3(2.7-4.1)	634	5.5(4.6-6.7)	627	4.3(3.5-5.2)	787	5.2(4.4-6.2)	881	5.4(4.6-6.4)
C statistics	0.617		0.624		0.668		0.655		0.689		0.687	

OR, odds ratio; CI, confidence intervals.

Year-specific weight quintiles: 1992 (<48, 48-50.9, 51-53.9, 54-57.9, ≥58kg), 1994 (<48, 48-50.9, 51-53.9, 54-57.9, ≥58kg), 1996 (<48, 48-51.9, 52-54.9, 55-58.9, ≥59kg), 1998 (<49, 49-51.9, 52-54.9, 55-59.9, ≥60kg), 2000 (<49, 49-52.9, 53-55.9, 56-59.9, ≥60kg), 2002 (<50, 50-52.9, 53-55.9, 56-59.9, ≥60kg), 2004 (<50, 50-52.9, 53-55.9, 56-59.9, ≥60kg).

†Adjusted for age, height, and smoking status.

ALT abnormality increased steadily with increasing body weight for both men and women, with the increase being slightly greater in men (Figure 3).

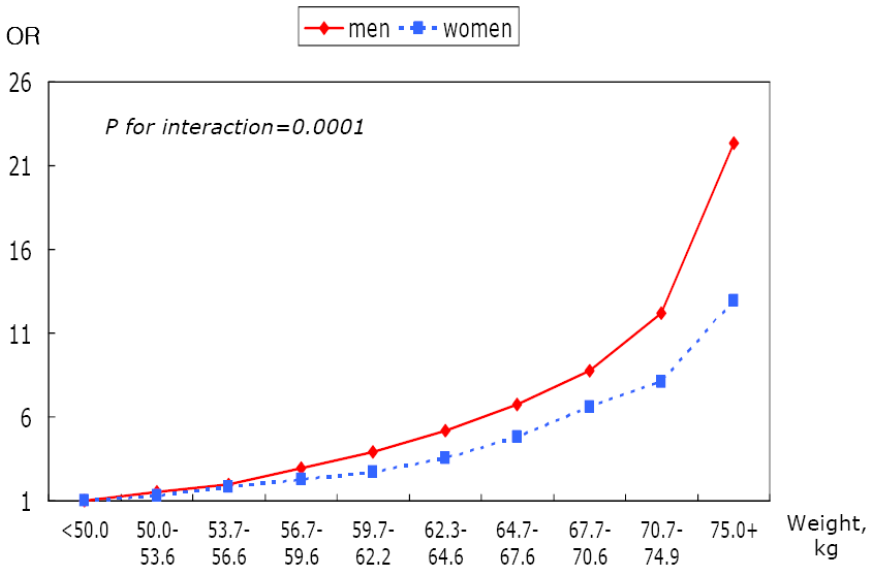


Figure 3. Odds ratio (OR) of abnormal ALT (≥40 IU/L) by body weight between 1994 and 1998 in men and women.

The distribution of abnormal ALT levels (ALT≥40 IU/L) at each examination is shown in Figure 4. The mean proportions of abnormal ALT in men and women were 10.5% and 2.0%, respectively.

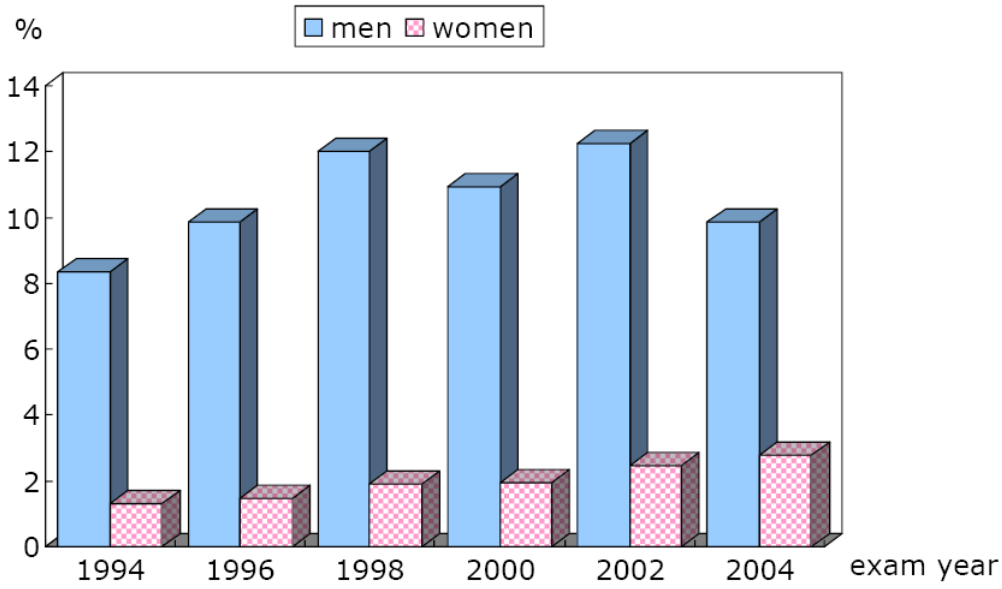


Figure 4. Distribution of abnormal ALT levels (ALT≥40 IU/L).

Slope of weight

Table 6 displays the clinical measurements of the study population according to the quintile of the slope of weight. Individuals were classified according to quintile of the slope of the weight; if a weight status was within the highest slope of weight, that weight status was more likely to increase during the follow-up period.

Men in the lowest quintile of the slope of weight had high BMI at baseline. However, the BMI was different within the highest quintile of the slope of weight. Another potentially important finding was that men with a lower slope of weight status tend to be older, are more likely to have hypertension and diabetes, and are less likely to be smokers or to be more physically active.

More interestingly, the highest prevalence of diabetes (7.5 %) in this study was observed in 2004 in men in quintile 1 (Q1). The lowest prevalence of diabetes (2.8 %) was observed among male subjects in 1992.

Table 7 displays clinical measurements of the study population according to the quintile of the slope of weight among females. Individuals were classified according to the quintile of the slope of the weight; if a weight status was within the highest slope of weight, that weight status was more likely to increase during the follow-up period. Women in the lowest quintile of the slope of weight had high BMI at baseline. However, the BMI was different within the highest quintile of the slope of weight. Another potentially important finding was that women with a lower slope of weight status tend to be older, are more likely to have hypertension and diabetes, and are less likely to be smokers or to be more physically active. The highest prevalence of diabetes (2.0%) was observed in 2004 in women who in Q1.

Table 6. Clinical measurements of study population according to the slope of weight in men.

	The slope of weight				
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
Slope of weight					
Mean	-0.27	0.08	0.26	0.45	0.83
Range	-3.95 – -0.02	-0.02 – 0.18	0.18 – 0.35	0.35 – 0.57	0.57 – 8.17
Baseline age, y	37.4	37.0	36.6	36.2	35.5
	Mean	Mean	Mean	Mean	Mean
At baseline	(1992, 2004)	(1992, 2004)	(1992, 2004)	(1992, 2004)	(1992, 2004)
Weight, kg	67.1, 64.3	65.8, 66.6	65.5, 68.2	65.1, 70.0	64.5, 73.2
BMI, kg/m^2	23.4, 22.6	23.0, 23.4	22.8, 23.9	22.6, 24.4	22.2, 25.3
SBP, mmHg	121.2, 123.9	120.0, 124.1	119.5, 124.5	118.8, 124.6	118.2, 125.3
FSG, mg/dL	90.4, 99.6	87.9, 93.9	87.2, 93.0	86.9, 92.8	86.5, 93.1
ALT, IU/L	21.2, 22.8	20.6, 24.1	20.4, 25.3	20.1, 26.9	19.6, 29.2
	(1992, 2004)	(1992, 2004)	(1992, 2004)	(1992, 2004)	(1992, 2004)
Hypertension† (%)	27.7, 20.7	24.4, 23.0	22.5, 24.5	20.7, 23.6	18.9, 23.2
Diabetes‡ (%)	2.8, 7.5	1.1, 3.8	0.7, 2.9	0.8, 2.5	0.7, 2.3
Current smoking (%)	51.7, 33.6	51.0, 32.5	52.1, 31.7	56.6, 32.3	62.3, 30.9
Regular exercise (%)	26.3, 34.8	25.4, 31.4	24.2, 28.6	22.4, 26.2	20.6, 24.0

Abbreviation: BMI, body mass index; SBP, systolic blood pressure; FSG, fasting serum glucose; ALT, alanine aminotransferase.

†Systolic blood pressure of at least 140 mmHg or diastolic blood pressure of at least 90 mmHg.

‡Fasting serum glucose level of at least 126 mg/dL.

Table 7. Clinical measurements of study population according to the slope of weight in women.

	The slope of weight				
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
Slope of weight					
Mean	-0.24	0.08	0.26	0.44	0.82
Range	-4.95 − -0.02	-0.02 − 0.18	0.18 − 0.35	0.35 − 0.57	0.57 − 4.40
Baseline age, y	35.7	35.4	35.0	34.9	34.6
	Mean	Mean	Mean	Mean	Mean
At baseline	(1992, 2004)	(1992, 2004)	(1992, 2004)	(1992, 2004)	(1992, 2004)
Weight, kg	54.8, 52.1	52.5, 53.3	52.3, 55.0	52.5, 57.3	53.7, 62.4
BMI, kg/m^2	21.9, 21.2	21.1, 21.6	20.9, 22.3	20.9, 23.1	21.3, 25.0
SBP, mmHg	112.5, 115.9	111.6, 115.9	111.3, 116.6	111.6, 117.8	111.8, 120.1
FSG, mg/dL	84.6, 88.9	83.8, 87.7	83.7, 87.9	83.8, 88.7	84.0, 90.0
ALT, IU/L	15.8, 17.2	15.5, 17.2	15.4, 17.5	15.4, 18.2	15.5, 20.1
	(1992, 2004)	(1992, 2004)	(1992, 2004)	(1992, 2004)	(1992, 2004)
Hypertension† (%)	9.2, 9.3	7.6, 10.1	6.5, 10.4	7.3, 11.4	7.5, 12.8
Diabetes‡ (%)	0.8, 2.0	0.4, 1.0	0.3, 0.8	0.3, 0.8	0.2, 1.0
Current smoking (%)	0.2, 0.2	0.1, 0.1	0.1, 0.1	0.1, 0.2	0.1, 0.2
Regular exercise (%)	10.5, 29.9	10.0, 25.4	9.9, 21.8	10.0, 19.5	10.2, 17.7

Abbreviation: BMI, body mass index; SBP, systolic blood pressure; FSG, fasting serum glucose; ALT, alanine aminotransferase.
†Systolic blood pressure of at least 140 mmHg or diastolic blood pressure of at least 90 mmHg.
‡Fasting serum glucose level of at least 126 mg/dL.

Figure 5 and Figure 6 show the means of weight at each biennial examination according to the slope of weight by quintiles among men and women. In Q1, the mean weight was 67.1 kg in 1992, and that weight status was decreased by 2.8 kg among men during the 12-year follow-up. The slope of the mean weight was 64.3 kg in 2004. In Q5, the mean weight was 64.5 kg in 1992, and that weight status was increased by 8.7 kg during the study, with the mean weight being 73.2 kg in 2004.

Quintile 1 shows that the mean weight of women was 54.8 kg in 1992, and although that weight status was decreased by 2.6 kg during the 12-year follow-up period. The mean weight was 52.2 kg in 2004. In women in quintile 5, the mean weight was 53.7 kg in 1992, and that weight status was increased by 8.7 kg, and with the mean weight being 62.4 kg in 2004.

Table 8. Mean body weight by each year in men.

	The slope of weight				
	Quintile 1 (n=31,551)	Quintile 2 (n=28,941)	Quintile 3 (n=30,757)	Quintile 4 (n=33,237)	Quintile 5 (n=38,446)
Year	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
1992	67.1 (8.8)	65.8 (7.9)	65.5 (7.5)	65.1 (7.4)	64.5 (7.5)
1994	66.6 (9.1)	65.9 (8.2)	65.8 (7.8)	65.7 (7.7)	65.6 (7.9)
1996	66.2 (9.3)	66.2 (8.3)	66.4 (8.0)	66.8 (7.9)	67.4 (8.1)
1998	65.5 (9.3)	66.1 (8.4)	66.8 (8.0)	67.5 (8.0)	69.0 (8.2)
2000	65.3 (9.2)	66.6 (8.3)	67.6 (8.0)	68.8 (7.9)	71.0 (8.1)
2002	64.9 (8.9)	66.9 (8.1)	68.2 (7.7)	69.8 (7.6)	72.7 (8.1)
2004	64.3 (8.7)	66.6 (7.9)	68.2 (7.5)	70.0 (7.5)	73.2 (7.8)

Table 9. Mean body weight by each year in women.

	The slope of weight				
	Quintile 1 (n=16,761)	Quintile 2 (n=18,497)	Quintile 3 (n=17,512)	Quintile 4 (n=14,431)	Quintile 5 (n=11,201)
Year	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
1992	54.8 (6.6)	52.5 (5.9)	52.3 (5.7)	52.5 (5.8)	53.7 (6.3)
1994	54.3 (6.7)	52.6 (6.1)	52.7 (6.0)	53.2 (6.1)	55.0 (6.8)
1996	53.8 (6.8)	52.8 (6.3)	53.2 (6.1)	54.0 (6.3)	56.7 (7.2)
1998	53.4 (6.8)	53.0 (6.3)	53.8 (6.1)	55.0 (6.4)	58.5 (7.4)
2000	53.0 (6.6)	53.3 (6.2)	54.4 (6.0)	56.1 (6.2)	60.2 (7.5)
2002	52.6 (6.3)	53.4 (6.0)	54.9 (5.9)	56.9 (6.1)	61.6 (7.7)
2004	52.2 (6.2)	53.3 (5.8)	55.0 (5.7)	57.3 (5.9)	62.4 (7.3)

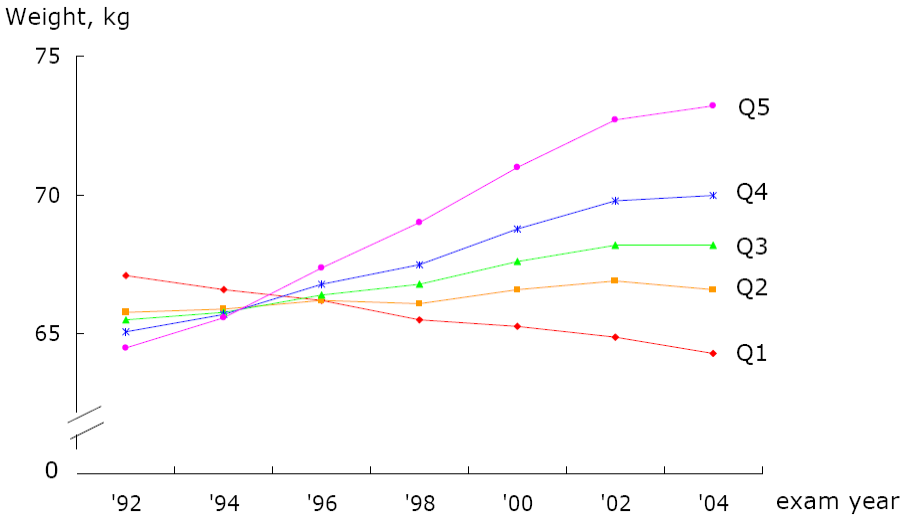


Figure 5. Mean weights at each exam year according to the slope of weight by quintiles among men.

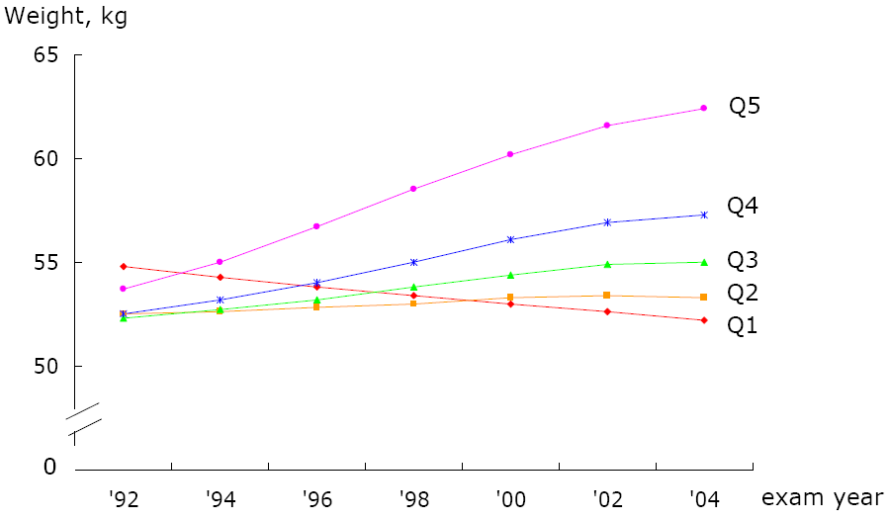


Figure 6. Mean weights at each exam year according to the slope of weight by quintiles among women.

Table 10 shows the odds ratio of abnormal ALT according to the slope of weight, initial weight, and weight fluctuation. The independent effects of the slope of weight, initial weight, and weight fluctuation on ALT abnormality were examined in GEE models that controlled for age, height, fasting serum glucose level, slope of weight, initial weight, and weight fluctuation. An increased slope of weight was associated with ALT abnormality. Compared with the lowest slope, the highest slope showed elevated ORs of abnormal ALT in men and women (2.58 and 2.30, respectively).

The latter was undertaken increasing 1 kg/yr of slope was elevated 2.32-fold for men and 2.15-fold for women at risk for ALT abnormality. Increased risk of ALT abnormality was also strongly associated with higher initial weight and weight fluctuation. Regarding all results of weight change, the initial weight can be a better predictor of the risk for abnormal ALT than the slope of weight and weight fluctuation.

Table 10. Odds ratio of abnormal ALT (≥40 IU/L) according to the slope of weight, initial weight, and weight fluctuation, using the GEE model.

	Men		Women	
	OR†	95% CI	OR†	95% CI
The slope of weight				
Q1 (-4.95 − -0.02)	1.00		1.00	
Q2 (-0.02 − 0.18)	1.21	1.17 - 1.25	1.12	1.03 - 1.21
Q3 (0.18 − 0.35)	1.45	1.40 - 1.50	1.28	1.19 - 1.39
Q4 (0.35 − 0.57)	1.82	1.76 - 1.88	1.59	1.47 - 1.73
Q5 (0.57 − 8.17)	2.58	2.50 - 2.66	2.30	2.12 - 2.49
Per 1 kg/yr	2.32	2.26 - 2.38	2.15	2.00 - 2.30
Initial weight*				
1st underweight	1.00		1.00	
2nd normal	1.75	1.70 - 1.79	1.35	1.26 - 1.44
3rd overweight	3.28	3.20 - 3.37	2.29	2.13 - 2.46
Weight fluctuation				
1st mild	1.00		1.00	
2nd moderate	1.03	1.01 - 1.06	1.14	1.07 - 1.21
3rd severe	1.12	1.10 - 1.15	1.53	1.44 - 1.62

OR, odds ratio; CI, confidence intervals.

† Adjusted for age, height, fasting serum glucose, slope of weight, initial weight, and weight fluctuation.

* Sex-specific tertiles for initial weight: men (<61.5, 61.5-68.4, ≥68.5 kg), women (<50.0, 50.0-55.1, ≥55.2 kg).

As shown in Figure 7, a lower slope of weight was associated with a modestly reduced risk for abnormal ALT (OR for highest vs. lowest quintiles, 0.39 [95% CI, 0.38 to 0.40] for men; OR for highest vs. lowest quintiles, 0.44 [95% CI, 0.40 to 0.47] for women).

Among men, subjects with a decreasing slope of weight showed a lower risk for abnormal ALT regardless of the weight change status. Nonetheless, even among women, decreasing weight was accompanied by a lower risk for abnormal ALT after adjustment for age, height, initial weight, fasting serum glucose, initial weight and weight fluctuation.

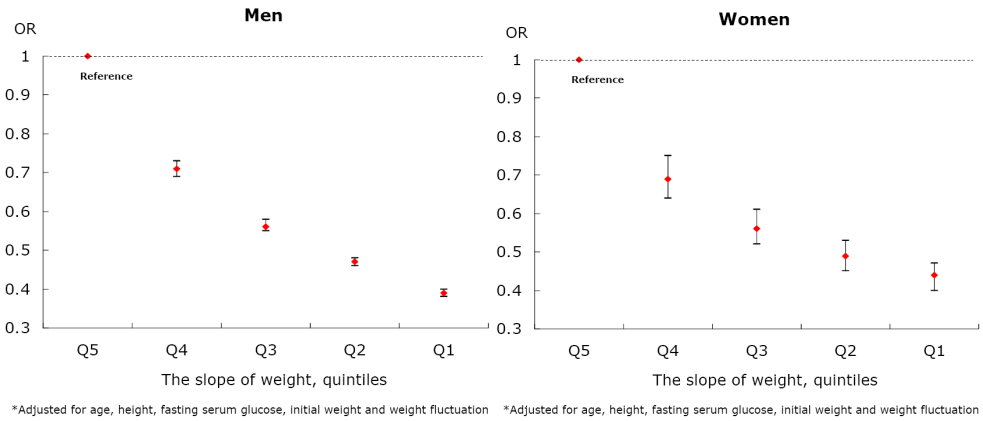


Figure 7. Odds ratio and 95% confidence intervals of abnormal ALT (≥40 IU/L) according to the slope of weight.

Stratification by initial weight, weight fluctuation, and baseline BMI

Figure 8 show the effect of an increased in the slope of weight on the risk for abnormal ALT according to the initial weight. The change in the slope of weight was significantly correlated with changes in the risk for abnormal ALT, particularly in those with a lower initial weight. In addition, a relationship was found between the slope of weight and ALT abnormality according to weight fluctuation, particularly in those with lower weight fluctuation (Figure 9). In addition, in male subjects with BMI<20, the risk for abnormal ALT was more strongly influenced by the initial weight compared to those with BMI≥25 at baseline (P for interaction <0.0001, Figure 10). However, no significant difference in the risk of ALT abnormality was observed in relation to the slope of weight according to initial weight, weight fluctuation, or baseline BMI in women.

The effect of an increased slope of weight on the risk of abnormal ALT according to smoking status is shown in Figure 11. No clear relationship was observed between baseline smoking status or regular exercise and weight change in terms of the risk of abnormal ALT. In addition, no clear relationship was observed between regular exercise and the risk of abnormal ALT (data not shown).

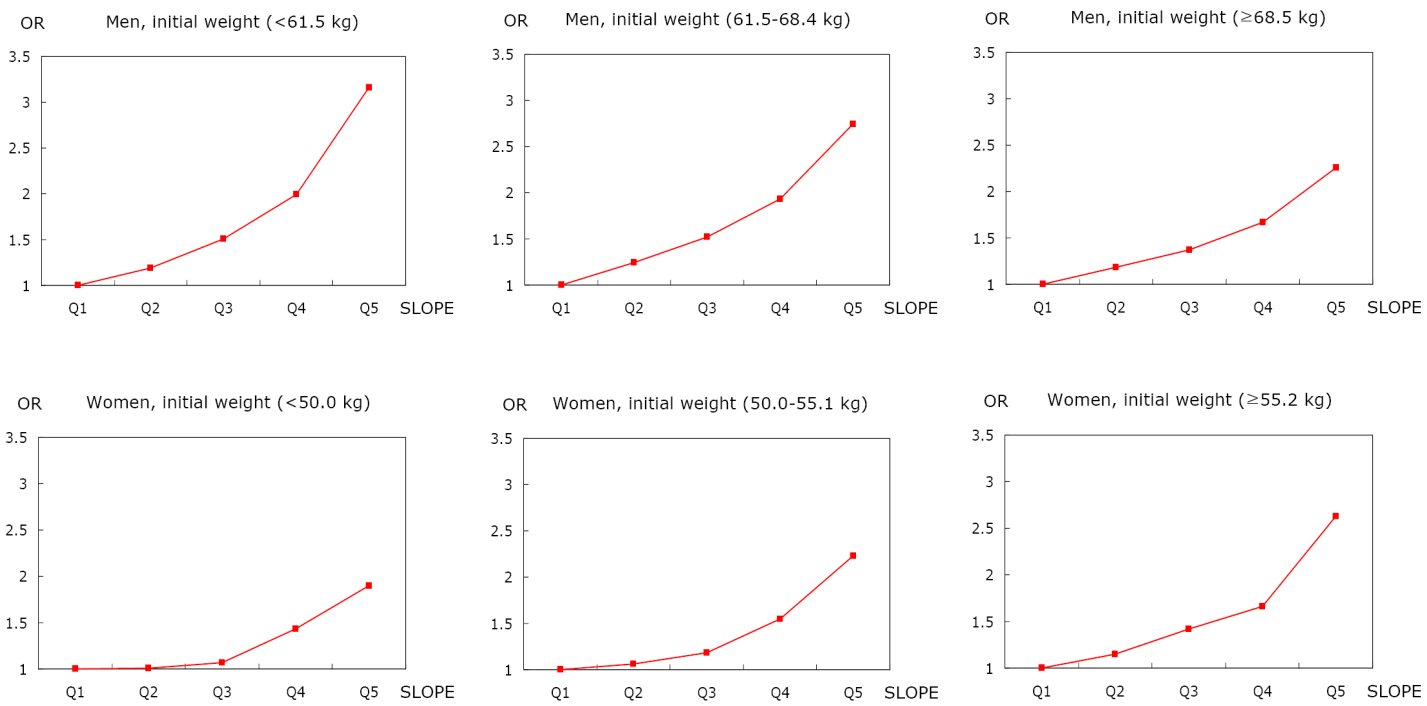


Figure 8. Odds ratio (OR) of abnormal ALT with increasing slope of weight according to initial weight.

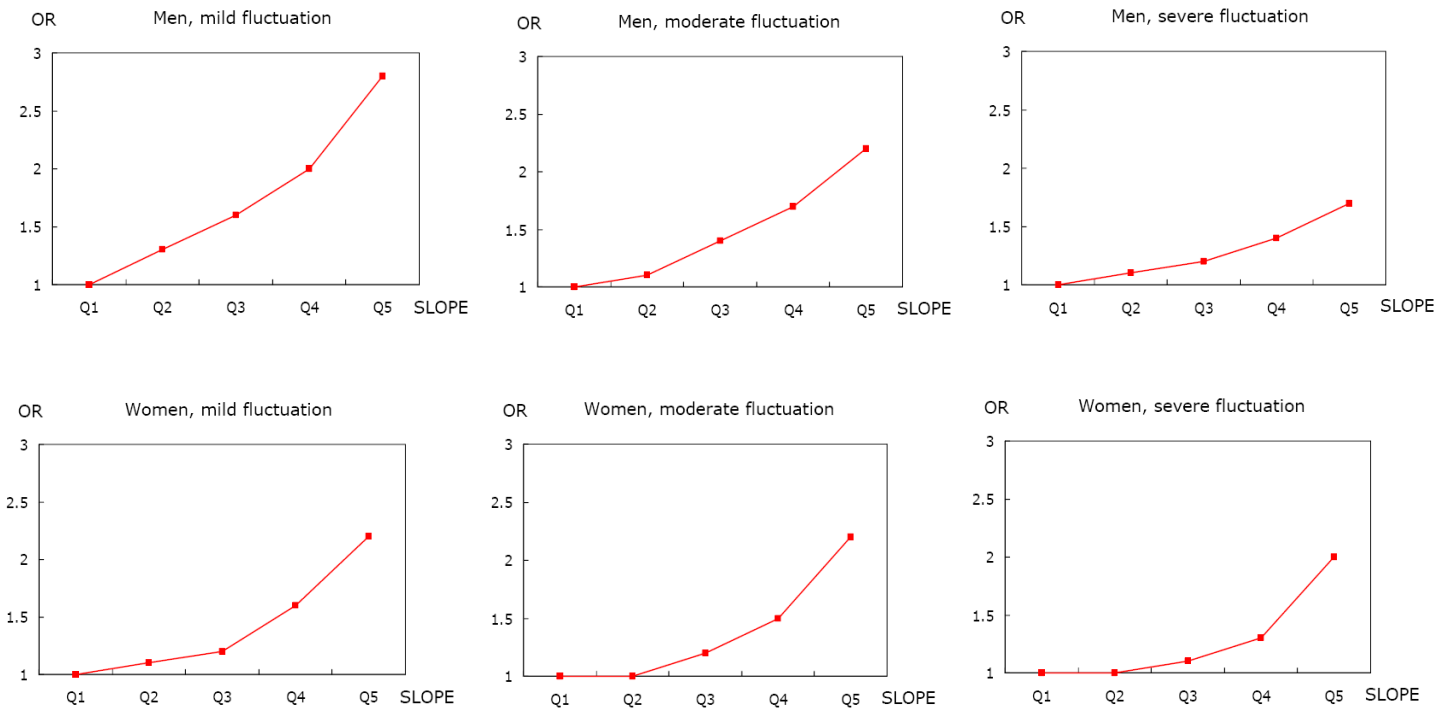


Figure 9. Odds ratio (OR) of abnormal ALT with increasing slope of weight according to weight fluctuation.

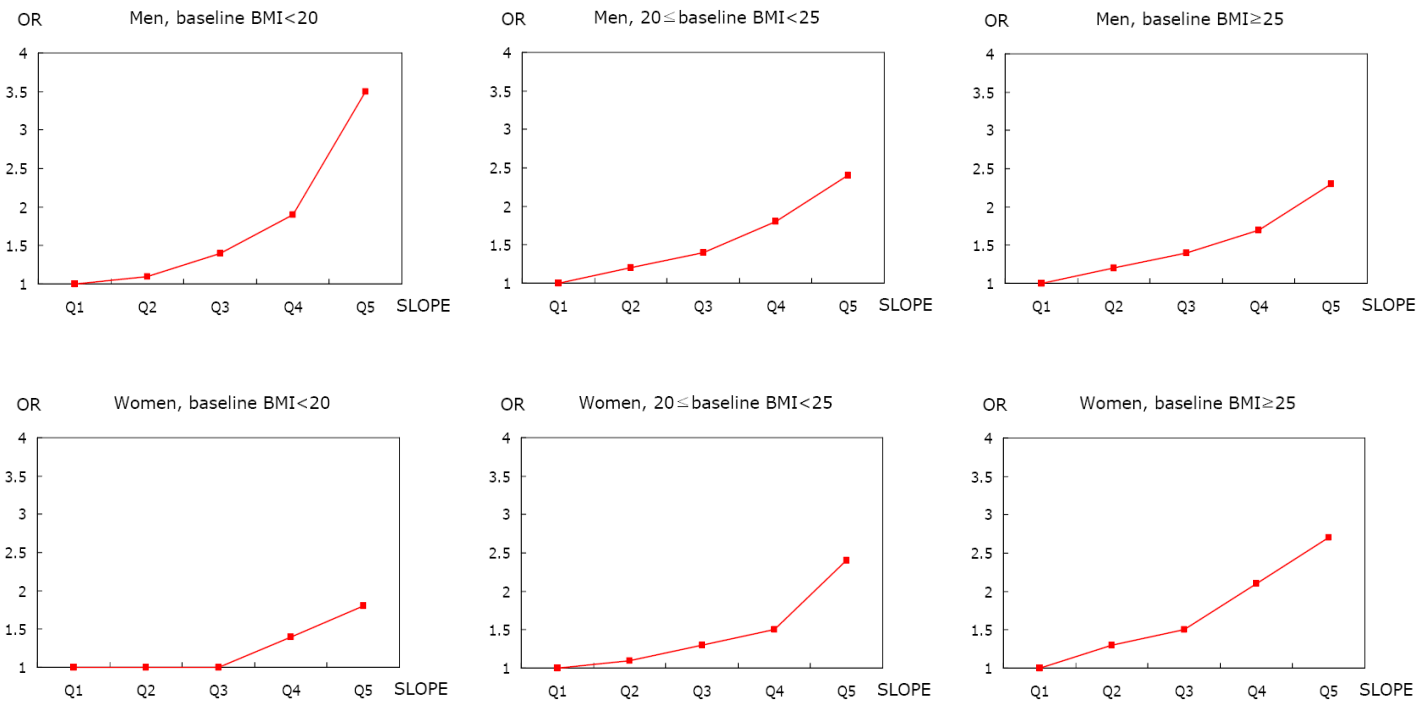


Figure 10. Odds ratio (OR) of abnormal ALT with increasing slope of weight according to baseline BMI.

Figure 11. Odds ratio (OR) of abnormal ALT with increasing slope of weight according to smoking status.

The interaction of the slope of weight and other factors

Table 11 and Table 12 show the effects of interaction of the slope of weight and initial weight on abnormal ALT. The subjects in the lowest quintile of the slope of weight and the lowest tertile of initial weight were used as the reference group. In men, the highest risk of abnormal ALT was observed among the overweight group (tertile 3) who experienced a profound increasing in weight (OR=8.7, 95% CI=8.1-9.4).

The slope of weight and initial weight were independent risk factors for abnormality ALT in men, and interaction was found between these two risk factors (P for interaction<0.0001). For men, changes in body weight were significantly correlated with changes in the risk of abnormal ALT, particularly in those with a lower initial weight.

Table 13 and Table 14 show the effects of interaction of the slope of weight and weight fluctuation on abnormal ALT. The subjects in the lowest quintile of the slope of weight and the lowest tertile of weight fluctuation were used as the reference group. The slope of weight and weight fluctuation were independent risk factors for ALT abnormality in men, and interaction was found between these two risk factors (P for interaction<0.0001). In addition, interaction of the slope of weight and baseline BMI affected the risk for abnormal ALT in men (P for interaction<0.0001). However, no significant differences were observed for the risk of ALT abnormality in relation to the slope of weight according to initial weight, weight fluctuation, and baseline BMI in women.

Table 11. Odds ratio (OR) of abnormal ALT with the slope of weight and initial weight in men.

	Initial weight, tertiles			
	<61.5 kg	61.5-68.4 kg	≥68.5 kg	
Slope of weight	OR[†](95% CI)	OR (95% CI)	OR (95% CI)	*P* for interaction
Quintile 1	1.0	1.8 (1.7 - 2.0)	3.6 (3.4 - 3.8)	<.0001
Quintile 2	1.2 (1.1 - 1.3)	2.3 (2.0 - 2.5)	4.3 (3.9 - 4.7)	
Quintile 3	1.5 (1.4 - 1.6)	2.7 (2.5 - 3.0)	5.1 (4.6 - 5.5)	
Quintile 4	1.9 (1.8 - 2.1)	3.4 (3.1 - 3.7)	6.3 (5.8 - 6.8)	
Quintile 5	3.0 (2.8 - 3.2)	4.7 (4.3 - 5.1)	8.7 (8.1 - 9.4)	

OR, odds ratio; CI, confidence intervals.
[†]Adjusted for age, height, and fasting serum glucose.

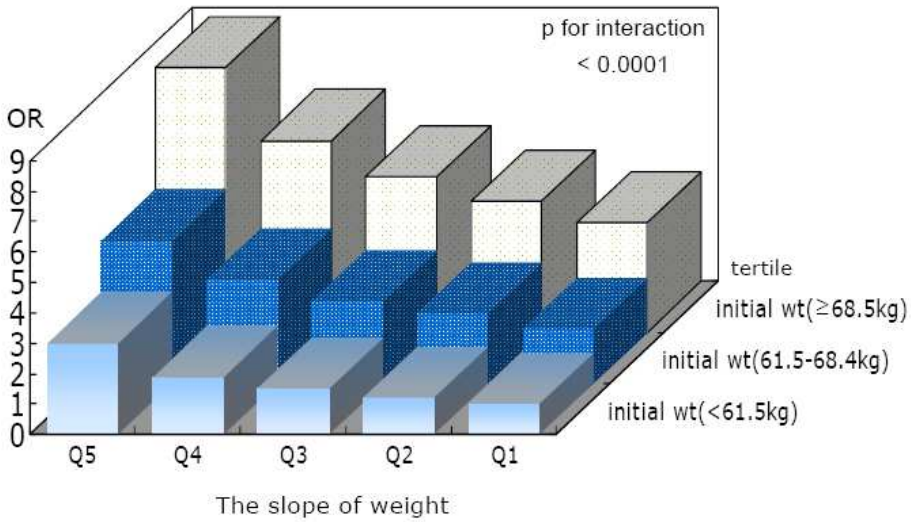


Figure 12. Odds ratio (OR) of abnormal alanine aminotransferase with the slope of weight and initial weight in men.

Table 12. Odds ratio (OR) of abnormal ALT with the slope of weight and initial weight in women.

	Initial weight, tertiles			
	<50.0 kg	50.0-55.1 kg	≥55.2 kg	
Slope of weight	OR[†](95% CI)	OR (95% CI)	OR (95% CI)	*P* for interaction
Quintile 1	1.0	1.3 (1.1 - 1.5)	2.1 (1.8-2.4)	0.3791
Quintile 2	1.0 (0.9-1.2)	1.4 (1.1-1.7)	2.3 (1.9-2.9)	
Quintile 3	1.1 (0.9-1.3)	1.5 (1.2-1.9)	2.9 (2.3-3.5)	
Quintile 4	1.5 (1.2-1.7)	2.0 (1.6-2.5)	3.3 (2.7-4.1)	
Quintile 5	2.0 (1.6-2.4)	2.9 (2.3-3.6)	5.2 (4.2-6.5)	

OR, odds ratio; CI, confidence intervals.
[†]Adjusted for age, height, and fasting serum glucose.

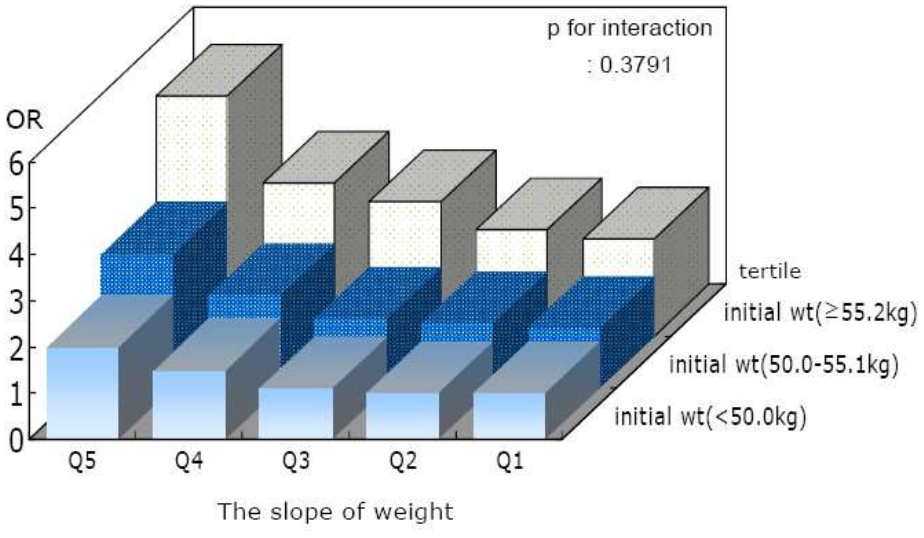


Figure 13. Odds ratio (OR) of abnormal alanine aminotransferase with the slope of weight and initial weight in women.

Table 13. Odds ratio (OR) of abnormal ALT with the slope of weight and weight fluctuation in men.

	Weight fluctuation, tertiles			
	Mild	Moderate	Severe	
Slope of weight	OR[†](95% CI)	OR (95% CI)	OR (95% CI)	*P* for interaction
Quintile 1	1.0	1.2 (1.1 - 1.3)	1.5 (1.4 - 1.6)	<.0001
Quintile 2	1.3 (1.2 - 1.3)	1.4 (1.3 - 1.5)	1.7 (1.6 - 1.8)	
Quintile 3	1.5 (1.4 - 1.6)	1.6 (1.5 - 1.8)	1.8 (1.7 - 2.0)	
Quintile 4	1.9 (1.8 - 2.1)	2.0 (1.8 - 2.1)	2.1 (1.9 - 2.3)	
Quintile 5	2.6 (2.5 - 2.8)	2.6 (2.4 - 2.8)	2.7 (2.5 - 2.9)	

OR, odds ratio; CI, confidence intervals.
[†]Adjusted for age, height, and fasting serum glucose.

Table 14. Odds ratio (OR) of abnormal ALT with the slope of weight and weight fluctuation in women.

	Weight fluctuation, tertiles			
	Mild	Moderate	Severe	
Slope of weight	OR[†](95% CI)	OR (95% CI)	OR (95% CI)	*P* for interaction
Quintile 1	1.0	1.2 (1.0 - 1.3)	1.6 (1.4 - 1.8)	0.8626
Quintile 2	1.1 (0.9 - 1.2)	1.2 (1.0 - 1.4)	1.6 (1.4 - 2.0)	
Quintile 3	1.2 (1.1 - 1.4)	1.3 (1.1 - 1.6)	1.8 (1.5 - 2.2)	
Quintile 4	1.5 (1.3 - 1.8)	2.1 (1.7 - 2.5)	2.2 (1.8 - 2.5)	
Quintile 5	2.2 (1.8 - 2.5)	2.5 (2.0 - 3.1)	3.2 (2.7 - 4.0)	

OR, odds ratio; CI, confidence intervals.
[†]Adjusted for age, height, and fasting serum glucose.

Comparable results after excluding ALT level≥40 IU/L in the first four measurements (1992-1998)

Figure 14 shows the odds ratio using GEE models of abnormal ALT according to the slope of weight after excluding measurements that were equal to or more than 40 IU/L in the first four measurements. The model that excluded four measurements was a better predictor of abnormal ALT than a model that excluded one measurement. The odds ratio for ALT abnormality of the model that excluded four measurements was higher than that indicated by the model that excluded one measurement model.

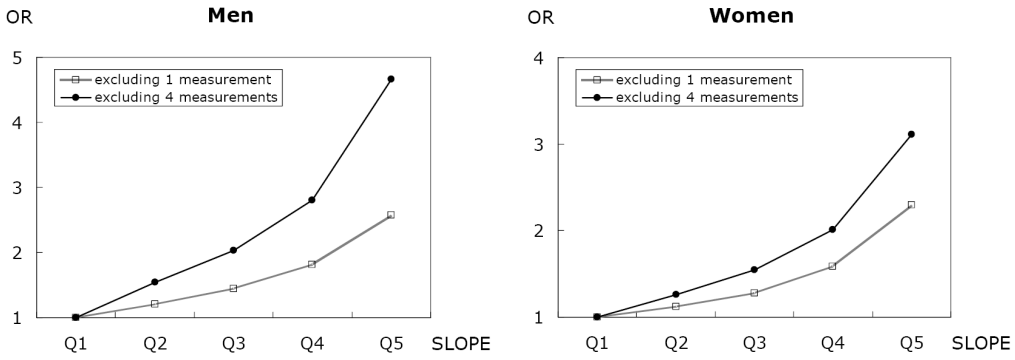


Figure 14. Odds ratio (OR) of abnormal ALT according to the slope of weight after excluding abnormal ALT (≥40 IU/L) in the first four measurements (1992-1998).

Ⅴ. Discussion

This study confirmed the findings of previous studies demonstrating a relationship between body weight and ALT levels. The study also examined the relationship between weight changes and ALT abnormality in Korean men and women, using repeatedly measured 12-year follow-up data. Increased ALT abnormality was strongly associated with an increased slope of weight, initial weight, and weight fluctuation. Specifically, a higher slope of weight was strongly associated with increased risk of ALT abnormality. Initial weight and weight fluctuation were also independent risk factors for ALT abnormality, and both of these modified the association between ALT abnormality and the slope of weight.

These results are consistent with earlier findings on the association between weight change and ALT levels in other populations. Previous studies have shown an association between obesity and serum ALT levels. In the Third National Health and Nutrition Examination Survey (NHANES), Ruhl and Everhart and Clark *et al*. (2003) reported that BMI was strongly associated with the prevalence of abnormal ALT activity. In the Dionysos study, Bedohni *et al*. (2003) reported that, in 6,315 adults in Northern Italy, overweight and obese participants had elevated ALT levels compared with those having BMI <24.9, OR=2.0 (95% CI=1.4-2.7) and OR=3.1 (95% CI=2.1-4.7), respectively. Among British women aged 60-79 years, Lawlor *et al*. (2005) found a linear association between BMI and ALT. Lee *et al.* (2001) also reported that ALT was strongly associated with BMI at baseline, and changes in BMI were strongly associated with having an abnormal ALT at follow-up.

However, most studies about weight change and ALT levels were cross-sectional studies and intervention studies, and no data have been reported from large

prospective studies. In addition, weight change (gain or loss) was assessed at only one or two points in time, and this may be partly explained by the benefit of fewer observations. Some clinical-based studies have also shown that the effect of weight loss seemed to be more crucial in normalizing the ALT liver enzyme than reduced alcohol consumption (Fagerberg et al, 1993; Powell et al, 1990). In a longitudinal cohort study, Suzuki *et al.* showed that weight reduction ≥5% and regular exercise were independently associated with a decrease in serum ALT levels (Suzuki et al, 2005).

Weight change was also associated other health outcomes. Observational studies suggest that changes in weight are predictors of health outcomes. For instance, weight gain has been associated with increased incidence of heart disease, stroke, cancer, and mortality (French et al, 1997; Woo et al, 2001; Keller et al, 1995; Eliassen et al, 2006). Weight is a modifiable risk factor for several medical conditions, including diabetes and cardiovascular disease. Based on the association between excess weight and the increased risk of cardiovascular disease morbidity and mortality, weight loss has been recommended for those individuals who are overweight or obese and have diabetes or cardiovascular diseases (Sjostrom et al, 1992). Weight loss is associated with several short-term benefits, such as improvements in lipid levels, blood pressure, and blood glucose metabolism (US PSTF, 2003), but thus far, there has been little evidence of longer-term effects on cancer risk (IARC, 2002).

In this study, subjects who showed a decreasing slope of weight also showed lower risk for abnormal ALT regardless of the weight change status. Because obesity is the most common condition associated with NAFLD, weight loss has traditionally been the most commonly suggested intervention. The effects of weight reduction on hepatic tests and physical findings were studied in a retrospective review of thirty-nine obese patients without primary liver disease. A weight loss of >10% corrected

abnormal liver tests, decreased hepatosplenomegaly, and resolved some stigmata of liver disease (Hourigan et al, 1999). In a study of 25 obese Japanese subjects (Ueno et al, 1997), fifteen underwent a program of restricted diet and exercise for a period of three months. Patients in the intervention group showed significant reductions in BMI, aminotransferases, and fasting plasma glucose levels. In addition, steatosis was significantly improved on liver biopsy in these patients. Studies reporting the effect of weight reduction in NAFLD to date have included small numbers of patients that were treated for a short period of time, and no data are available from large prospective studies (Wang et al, 2003; Ueno et al, 1997). This study confirmed that weight reductions were associated with the improvement of ALT levels and normalization over the 12-year follow-up.

Specifically, a change in the slope of weight was significantly correlated with change in abnormal ALT risk, particularly in those with lower initial weight. However, we found a slight difference between initial weight (underweight, normal, overweight) and exercise status. More interestingly, among overweight subjects, the exercise activity was higher than in those who had low or normal weight. According to the exercise status (yes, no), results showed a similar trend after controlling for exercise (data not shown). In addition, in subjects with BMI<20, the risk for abnormal ALT was more strongly influenced than in those with BMI≥25 at baseline. Human insulin secretion is strongly associated with body change. More specifically, insulin secretion does not increase when body weight increases among people with low body weight. In many cases, because East Asian people easily develop insulin resistance upon a slight increase in visceral fat, they tend to have lower secretory capacities than Westerners (Teramoto et al, 2007).

Several prospective studies have shown weight fluctuation (or weight variability, defined as the coefficient of variation of weight) to be associated with increased coronary heart disease (CHD), cancer, or all-cause mortality. In the

Framingham study, weight fluctuation was positively associated with total and CHD mortality in men and women in Framingham, Massachusetts; this was independent of the direction of weight change (Lissner et al, 1991). In the Gothenburg study, weight variability was associated with increased mortality in men and women (Lissner et al, 1989). However, in the British Regional Heart Study, it was found that weight change and weight fluctuation were not associated with mortality in healthy non-smokers (Wannamethee et al, 2002). In this study, it was found that weight fluctuation was positively associated the risk of ALT abnormality. Notably, an increase in the slope of weight was significantly associated with a change in abnormal ALT risk among those who had mild weight fluctuation in men. This showed that male subjects that were stable and those that showed a simultaneously increased slope of weight was associated with a higher risk of abnormal ALT.

The effect of regular exercise in NAFLD remains unknown. Suzuki *et al.* reported that regular exercise was associated with significantly greater ALT improvement and normalization. Regular exercise may have shown an effect by controlling body weight. However, since the effect was observed even after adjusting for weight change, it is likely that there may be some additional beneficial effect of regular exercise itself. For instance, exercise is known to improve the sensitivity of muscle mass to insulin (Dela et al, 1992; Mikines et al, 1988; Perseghin et al, 1996). Furthermore, in a recent clinical trial, exercise that was not enough to reduce body weight showed a modest therapeutic effect by reducing visceral fat and improving glucose intolerance (Ross et al, 2000). Lifestyle has been considered essential to the development of NAFLD/NASH, and modifications in individual habits and diets have been combined in these patients. Gradual weight loss with diet and exercise have been associated with control of risk factors of NAFLD, decrease of insulin resistance indexes, and improvement of liver enzymes and histology (Luyckx et al, 2000; Okita et al, 2001). In this study, no clear relationship was found between regular exercise and the risk of abnormal ALT (data not shown).

Several previous studies suggested that starting smoking may have some adverse effect on hypertransaminasemia due to NAFLD. For instance, smoking is known to be one of the strongest inducers of oxidative stress (Scheffler et al, 1992). There is also some evidence of an association between smoking and insulin resistance from a lifelong cohort study and a large prospective cohort study (Carnethon et al, 2003; Parker et al, 2003). Oxidative stress and insulin resistance are both well-known conditions that may lead to development and progression of NAFLD to more advanced stages (Day and James, 1998). However, in this study, no clear relationship was found between smoking status and the risk of abnormal ALT.

This study has several limitations. First, we used self-reported alcohol consumption. The validity of self-reported alcohol consumption has been evaluated in multiple settings, and is generally found to be valid (Midanik et al, 1982). One study in Korea, based in the NHIC, found self-reported alcohol consumption to be reliable among an older group; reliability is an indirect indicator of validity (Park et al, 1998).

Second, waist or body fat measures unfortunately were not available in this study. Several previous studies have found that there may be a stronger association between ALT abnormality and waist circumference than with body weight (Marchesini and Forlani, 2002; Omagari et al, 2002). The pathogenesis of NAFLD is not clear, but it has been suggested that the presence of insulin resistance and visceral adiposity plays a major role (Angelico et al, 2005; Chitturi et al, 2002; Marchesini et al, 1999). Recent findings have shown that central adiposity can be an independent predictor of hepatic steatosis (fatty liver) (Kral et al, 1993; Omagari et al, 2002).

Third, biennial health examinations were conducted at hundreds of hospitals throughout the country, and the laboratory technique was not standardized. However, quality control procedures were in accordance with those specifiined by the Korean Association of Laboratory Quality Control.

Finally, some studies showed that the clinical diagnosis of NAFLD required the exclusion of alcoholic, viral, autoimmune, genetic, and drug-included liver disease determined in conjunction with laboratory testing and ultrasonographic or histologic evidence of hepatic steatosis. Drug interventions have also been used to reduce hepatic fat and improve liver histology (Bugianesi et al, 2005; Tiikkainen et al, 2004; Promrat et al, 2004; Mayerson et al, 2002; Osono et al, 2000). However, data on these factors were not available in this study. Thus, the effects of these factors indicate a need for further study.

The size of this study one of its major strengths, as is the availability of repeatedly measured weight and ALT levels in a nonalcoholic population. The finding showed that the effect of weight change on abnormal ALT risk could be examined between subjects as well as within same subject. In addition, the results could be generalized to the broader Korean population, and likely to other populations.

Ⅵ. Conclusions

In conclusion, these longitudinal data indicate a strong association between weight change and the risk of ALT abnormality. Using repeatedly measured 12-year follow-up data, the relationship between changes in weight and ALT abnormality in Korean men and women was examined. A higher slope of weight was strongly associated with increased risk of ALT abnormality. Increased ALT abnormality was also strongly associated with increased initial weight and weight fluctuation. The association between the slope of weight and ALT abnormality was modified by initial weight and weight fluctuation. The findings suggest that the avoidance of weight gain and the reduction of weight should lower the risk of abnormal ALT.

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Appendix Table 1. Odds ratio (OR) of abnormal alanine aminotransferase by weight and body mass index in men and women, using the GEE model, KCPS, 1992-2004

		Men		Women	
Variables	Categories	OR	95% CI	OR	95% CI
Weight, kg†	1st	1.00		1.00	
	2nd	2.01	1.82 - 2.22	1.28	0.95 - 1.74
	3rd	3.17	2.86 - 3.51	1.82	1.39 - 2.39
	4th	5.09	4.60 - 5.63	2.68	2.03 - 3.53
	5th	10.06	9.08 - 11.13	4.79	3.65 - 6.29
	Per 1kg	1.11	1.10 - 1.11	1.09	1.08 - 1.11
	Per 2kg	1.23	1.22 - 1.23	1.19	1.16 - 1.22
	Per 3kg	1.36	1.34 - 1.37	1.30	1.25 - 1.35
Body mass index, kg/m^2	< 20.0	1.00		1.00	
	20.0 - 22.9	2.10	1.82 - 2.43	1.29	1.02 - 1.62
	23.0 - 24.9	4.44	3.84 - 5.13	2.26	1.77 - 2.89
	≥ 25.0	9.12	7.90 - 10.53	5.12	4.01 - 6.53
	Per 1 kg/m^2	1.34	1.33 - 1.36	1.27	1.23 - 1.30
	Per 2 kg/m^2	1.81	1.77 - 1.84	1.60	1.52 - 1.69

OR, odds ratio; CI, confidence intervals

*Adjusted for age

† Sex specific quintiles weight: men (<61, 61-65, 65-70, 70-75, ≥75kg), women (<49, 49-52, 52-56, 56-60, ≥60kg)

Appendix table 2. Odds ratio (OR) of abnormal alanine aminotransferase by weight and body mass index in men and women, cross-sectional analysis, 1992

		Men		Women	
Variables	Categories	OR	95% CI	OR	95% CI
Weight, kg†	1st	1.00		1.00	
	2nd	1.65	1.35 - 2.02	0.69	0.35 - 1.37
	3rd	2.55	2.12 - 3.07	0.84	0.46 - 1.55
	4th	4.45	3.69 - 5.37	0.75	0.36 - 1.55
	5th	8.39	6.89 - 10.21	2.37	1.30 - 4.32
	Per 1kg	1.10	1.09 - 1.11	1.07	1.04 - 1.10
	Per 2kg	1.22	1.20 - 1.24	1.14	1.07 - 1.22
	Per 3kg	1.35	1.32 - 1.38	1.22	1.11 - 1.34
Body mass index, kg/m^2	< 20.0	1.00		1.00	
	20.0 - 22.9	2.41	1.73 - 3.35	0.93	0.55 - 1.56
	23.0 - 24.9	4.38	3.16 - 6.08	1.95	1.09 - 3.50
	≥ 25.0	9.81	7.09 - 13.58	3.55	1.87 - 6.73
	Per 1 kg/m^2	1.33	1.30 - 1.36	1.18	1.09 - 1.27
	Per 2 kg/m^2	1.76	1.69 - 1.84	1.39	1.19 - 1.62

OR, odds ratio; CI, confidence intervals
*Adjusted for age
† Sex specific quintiles weight: male (<61, 61-65, 65-70, 70-75, ≥75kg), female (<49, 49-52, 52-56, 56-60, ≥60kg)

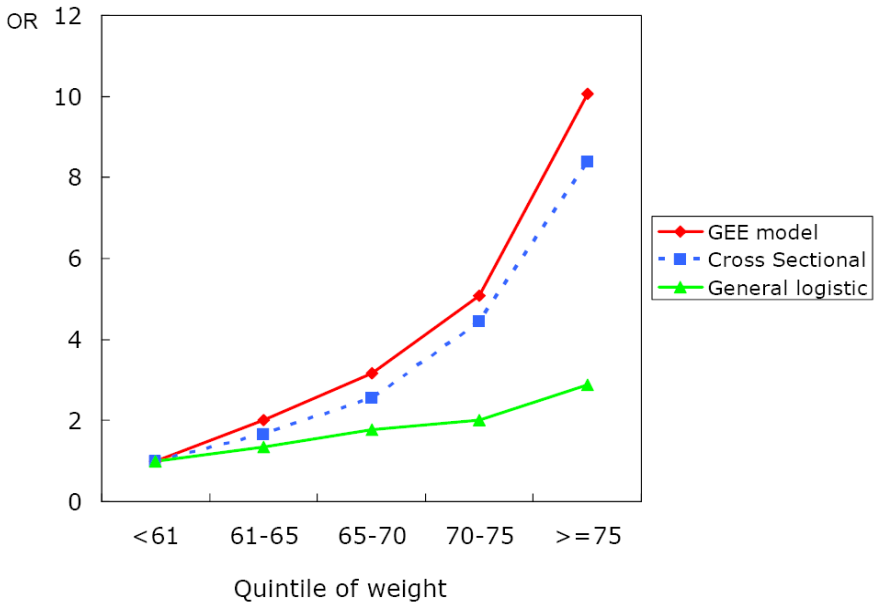
Appendix table 3. Odds ratio (OR) of abnormal alanine aminotransferase by weight and body mass index in men and women, general logistic model, 1992 and 2004

		Men		Women	
Variables	Categories	OR	95% CI	OR	95% CI
Weight, kg†	1st	1.00		1.00	
	2nd	1.35	1.17 - 1.56	1.21	0.77 - 1.89
	3rd	1.77	1.55 - 2.02	1.40	0.93 - 2.11
	4th	2.01	1.82 - 2.42	2.17	1.42 - 3.31
	5th	2.88	2.48 - 3.36	3.33	2.18 - 5.06
	Per 1kg	1.05	1.05 - 1.06	1.07	1.05 - 1.09
	Per 2kg	1.11	1.09 - 1.12	1.15	1.10 - 1.19
	Per 3kg	1.16	1.14 - 1.19	1.23	1.16 - 1.30
Body mass index, kg/m^2	< 20.0	1.00		1.00	
	20.0 - 22.9	1.85	1.52 - 2.25	1.48	1.05 - 2.08
	23.0 - 24.9	2.63	2.16 - 3.21	2.11	1.42 - 3.13
	≥ 25.0	3.48	2.85 - 4.26	3.79	2.46 - 5.82
	Per 1 kg/m^2	1.16	1.14 - 1.18	1.18	1.13 - 1.24
	Per 2 kg/m^2	1.34	1.29 - 1.39	1.40	1.27 - 1.54

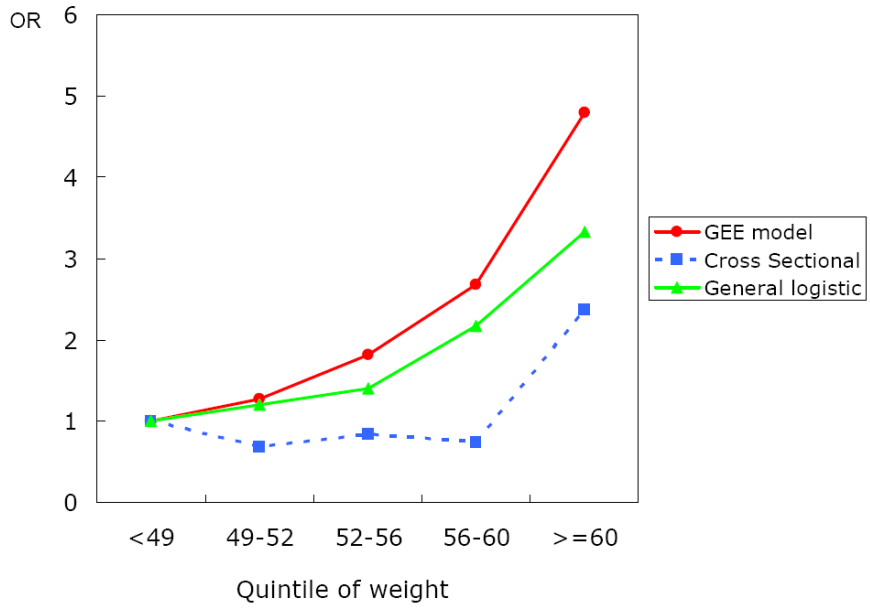
OR, odds ratio; CI, confidence intervals

*Adjusted for age

† Sex specific quintiles weight: male (<61, 61-65, 65-70, 70-75, ≥75kg), female (<49, 49-52, 52-56, 56-60, ≥60kg)



Appendix figure 1. Comparison of GEE model and logistic model in men.



Appendix figure 2. Comparison of GEE model and logistic model in women.

Abstract in Korean

비음주집단에서 체중변화와 ALT 위험도와의 관련성

연세대학교 대학원 보건학과
윤 지 은

비알코올성 지방간질환은 간에서 가장 많이 발생하는 질환일 뿐만 아니라 일부에 있어서는 간염, 간경변 등의 만성 간질환으로 진행함이 밝혀지면서 최근 그 중요성이 점차 강조되고 있다. 비알코올성 지방간질환의 주요원인으로는 과체중이나 비만으로 추정하고 있다. 혈청 아미노산전환효소(AST 및 ALT) 검사는 간질환의 진단과 조기검진에 가장 널리 사용되는 생화학 검사이며, ALT 는 AST 보다 비만과 관련성이 높다고 보고되고 있다. 하지만 비만 또는 체중 변화와 간질환에 대한 전향적 연구 결과는 거의 없는 실정이다. 따라서 본 연구에서는 알코올과 바이러스에 의한 영향을 배제하고, 체중 변화에 따른 ALT 위험도와의 관련성을 알아보고자 하였다.

본 연구는 한국인 암 예방연구(Korean Cancer Prevention Study, KCPS)의 자료를 이용하였으며, 1992 년부터 2004 년까지 2 년에 한번 건강검진을 실시한 공무원 및 사립학교 교직원 건강보험 가입자이다. 연구대상은 1992 년 건강검진에 참여한 30-44 세 남녀 중 1994 년부터 2004 년까지 적어도 세 번이상 건강검진에 참여한 245,919 명이다. 간질환에 대한 알코올의 영향을 배제하기 위해 하루에 알코올을 20g 미만 섭취하는 대상자들로만 구성되었고, 이들을 비음주 집단으로 정의하였다. 1992 년 당시 간질환을 포함한 과거질환을 가지고 있다고 응답한 사람은 대상에서 제외하였고, 최종 분석대상자는 남녀 241,334 명이었다. 결과변수인 ALT 비정상군은 ALT 40 IU/L 이상으로 정의하였다. 본 연구에서 사용한 체중의 기울기는 각 건강검진시점 에서 측정된 체중의 평균으로 만들었고, 그 값에 따라 5 분위 (quintile)로 나누고 기울기에 따른 ALT 비정상 위험도와의 연관성을 살펴보았다. 또한 체중의 변동과 초기(initial) 체중은 기울기를 통해

값을 추정하였는데 그 값에 따라 각각 3 분위(tertile)로 나누었다. 체중의 변화와 ALT 위험도와의 관련성은 GEE(Generalized Estimating Equation) 모형을 통해 분석하였다.

연구 대상자의 1992 년 남녀 평균 연령은 각각 36.5 세, 35.2 세 이었고, 평균 체중은 남자 65.5kg, 여자 53.1kg, 평균 ALT 수치는 남자 20.3 IU/L, 여자 15.5 IU/L 으로 남자가 여자보다 높았다. 다른 영향을 통제한 상태에서 체중의 기울기가 증가할수록 ALT 비정상 위험도는 남녀 모두 증가하였다. ALT 비정상 위험도는 남자의 경우, 체중의 기울기가 가장 낮은 1 군에 비해 2 군이 1.21 배, 3 군이 1.45 배, 4 군이 1.82 배, 5 군이 2.58 배 높았고, 여자의 경우 체중의 기울기가 가장 낮은 1 군에 비해 2 군이 1.12 배, 3 군이 1.28 배, 4 군이 1.59 배, 5 군이 2.30 배 높았다. 또한 initial 체중이 증가할수록 ALT 비정상 위험도가 증가하였는데, 남자의 경우 초기 체중이 가장 낮은 1 군에 비해 초기 체중이 가장 높은 3 군의 위험도가 남자는 3.28 배, 여자는 2.29 배 높았다. 체중의 변동과 ALT 비정상 위험도간에도 양의 관련성이 있었는데, 체중의 변동이 거의 없는 1 군에 비해 변동이 심한 3 군이 ALT 비정상 위험도가 남자 1.12 배, 여자 1.53 배 높았다. 또한, 남자에 있어서 체중의 기울기와 초기 체중, 체중의 변동과는 상호작용이 있었는데, 특히 초기 체중이 적은 그룹(<61.5kg)에서 초기 체중이 많은 그룹(≥68.5kg)에 비해 체중의 기울기가 증가할수록 ALT 비정상 위험도는 더 많이 증가하였고, 체중의 변동이 적은 그룹이 변동이 많은 그룹에 비해 체중의 기울기가 증가할수록 ALT 비정상 위험도는 더 많이 증가하였다.

알코올의 영향을 배제한 상태에서 ALT 비정상 위험도는 체중의 변화(기울기, 초기 체중, 변동)와 유의한 양의 관련성이 있었다. 또한, 남자에 있어서 체중의 기울기와 초기 체중, 체중의 변동과는 상호작용이 있었다. 이 결과는 체중 유지 또는 조절을 함으로써 ALT 비정상 위험도를 낮추고 간질환을 예방할 수 있을 것으로 생각된다.

핵심되는 말: 체중변화, 비만, ALT, 아미노산전환효소