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Original Article

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Association between long working hours and liver enzymes: evidence from the Korea National Health and Nutrition Examination Survey, 2007–2017

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ABSTRACT

Background: Long working hours causes several health risks, but little is known about its effects on the liver. This study aimed to examine the correlation between working hours and abnormal liver enzyme levels.
Methods: We used data from the Korea National Health and Nutrition Examination Survey IV–VII. For the final 15,316 study participant, the information on working hours was obtained through questionnaires, and liver enzyme levels, consisting of serum levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT), through blood tests. The relationship between weekly working hours and abnormal levels of liver enzymes was analyzed using multiple logistic regression, and a trend test was also conducted.
Results: In male, working ≥ 61 hours per week was significantly associated with elevated AST and ALT levels compared with working 35–52 hours per week. Even after adjusting for covariates, the odds ratios (ORs) of abnormal AST and ALT increased by 1.51 (95% confidence interval: 1.20–2.05) and 1.25 (1.03–1.52), respectively, and a dose-response relationship was observed. This association was more prominent among the high-risk group, such as those aged > 40 years, obese individuals, worker on non-standard work schedule, pink-collar workers, or temporary worker. No correlation was observed in female.
Conclusions: Long working hours are associated with abnormal liver function test results in male. Strict adherence to statutory working hours is necessary to protect workers' liver health.

Keywords: Long working hours; Liver; Abnormal liver enzymes; KNHANES

BACKGROUND

In 2020, Koreans had a total of 1,908 annual working hours and ranks 4th among the Organization for Economic Cooperation and Development (OECD) countries with long working hours, meaning that they work 221 hours more than the OECD average of 1,687 hours.[1] Long working hours have been recognized as a major social problem since the 1970s. In several epidemiological studies, long working hours increase the risk of chronic diseases[2] such as metabolic syndrome, hypertension, diabetes, and hyperlipidemia, and cardiovascular

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Abbreviations

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; CI: confidence interval; DM: diabetes mellitus; HDL: high-density lipoprotein; KNHANES: Korea National Health and Nutrition Examination Survey; LC: liver cirrhosis; LFT: liver function test; LTPA: leisure-time physical activity; NAFLD: non-alcoholic fatty liver disease; OECD: Organization for Economic Cooperation and Development; OR: odds ratio; SD: standard deviation.

Competing interests

The authors declare that they have no competing interests.

Authors contributions

Conceptualization: Kang MY; Data curation: Song JH; Formal analysis: Song JH; Validation: Kang MY; Visualization: Song JH; Writing - original draft: Song JH; Writing - review & editing: Lee DW, Kim HR, Min JH, Lee YM, Kang MY.

diseases.[3] It can also adversely affect the mental health[2,4] and cause psychological stress and work stress.[5] In addition, it can promote poor lifestyle habits[6,7] such as alcohol abuse, smoking, and physical inactivity, and can cause obesity.[8] Although psychosocial job stress or changes in health behavior due to long working hours are likely have an negative effect on the liver,[9,10] little is known about its effect on the liver.

The liver, which is called the factory of our body, controls various metabolic processes, and plays an essential role in maintaining homeostasis and health. An initial indicator of liver damage is aminotransferase, which consists of aspartate aminotransferase (AST) and alanine aminotransferase (ALT), and is collectively referred to as a liver function test (LFT). They may be elevated due to chronic hepatitis, alcohol or drug overdose, NAFLD, liver cirrhosis, hepatocellular carcinoma, and abnormal immune reactions.[11] In addition, there were studies that elevation of LFT is associated with various metabolic disease,[12] and increase the mortality rate due to liver disease beyond the occurrence of various liver disase.[13,14] Liver disease is a burden not only in Korea but also in various countries, and its pattern is constantly changing.[15] In the past, viral hepatitis and alcoholic hepatitis were the primary causes of chronic liver disease; however, the incidence of non-alcoholic fatty liver disease (NAFLD) has been increasing.[16] Recent studies have reported that long working hours are associated with the risk of NAFLD, thus it is thought that they may have a harmful effect on the liver, but there are few studies on this.[17,18]

A recent study suggested a correlation between weekly working hours and liver damage, but it is difficult to generalize because this study only targeted a specific patient group.[19,20] Therefore, this study aimed to examine the relationship between weekly working hours and abnormal LFT using the data from the Korea National Health and Nutrition Examination Survey (KNHANES), which is a representative sample survey conducted in the Korean population. Considering that the liver is an organ that represents sexual dimorphism[21] and the health effects of long working hours may differ by sex, all analyses were conducted separately by sex.

METHODS

Participants

This study was conducted based on the data from the KNHANES 2007–2017. The KNHANES is a cross-sectional, nationally representative survey conducted periodically by the Korea Disease Control and Prevention Agency and is designed using a 2-stage stratified cluster sampling. During the survey, the participants' demographic data, socioeconomic status, health problems, health examinations, and nutrient intake are obtained. Of the 89,630 individuals who participated in the 4th, 5th, 6th, and 7th KNHANES (2007–2017), 20,979 salaried workers aged 19–64 years were the target study population. Individuals with liver cancer, liver cirrhosis, hepatitis B, or hepatitis C were excluded from the analysis. Individuals who worked less than 35 hours per week were also excluded as they were considered to have a greater socioeconomic impact than working hours. In addition, individuals with missing data on major variables and covariates were excluded. Finally, 5,663 participants were excluded, and a total of 15,316 participants were selected for analysis (**Fig. 1**).

Assessment of working hours

In KNHANES, the weekly working hours were measured using the following questions: "What is the average number of working hours per week (including overtime/overtime work)

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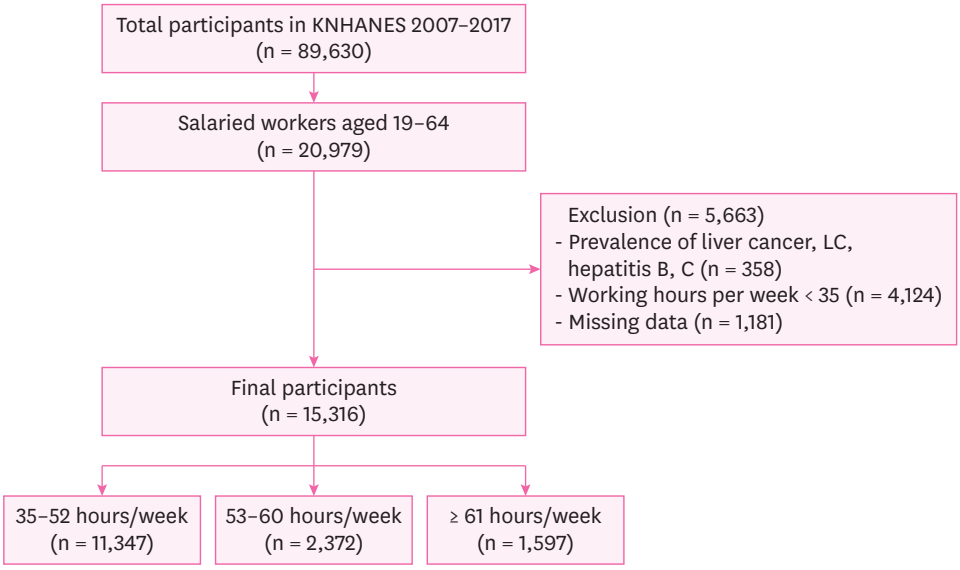

Fig. 1. Flow chart of study participants.
KNHANES: Korea National Health and Nutrition Examination Survey; LC: liver cirrhosis.

at your workplace? (excluding meal time)." According to the Korean Labor Standards Act, the maximum number of working hours per week is 52, including overtime.[22] According to the Korean Enforcement Decree of the Industrial Accident Compensation Insurance Act and Public Notice of the Korean Ministry of Employment and Labour, the compensation for chronic overwork-related cerebrovascular and cardiovascular diseases are approved in workers who worked over 60 hours in the past 12 weeks.[23] The above hours are 30% and 50% added hours, respectively, through social agreement based on the 40-hour workweek, the statutory weekly working hour under the Korean Labor Standards Act. Therefore, we classified the working hour group as follows: 35–52 hours/week, 53–60 hours/week, and ≥ 61 hours/week.

Definition of abnormal liver enzymes

In KNHANES, blood sampling was performed in the mobile examination centers by a trained nurse or medical laboratory technician, who completed 2–4 weeks of training and received retraining sessions every year to reinforce the proper protocols and techniques. Serum AST and ALT levels were measured with a Hitachi Automatic Analyzer 7600-2100 (Hitachi, Tokyo, Japan) using the International Federation of Clinical Chemistry and Laboratory Medicine UltraViolet without pyridoxal-5-phospate method. According to the administrative criteria for health examination, the abnormal serum AST level (abnormal AST) is > 40 units per liter, while the abnormal serum ALT level (abnormal ALT) is > 35 units per liter.[24]

Other variables

Data on demographic characteristics such as sex and age, health behaviors such as smoking and drinking alcohol, and work-related factors were obtained using a standardized questionnaire. Age was divided into 4 groups: 19–29 years, 30–39 years, 40–49 years, and 50–64 years. Household income was divided into 4 quartiles: low, low-middle, middle-high, and high. Drinking status was classified into normal and heavy drinking, which was defined as drinking more than twice a week and drinking at an average of 7 or more units of alcohol for male and 5 or more units of alcohol for female.[25] Body mass index (BMI) was calculated by dividing

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body weight by height in meter squared (kg/m^2). BMI was classified into 2 groups: < 25 kg/m^2 and ≥ 25 kg/m^2. Metabolic syndrome was diagnosed when 3 of the following 5 criteria of the National Cholesterol Education Program's Adult Treatment Panel III were satisfied: abdominal obesity (waist circumference: ≥ 90 cm in male and ≥ 85 cm in female), elevated blood pressure (systolic blood pressure of ≥ 130 mmHg, diastolic blood pressure of ≥ 85 mmHg, or use of antihypertensive drugs), elevated fasting blood sugar (≥ 100 mg/dL or use of glycemic control drugs), reduced high-density lipoprotein (HDL) cholesterol level (< 40 mg/dL in male and < 50 mg/dL in female, or use of drugs to treat low HDL), elevated triglyceride levels (> 150 mg/dL or use of medications to treat hypertriglyceridemia). Diabetes mellitus (DM) were defined as those with a fasting blood glucose of 126 or higher, who responded that they were taking diabetes medications or insulin injections, or had been diagnosed with diabetes.

In KNHANES, occupation was classified into ten categories according to the Korean Standard Classification of Occupations, which is based on the International Standard Classification of Occupations (ISCO-08) adopted by the International Labor Organization. After excluding armed forces, we divided the remaining workers into 3 occupational categories (white-collar, pink-collar, and blue-collar) according to their job characteristics. The white-collar group consisted of managers, professionals and related workers, and clerks. The pink-collar group consisted of service and sales workers. Finally, the blue-collar group consisted of skilled agricultural; forestry and fishery workers; craft and related trade workers; equipment, machine operation, and assembly workers; and elementary workers. Employment status was categorized as follows based on the participants' position at the workplace: permanent and temporary. Regular workers were categorized as permanent workers, while temporary employees or daily workers were defined as temporary workers. Type of work schedule was defined by the following question: "Do you usually work during the day (between 6 am and 6 pm)? Or do you work at a different time?" Those who answered "Mainly work during the day" were classified as on standard work schedule, while all others were classified as on non-standard work schedule.

Statistical analysis

After stratifying the data into male and female, the general characteristics of the study participants were described. Continuous variables were expressed as means and standard deviations (SDs), while categorical variables were expressed as frequencies and percentages (%). A χ^2 test was performed to examine the ratio between abnormal AST and ALT levels according to working hours. Age, household income, obesity, metabolic syndrome, DM, job category, type of work schedule, and employment status were considered potential confounders. In general, education and job category are significantly connected, the effect of smoking on the liver is unknown, and liver cancer patients were excluded from the study, thus these variables were not considered as confounders. Drinking status was considered a mediator and excluded from covariates.

Multiple logistic regression was performed to evaluate the relationship between working hours and abnormal LFT and the integrated survey weight was used to consider the complex sampling design. To reduce the confounding bias, Model 1 was adjusted for age, household income, obesity, metabolic syndrome, and DM while Model II was further adjusted job category, type of work schedule, and employment status. The analysis presented the odds ratio (OR) and 95% confidence interval (CI). In addition, a trend test was conducted to examine the increase in the OR of abnormal LFT according to the increase in working hours. All statistical analyses were performed using SAS (version 9.4; SAS Institute, Cary, NC, USA). Statistical significance was defined as a p value of < 0.05.

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Ethics statement

The present study protocol was exempted from review by the Institutional Review Board of Seoul St. Mary's Hospital, the Catholic University of Korea (approval No. KC21ZASI0536). Informed consent was obtained from all participants enrolled in the study.

RESULTS

The general characteristics of the participants are listed in **Table 1**. Of the total 15,316 participants, 8,800 (57.46%) were male and 6,516 (42.54%) were female. The proportion of working more than 60 hours per week was higher in male than in female. The average AST and ALT levels of male were 24.09 IU/L and 27.59 IU/L, respectively, which were higher than those of female, 18.92 IU/L and 16.03 IU/L. The abnormal AST and ALT levels were 5.69% and 19.51% in male, respectively, and 1.40% and 3.70% in female.

Table 2 shows the results of the analysis of the ratio of abnormal LFT levels according to working hours in male and female. In male, the ratio of abnormal AST levels was statistically significant different depending on working hours ($p < 0.05$), and it was observed that the ratio increased as the working hours increased. The ratio of abnormal ALT levels also was different with statistical significance ($p < 0.05$), and it seems to be increasing. No difference was observed in the ratio of abnormal LFT according to working hours in female.

Table 3 shows the association between weekly working hours and abnormal LFT by multiple logistic regression; and the calculated crude and adjusted ORs and their 95% CIs. For male, the ORs of abnormal AST and abnormal ALT levels in those working ≥ 61 hours were 1.52 (95% CI: 1.14–2.03) and 1.22 (95% CI: 1.02–1.46) compared with those of the 35–52 weekly working hour group, respectively. After adjusting for age, income, obesity, metabolic syndrome, DM, the ORs of abnormal AST and ALT were significantly high at 1.51 (95% CI: 1.12–2.02) and 1.23 (95% CI: 1.01–1.48), respectively. Similar results were obtained with ORs of 1.51 (95% CI: 1.20–2.05) and 1.25 (95% CI: 1.03–1.52), even after further adjusting for income, job category, employment status, and shift work. Moreover, a statistically significant dose-response relationship was found consistently between weekly working hours and abnormal LFT, with or without adjustment (p for trend < 0.05). Meanwhile, no significant relationship was observed in female.

DISCUSSION

This study aimed to examine the correlation between weekly working hours and abnormal LFT in a Korean population. The results of the current study showed that long working hours were associated with abnormal LFT even after adjusting for age, income, obesity, metabolic syndrome, DM, job category, type of work schedule, and employment status in male, with a dose-response relationship. As a result of sensitivity analysis by dividing weekly working hours into 4 groups (35–40/41–52/53–60/≥ 61), the ORs of abnormal AST and ALT were also significantly increased in the ≥ 61 hours group compared to 35–40 hours of work (**Supplementary Table 1**). The dose-response relationship between weekly working hours and abnormal LFT was maintained in ALT (p for trend < 0.05). However, no such relationship was observed in female.

The number of literatures on the relationship between working hours and liver function is limited. In a cross-sectional study of 6,086 Japanese workers conducted by Ochiai et al.,[20] no

Table 1. General characteristics of the participants

Characteristics	Weekly working hours		
	35–52	53–60	≥ 61
Sex			
Male	6,078 (53.56)	1,620 (68.30)	1,102 (69.00)
Female	5,269 (46.44)	752 (31.70)	495 (31.00)
Age groups (years)			
19–29	2,013 (17.74)	425 (17.92)	227 (14.21)
30–39	3,397 (29.94)	708 (29.85)	422 (26.42)
40–49	3,262 (28.75)	662 (27.91)	409 (25.61)
50–64	2,675 (23.57)	577 (24.33)	539 (33.75)
Education			
Middle school or less	1,372 (12.09)	410 (17.28)	432 (27.05)
High school	3,839 (33.83)	950 (40.05)	649 (40.64)
College or above	6,136 (54.08)	1,012 (42.66)	516 (32.31)
Income			
Q1	1,981 (17.46)	517 (21.80)	431 (26.99)
Q2	2,785 (24.54)	691 (29.13)	450 (28.18)
Q3	3,148 (27.74)	655 (27.61)	416 (26.05)
Q4	3,433 (30.25)	509 (21.46)	300 (18.79)
Smoking status			
Never-smoker	6,391 (56.32)	1,019 (42.96)	657 (41.14)
Ex-smoker	1,601 (14.11)	352 (14.84)	230 (14.40)
Current smoker	3,355 (29.57)	1,001 (42.20)	710 (44.46)
Drinking status			
Normal	9,668 (85.20)	1,944 (81.96)	1,257 (78.71)
Heavy drinking	1,679 (14.80)	428 (18.04)	340 (21.29)
BMI (kg/m^2)			
< 25	7,868 (69.34)	1,560 (65.77)	987 (61.80)
≥ 25	3,479 (30.66)	812 (34.23)	610 (38.20)
Metabolic syndrome			
No	9,240 (81.43)	1,902 (80.19)	1,235 (77.33)
Yes	2,107 (18.57)	470 (19.81)	362 (22.67)
Diabetes mellitus			
No	10,761 (94.84)	2,220 (93.59)	1,477 (92.49)
Yes	586 (5.16)	152 (6.41)	120 (7.51)
Job category			
White-collar	6,562 (57.83)	914 (38.53)	418 (26.17)
Pink-collar	1,558 (13.73)	419 (17.66)	363 (22.73)
Blue-collar	3,227 (28.44)	1,039 (43.80)	816 (51.10)
Type of work schedule			
Standard work schedule	7,563 (66.65)	1,416 (59.70)	751 (47.03)
Non-standard work schedule	3,784 (33.35)	956 (40.30)	846 (52.97)
Employment status			
Permanent	9,469 (83.45)	1,934 (81.53)	1,204 (75.39)
Temporary	1,878 (16.55)	438 (18.47)	393 (24.61)
AST status			
Normal	10,943 (96.44)	2,274 (95.87)	1,507 (94.36)
Abnormal[a]	404 (3.56)	98 (4.13)	90 (5.64)
ALT status			
Normal	10,011 (88.23)	2,021 (85.20)	1,326 (83.03)
Abnormal[b]	1,336 (11.77)	351 (14.80)	271 (16.97)

BMI: body mass index; AST: aspartate aminotransferase; ALT: alanine aminotransferase.
[a]Serum AST > 40; [b]Serum ALT > 35.

correlation was observed between weekly working hours and abnormal LFT. However, since this study was conducted only in Japanese tertiary industry workers, there are limitations to the generalization of the results. A cross-sectional study using the Kangbuk Samsung Health Study showed that HBsAg(+) (hepatitis B surface antigen) participants who worked more than 60 hours per week had significantly higher OR of abnormal ALT, but no correlation

Table 2. Categorical analysis between working hour and abnormal liver function test stratified by sex

Sex	Working hours	AST			ALT		
		Normal	Abnormal	*p*-value	Normal	Abnormal	*p*-value
Male	35–52	5,745 (94.52)	333 (5.48)	**0.039**	4,928 (81.08)	1,150 (18.92)	**0.047**
	53–60	1,533 (94.63)	87 (5.37)		1,296 (80.00)	324 (20.00)	
	≥ 61	1,021 (92.65)	81 (7.35)		859 (77.95)	243 (22.05)	
Female	35–52	5,198 (98.65)	71 (1.35)	0.686	5,083 (96.47)	186 (3.53)	0.056
	53–60	741 (98.54)	11 (1.46)		725 (96.41)	27 (3.59)	
	≥ 61	486 (98.18)	9 (1.82)		467 (94.34)	28 (5.66)	

Bold font indicates statistically significant results ($p < 0.05$).
AST: aspartate aminotransferase; ALT: alanine aminotransferase.

Table 3. Crude and adjusted odds ratio for abnormal liver function test by weekly working hours in male and female participants

Sex	Liver enzyme	Weekly working hours	Crude	Model I[a]	Model II[b]
Male	AST	35–52	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
		53–60	1.01 (0.77–1.32)	1.01 (0.77–1.34)	1.03 (0.78–1.36)
		≥ 61	**1.52 (1.14–2.03)**	**1.51 (1.12–2.02)**	**1.51 (1.12–2.05)**
		p for trend	**0.015**	**0.019**	**0.019**
	ALT	35–52	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
		53–60	1.11 (0.95–1.29)	1.11 (0.95–1.30)	1.13 (0.97–1.33)
		≥ 61	**1.22 (1.02–1.46)**	**1.23 (1.01–1.48)**	**1.25 (1.03–1.52)**
		p for trend	**0.018**	**0.023**	**0.013**
Female	AST	35–52	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
		53–60	1.04 (0.53–2.07)	1.02 (0.51–2.03)	0.96 (0.48–1.93)
		≥ 61	0.95 (0.45–1.99)	0.68 (0.32–1.47)	0.64 (0.29–1.42)
		p for trend	0.963	0.448	0.361
	ALT	35–52	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
		53–60	1.01 (0.61–1.66)	0.92 (0.56–1.52)	0.93 (0.56–1.53)
		≥ 61	**1.66 (1.04–2.66)**	1.14 (0.70–1.85)	1.15 (0.70–1.92)
		p for trend	0.080	0.758	0.717

Bold font indicates statistically significant results ($p < 0.05$).
AST: aspartate aminotransferase; ALT: alanine aminotransferase.
[a]Model I: adjusted for age, income, obesity, metabolic syndrome, diabetes mellitus.
[b]Model II: Model I + adjusted for job category, type of work schedule, employment status.

was observed in all study participants.[19] In addition, the above study has limitations in generalization because it was conducted only in white-collar workers with high educational levels. By contrast, the current study showed a consistent increase in male.

There are several plausible mechanisms by which working hours can lead to abnormal LFT. First, recent studies have reported that long working hours increase the risk of NAFLD,[17,18] a known hepatic manifestation of metabolic syndrome.[26] In general, when workers work overtime, they feel physically tired, and their interest in physical activity decreases, which can limit leisure-time physical activity (LTPA).[27,28] Decreased LTPA may increase insulin resistance,[29] which is one of the mechanisms of NAFLD development. Moreover, long working hours are associated with poor dietary behaviors, such as skipping breakfast, eating out, and eating instant food[30] These are known independent risk factors for NAFLD.[31] In short, long working hours may increase the risk of developing NAFLD, which may have increased the LFT.

Second, long working hours cause psychosocial job stress, and stress can affect the liver. Joung et al.[32] conducted several animal experiments and suggested that stress can induce an inflammatory response in the liver through certain mechanisms such as overproduction of stress hormones and activation of the sympathetic nerve. Vere et al.[9] reported that psychosocial stress can adversely affect the course of liver disease, and Chida et al.[33] reported that the activation of the hypothalamic-pituitary-adrenal axis and the sympathetic nervous

system play a key role in this process. It has been reported that these reactions may disrupt the inflammatory response,[34] increase fat accumulation[35] and inhibit regeneration in the liver.[36] In addition, a cohort study conducted by Russ et al.[37] found that mental stress increased the risk of death from liver disease, and a dose-response relationship was observed, suggesting that psychosocial stress caused by long working hours may partially contribute to liver damage. However, current study did not perform a quantitative stress evaluation; hence, it was not possible to analyze the association between stress and liver damage.

Third, long working hours may increase the risk of heavy drinking,[7] which may adversely affect the liver. This is presumed to be because drinking reduces the level of stress that can occur in a work environment, such as long working hours, which is so called tension-reduction hypothesis.[38,39] Heavy drinking increases the risk of diseases such as alcoholic hepatitis,[40] and heavy drinking itself adversely affects the LFT, and shows a dose-response relationship.[41] This may result in an abnormal LFT. The analysis results of the relationship between weekly working hours and heavy drinking in male are presented in **Supplementary Table 2**. It was statistically significant in male working ≥ 61 hours per week than in those working 35–52 hours per week, which is thought to partially support this hypothesis.

As a result of analysis of variance analysis of the mean of LFT for each group, no significant difference was observed, but the SD was large (**Supplementary Table 3**). This suggests that long working hours might not simply increase LFT overall, but rather increase in certain high-risk groups. Taking this into consideration, the results of a stratified analysis in male are summarized in **Supplementary Table 4**. As a result, the OR of abnormal LFT increased when working for a long time for each stratification variable, but only a few cases occurred in which the OR of abnormal AST and ALT levels significantly increased at the same time. Nevertheless, the stratified analyses showed 4 findings. First, the OR of abnormal LFT was significantly increased in the group aged 40 years or older. Second, it was also significantly increased in the BMI 25 kg/m^2 or higher group, further suggesting a dose-response relationship (p for trend < 0.05). It is assumed that the association is stronger in middle-aged people aged 40 years or in obese individuals Third, it was also significantly increased in worker with non-standard work schedule. Age and obesity are well-known risk factors for NAFLD[42] and non-standard working schedule may disrupt circadian rhythm and affect liver homeostasis,[43] suggesting that weekly working hours may affect the LFT in these high-risk groups; therefore, intervention is considered necessary in this group. Finally, considering that ALT is a more specific indicator of liver damage than AST, in pink-collar and temporary workers, the ORs of abnormal ALT increases to 2.03 (95% CI: 1.20–3.43) and 1.63 (95% CI: 1.04–2.54), respectively. This is presumed to be because a pink-collar job causes high job stress due to the exceptional amounts of emotional labor involved,[44] and the temporary worker is high-risk for job stress due to job instability.[45] These are all high-risk groups, and it is considered that preventive intervention is necessary.

However, no correlation was observed between long working hours and abnormal LFT in female. The reasons for this finding are not clear, but this can be explained by the following mechanisms: First, it is due to the biological protective effect of estrogen. Estrogen is known to reduce fat peroxidation[46] and may exhibit anti-inflammation effect.[47] This action can be applied as a protective action against the risk of NAFLD and an increase in inflammation caused by stress. Second, it is because of the difference between male and female in response to psychosocial stress. Alcohol consumption due to psychological job stress is known to show a gender difference.[48,49] It is presumed that this is because male try to relieve stress by drinking alcohol, while female relieve it by searching for social support or talking with

a partner.[50] Third, long working hours may act as promoters of abnormal LFT, rather than as an initiator. In general, obesity rates are higher in male than in female, which is closely linked to increased LFT. Likewise, the female who participated in this study were relatively younger than male, had lower BMI levels, lower prevalence of metabolic syndrome, and lower prevalence of heavy drinking; therefore, they are a relatively healthy group with a lower risk of abnormal LFT (**Supplementary Table 5**). This is presumed to potentiate the risk of abnormal liver enzymes in the high-risk group, rather than simply affecting the liver enzymes. However, these interpretations are limited, and further studies are required.

A consistent significance was observed for male working more than 60 hours per week, whereas no significant results was observed between 53–60 hours per week. In July 2018, with the enforcement of the Korea Labor Standards Act, the maximum statutory working hours per week was reduced from 68 hours to 52 hours. As a result, the number of people working more than 60 hours per week has decreased. However, in the case of exceptional industries such as health care and transportation, if the flexible work system is implemented, and in workplaces with fewer than 5 employees to which the Labor Standards Act does not apply, those who work in the relevant industry may work more than 60 hours per week. So health management for them is necessary. Longitudinal studies with different populations or larger sample sizes are also needed.

The limitations of this study are as follows. First, there is a risk of recall bias because working hours were measured using self-reported questionnaires. However, recent studies found that standardized self-administered questionnaires were not inferior to the measurement of actual working hours.[51,52] Second, it was evaluated only based on simple LFT values, and the presence of clinical diseases was not sufficiently considered. However, in this study, participants with a history of viral hepatitis, cirrhosis, and liver cancer were excluded; moreover, ALT itself has a close correlation with NAFLD and has predictive power.[53] Third, because cross-sectional studies conducted for 11 years were integrated, the characteristics of the participants may be different by year. However, even if the characteristics of the participants change every year, we assumed that the relationship between long working hours and abnormal liver enzyme levels would not change. Fourth, since hepatitis B or C, which have a large burden of disease on the liver,[54] was excluded from the study design stage, this study has limitations in consideration of the above diseases. Although working hours may be linked to the risk of viral hepatitis, the discussion was excluded because it is beyond the subject of this study. Finally, the temporal relationship between weekly working hours and abnormal LFT could not be identified. However, in general, liver damage causes fatigue[55]; because of this, people try to avoid working long hours. Hence, the possibility of reverse causation is thought to be low. Nonetheless, selection would probably lead to an underestimation of the true risk; therefore, a longitudinal study of the association between weekly working hours and abnormal LFT is needed in the future.

On the contrary, this study has several strengths. To the best of our knowledge, this was the first study to analyze the relationship between long working hours and abnormal LFT in a representative Korean population. In addition, the stratification analysis provided information on high-risk populations.

CONCLUSIONS

Compared with the 35–52 hours working group, no significant increase in LFT was observed in the 53–60 hours working group, but it did increase significantly in the ≥ 61 hours working

group. Nevertheless, it would be premature to conclude that long working hours is an independent risk factor for liver disease, until there is sufficient evidence to confirm these results. The results of stratification analysis suggest that long working hours could affect the liver and emphasize the need for intervention in high-risk groups, such as those aged > 40 years, obese individuals, worker on non-standard work schedule, pink-collar workers, or temporary workers. To reduce overwork-related liver diseases, compliance with appropriate working hours is necessary, especially in high-risk groups. In order to develop the best preventive strategies, more research on this topic is needed in order to clearly understand the mechanism by which long working hours affect the liver.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1
Sensitivity analysis in men participants

Click here to view

Supplementary Table 2
Adjusted OR (95% CI) for heavy drinking by weekly working hours in male participants

Click here to view

Supplementary Table 3
Analysis of variance analysis between weekly working hour and abnormal LFT in male participants

Click here to view

Supplementary Table 4
Subgroup analysis of abnormal LFT by weekly working hours in male participants

Click here to view

Supplementary Table 5
General characteristics of the participants

Click here to view

REFERENCES

1. Organization for Economic Cooperation and Development (OECD). *Hours Worked (Indicator)*. Paris, France: OECD; 2021.
2. Bannai A, Tamakoshi A. The association between long working hours and health: a systematic review of epidemiological evidence. Scand J Work Environ Health 2014;40(1):5-18.
PUBMED | CROSSREF
3. Kivimäki M, Jokela M, Nyberg ST, Singh-Manoux A, Fransson EI, Alfredsson L, et al. Long working hours and risk of coronary heart disease and stroke: a systematic review and meta-analysis of published and unpublished data for 603,838 individuals. Lancet 2015;386(10005):1739-46.
PUBMED | CROSSREF
4. Park S, Kook H, Seok H, Lee JH, Lim D, Cho DH, et al. The negative impact of long working hours on mental health in young Korean workers. PLoS One 2020;15(8):e0236931.
PUBMED | CROSSREF
5. Sato Y, Miyake H, Thériault G. Overtime work and stress response in a group of Japanese workers. Occup Med (Lond) 2009;59(1):14-9.
PUBMED | CROSSREF
6. Artazcoz L, Cortès I, Escribà-Agüir V, Cascant L, Villegas R. Understanding the relationship of long working hours with health status and health-related behaviours. J Epidemiol Community Health 2009;63(7):521-7.
PUBMED | CROSSREF
7. Virtanen M, Jokela M, Nyberg ST, Madsen IE, Lallukka T, Ahola K, et al. Long working hours and alcohol use: systematic review and meta-analysis of published studies and unpublished individual participant data. BMJ 2015;350:g7772.
PUBMED | CROSSREF
8. Zhu Y, Liu J, Jiang H, Brown TJ, Tian Q, Yang Y, et al. Are long working hours associated with weight-related outcomes? A meta-analysis of observational studies. Obes Rev 2020;21(3):e12977.
PUBMED | CROSSREF
9. Vere CC, Streba CT, Streba LM, Ionescu AG, Sima F. Psychosocial stress and liver disease status. World J Gastroenterol 2009;15(24):2980-6.
PUBMED | CROSSREF
10. Lee EY, Choi HY, Cho H, Kim BH, Ki M. Health behavior associated with liver enzymes among obese Korean adolescents, 2009-2014. PLoS One 2018;13(1):e0190535.
PUBMED | CROSSREF
11. Agrawal S, Dhiman RK, Limdi JK. Evaluation of abnormal liver function tests. Postgrad Med J 2016;92(1086):223-34.
PUBMED | CROSSREF
12. Patel DA, Srinivasan SR, Xu JH, Chen W, Berenson GS. Persistent elevation of liver function enzymes within the reference range is associated with increased cardiovascular risk in young adults: the Bogalusa Heart Study. Metabolism 2007;56(6):792-8.
PUBMED | CROSSREF
13. Ruhl CE, Everhart JE. Elevated serum alanine aminotransferase and gamma-glutamyltransferase and mortality in the United States population. Gastroenterology 2009;136(2):477-485.e11.
PUBMED | CROSSREF
14. Kim HC, Nam CM, Jee SH, Han KH, Oh DK, Suh I. Normal serum aminotransferase concentration and risk of mortality from liver diseases: prospective cohort study. BMJ 2004;328(7446):983.
PUBMED | CROSSREF
15. Asrani SK, Devarbhavi H, Eaton J, Kamath PS. Burden of liver diseases in the world. J Hepatol 2019;70(1):151-71.
PUBMED | CROSSREF
16. Paik JM, Golabi P, Younossi Y, Mishra A, Younossi ZM. Changes in the global burden of chronic liver diseases from 2012 to 2017: the growing impact of NAFLD. Hepatology 2020;72(5):1605-16.
PUBMED | CROSSREF
17. Song E, Kim JA, Roh E, Yu JH, Kim NH, Yoo HJ, et al. Long working hours and risk of nonalcoholic fatty liver disease: Korea National Health and Nutrition Examination Survey VII. Front Endocrinol (Lausanne) 2021;12:647459.
PUBMED | CROSSREF
18. Lee Y, Mun E, Park S, Lee W. Long working hours are associated with a higher risk of non-alcoholic fatty liver disease: a large population-based Korean cohort study. PLoS One 2021;16(7):e0255118.
PUBMED | CROSSREF

19. Mun E, Lee W, Nam MW, Kim HI, Kim H, Lee Y, et al. Cross-sectional association between long working hours and liver function: the Kangbuk Samsung Health Study. BMJ Open 2020;10(12):e041595.
PUBMED | CROSSREF

20. Ochiai Y, Takahashi M, Matsuo T, Sasaki T, Fukasawa K, Araki T, et al. Objective and subjective working hours and their roles on workers' health among Japanese employees. Ind Health 2020;58(3):265-75.
PUBMED | CROSSREF

21. Lefebvre P, Staels B. Hepatic sexual dimorphism - implications for non-alcoholic fatty liver disease. Nat Rev Endocrinol 2021;17(11):662-70.
PUBMED | CROSSREF

22. Chapter IV: working hours and recess. Labor Standard Act. https://elaw.klri.re.kr/kor_service/lawView.do?hseq=54708&lang=ENG. Updated 2020. Accessed October 1, 2021.

23. Korean Enforcement Decree of the Industrial Accident Compensation Insurance Act and Public Notice of what is necessary to determine approval for cerebro-cardiovascular disease and musculoskeletal disease as occupational diseases. https://www.law.go.kr/LSW//admRulInfoP.do?admRulSeq=2100000196483. Updated 2020. Accessed October 1, 2021.

24. Health examination implementation guidelines (Korean): No. 2020-313. https://mohw.go.kr/react/modules/viewHtmlConv.jsp?BOARD_ID=5900&CONT_SEQ=362673&FILE_SEQ=310166. Updated 2020. Accessed January 4, 2022.

25. Korea National Health and Nutrition Examination Survey: statistical survey outlines (Korean). http://meta.narastat.kr/metasvc/svc/SvcMetaDcDtaPopup.do?orgId=117&confmNo=117002&kosisYn=Y. Updated 2019. Accessed January 4, 2022.

26. Yki-Järvinen H. Non-alcoholic fatty liver disease as a cause and a consequence of metabolic syndrome. Lancet Diabetes Endocrinol 2014;2(11):901-10.
PUBMED | CROSSREF

27. Kim C, Cho Y. Working conditions and leisure-time physical activity among waged workers in South Korea: a cross-sectional study. J Occup Health 2015;57(3):259-67.
PUBMED | CROSSREF

28. Schneider S, Becker S. Prevalence of physical activity among the working population and correlation with work-related factors: results from the first German National Health Survey. J Occup Health 2005;47(5):414-23.
PUBMED | CROSSREF

29. Kaizu S, Kishimoto H, Iwase M, Fujii H, Ohkuma T, Ide H, et al. Impact of leisure-time physical activity on glycemic control and cardiovascular risk factors in Japanese patients with type 2 diabetes mellitus: the Fukuoka Diabetes Registry. PLoS One 2014;9(6):e98768.
PUBMED | CROSSREF

30. Tanaka R, Tsuji M, Kusuhara K, Kawamoto T; Japan Environment and Children's Study Group. Association between time-related work factors and dietary behaviors: results from the Japan Environment and Children's Study (JECS). Environ Health Prev Med 2018;23(1):62.
PUBMED | CROSSREF

31. Fazel Y, Koenig AB, Sayiner M, Goodman ZD, Younossi ZM. Epidemiology and natural history of non-alcoholic fatty liver disease. Metabolism 2016;65(8):1017-25.
PUBMED | CROSSREF

32. Joung JY, Cho JH, Kim YH, Choi SH, Son CG. A literature review for the mechanisms of stress-induced liver injury. Brain Behav 2019;9(3):e01235.
PUBMED | CROSSREF

33. Chida Y, Sudo N, Kubo C. Does stress exacerbate liver diseases? J Gastroenterol Hepatol 2006;21(1 Pt 2):202-8.
PUBMED | CROSSREF

34. Swain MG. I. Stress and hepatic inflammation. Am J Physiol Gastrointest Liver Physiol 2000;279(6):G1135-8.
PUBMED | CROSSREF

35. Liu YZ, Chen JK, Zhang Y, Wang X, Qu S, Jiang CL. Chronic stress induces steatohepatitis while decreases visceral fat mass in mice. BMC Gastroenterol 2014;14(1):106.
PUBMED | CROSSREF

36. Ishtiaq SM, Khan JA, Arshad MI. Psychosocial-stress, liver regeneration and weight gain: a conspicuous pathophysiological triad. Cell Physiol Biochem 2018;46(1):1-8.
PUBMED | CROSSREF

37. Russ TC, Kivimäki M, Morling JR, Starr JM, Stamatakis E, Batty GD. Association between psychological distress and liver disease mortality: a meta-analysis of individual study participants. Gastroenterology 2015;148(5):958-966.e4.
PUBMED | CROSSREF

38. Okechukwu CA. Long working hours are linked to risky alcohol consumption. BMJ 2015;350:g7800.
PUBMED | CROSSREF

39. Frone MR. Are work stressors related to employee substance use? The importance of temporal context assessments of alcohol and illicit drug use. J Appl Psychol 2008;93(1):199-206.
PUBMED | CROSSREF

40. Friedmann PD. Clinical practice. Alcohol use in adults. N Engl J Med 2013;368(4):365-73.
PUBMED | CROSSREF

41. Agarwal S, Fulgoni VL 3rd, Lieberman HR. Assessing alcohol intake & its dose-dependent effects on liver enzymes by 24-h recall and questionnaire using NHANES 2001-2010 data. Nutr J 2016;15(1):62.
PUBMED | CROSSREF

42. Iqbal U, Perumpail BJ, Akhtar D, Kim D, Ahmed A. The epidemiology, risk profiling and diagnostic challenges of nonalcoholic fatty liver disease. Medicines (Basel) 2019;6(1):41.
PUBMED | CROSSREF

43. Choi H, Oh HJ, Shin JS, Lim M, Kim SK, Kang HT, et al. Relationship between shift work and liver enzymes: a cross-sectional study based on the Korea National Health and Examination Survey (2007-2015). Ann Occup Environ Med 2019;31:e15.
PUBMED | CROSSREF

44. Chun HR, Cho I, Choi Y, Cho SI. Effects of emotional labor factors and working environment on the risk of depression in pink-collar workers. Int J Environ Res Public Health 2020;17(14):5208.
PUBMED | CROSSREF

45. Virtanen M, Kivimäki M, Joensuu M, Virtanen P, Elovainio M, Vahtera J. Temporary employment and health: a review. Int J Epidemiol 2005;34(3):610-22.
PUBMED | CROSSREF

46. Palmisano BT, Zhu L, Stafford JM. Role of estrogens in the regulation of liver lipid metabolism. Adv Exp Med Biol 2017;1043:227-56.
PUBMED | CROSSREF

47. Shi L, Feng Y, Lin H, Ma R, Cai X. Role of estrogen in hepatocellular carcinoma: is inflammation the key? J Transl Med 2014;12(1):93.
PUBMED | CROSSREF

48. Chaplin TM, Hong K, Bergquist K, Sinha R. Gender differences in response to emotional stress: an assessment across subjective, behavioral, and physiological domains and relations to alcohol craving. Alcohol Clin Exp Res 2008;32(7):1242-50.
PUBMED | CROSSREF

49. Crum RM, Muntaner C, Eaton WW, Anthony JC. Occupational stress and the risk of alcohol abuse and dependence. Alcohol Clin Exp Res 1995;19(3):647-55.
PUBMED | CROSSREF

50. Esper LH, Furtado EF. Gender differences and association between psychological stress and alcohol consumption: a systematic review. J Alcohol Drug Depend 2013;1(3):116-20.

51. Jacobs JA. Measuring time at work: are self-reports accurate. Mon Labor Rev 1998;121:42-53.

52. Imai T, Kuwahara K, Miyamoto T, Okazaki H, Nishihara A, Kabe I, et al. Validity and reproducibility of self-reported working hours among Japanese male employees. J Occup Health 2016;58(4):340-6.
PUBMED | CROSSREF

53. Chang Y, Ryu S, Sung E, Jang Y. Higher concentrations of alanine aminotransferase within the reference interval predict nonalcoholic fatty liver disease. Clin Chem 2007;53(4):686-92.
PUBMED | CROSSREF

54. Sarin SK, Kumar M, Eslam M, George J, Al Mahtab M, Akbar SM, et al. Liver diseases in the Asia-Pacific region: a Lancet Gastroenterology & Hepatology Commission. Lancet Gastroenterol Hepatol 2020;5(2):167-228.
PUBMED | CROSSREF

55. Swain MG. Fatigue in liver disease: pathophysiology and clinical management. Can J Gastroenterol 2006;20(3):181-8.
PUBMED | CROSSREF