



저작자표시-비영리-변경금지 2.0 대한민국

이용자는 아래의 조건을 따르는 경우에 한하여 자유롭게

- 이 저작물을 복제, 배포, 전송, 전시, 공연 및 방송할 수 있습니다.

다음과 같은 조건을 따라야 합니다:



저작자표시. 귀하는 원저작자를 표시하여야 합니다.



비영리. 귀하는 이 저작물을 영리 목적으로 이용할 수 없습니다.



변경금지. 귀하는 이 저작물을 개작, 변형 또는 가공할 수 없습니다.

- 귀하는, 이 저작물의 재이용이나 배포의 경우, 이 저작물에 적용된 이용허락조건을 명확하게 나타내어야 합니다.
- 저작권자로부터 별도의 허가를 받으면 이러한 조건들은 적용되지 않습니다.

저작권법에 따른 이용자의 권리는 위의 내용에 의하여 영향을 받지 않습니다.

이것은 [이용허락규약\(Legal Code\)](#)을 이해하기 쉽게 요약한 것입니다.

[Disclaimer](#)

Relationship between shift work and liver enzymes:  
A cross-sectional study based on the Korea  
National Health and Examination Survey  
(2007-2015)

Hyeongyeong Choi

The Graduate School  
Yonsei University  
Department of Medicine

Relationship between shift work and liver enzymes:  
A cross-sectional study based on the Korea  
National Health and Examination Survey  
(2007-2015)

A Dissertation

Submitted to the Department of Medicine  
and the Graduate School of Yonsei University  
in partial fulfillment of the  
requirements for the degree of  
Master of Medicine

Hyeongyeong Choi

June 2019

This certifies that the Dissertation  
of Hyeongyeong Choi is approved.

---

Thesis Supervisor : Sang-Baek Koh

---

Thesis Committee Member #1 : Yeon-Soon Ahn

---

Thesis Committee Member #2 : Sung-Soo Oh

The Graduate School  
Yonsei University  
June 2019

## 감사의 글

본 논문의 처음 연구 계획에서부터 완성에 이르기까지 학문적 기틀을 잡아주시고 관심과 소상한 가르침으로 지도해 주신 고상백 지도 교수님께 진심으로 감사드립니다. 바쁜 일정 속에서도 귀중한 시간을 내어 논문 작성과 심사에 조언과 격려를 해주신 안연순 교수님, 오성수 교수님께도 깊이 감사드립니다.

또한 본 논문을 준비하는 동안 항상 관심을 가지고 지켜봐주신 장세진 교수님, 김춘배 교수님, 강희태 교수님, 김성경 교수님께도 감사드립니다. 논문 작성에 여러 도움을 주신 직업환경의학과 의국, 외래, 보건관리대행, 예방의학교실, 직업 및 환경의학연구소 모든 선생님들께도 감사드립니다.

논문의 시작부터 맺기까지 많은 분들의 도움이 있었기에 가능했습니다. 그 동안 저를 지도해주시고 격려해 주신 모든 분들께 이 자리를 빌어 감사의 말씀을 드립니다.

지금에 있기까지 언제나 사랑으로 지원해주신 부모님과 시부모님, 사랑하는 자매들에게 감사드리며, 가장 가까운 곳에서 든든한 버팀목이 되어준 사랑하는 남편 강희승에게 감사의 말을 전합니다.

2019년 6월  
최 현 경 드림

## Contents

Figures and Tables	ii
Abstract	iii
I . Background	1
II . Methods	3
A. Participants	3
B. Shift work and Day work	5
C. Definition of abnormal level of liver enzymes	5
D. Covariates	5
E. Statistical analysis	6
III. Results	8
A. General characteristics	8
B. Odds ratios of abnormal AST and abnormal ALT according to shift work	11
C. Odds ratios of abnormal AST and abnormal ALT according to work patterns	13
IV. Discussion	15
V. Conclusion	20
References	21
Abstract in Korean	27

## Figures

<b>Fig. 1.</b> A flow of the study design. ....	4
---	---

## Tables

<b>Table 1.</b> General characteristics of the subjects. ....	9
<b>Table 2.</b> Crude and adjusted odds ratio for abnormal AST and abnormal ALT by shift work in male and female subjects. ....	12
<b>Table 3.</b> Crude and adjusted odds ratio for abnormal AST and abnormal ALT by shift work patterns male and female subjects. ....	14

## Abstract

### Relationship between shift work and liver enzymes: A cross-sectional study based on the Korea National Health and Examination Survey (2007-2015)

Hyeongyeong Choi

*Department of Medicine  
The Graduate School of Yonsei University*

(Directed by Professor Sang-Baek Koh)

**Background** : Shift work has well-known adverse effects on health. However, few studies have investigated the relationship between shift work and hepatic disorders. This study aimed to evaluate the association between shift work and abnormal level of liver enzymes.

**Methods** : The aggregated data from the 2007 - 2009, 2010 - 2012, and 2013 - 2015 cycles of the Korea National Health and Nutrition Examination Survey (KNHANES) was used for this study. The chi-square test and multiple logistic regression analysis were used to assess relationship between shift work and abnormal level of liver enzymes stratified by gender.

**Results** : The odds ratio of abnormal level of alanine aminotransferase (abnormal ALT) in female shift workers was higher with 1.31 (95% CI 1.00-1.71) compared with day workers after adjusting for covariates. After dividing into subgroups of the shift work pattern, the odds ratios of abnormal liver enzymes for each patterns compared with day work were not significantly higher.

**Conclusion** : This study provides limited support for the hypothesis that shift work is related to liver enzyme abnormalities, but offers some evidence in favor of the idea that shift work affects female workers more than males on abnormal ALT. Further studies are needed to define the relationship between shift work and abnormal liver enzymes to be carried out as well as the gender difference in the association.

---

**Key words** : Shift work, Abnormal level of liver enzymes, Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), KNHANES

# Relationship between shift work and liver enzymes: A cross-sectional study based on the Korea National Health and Examination Survey (2007–2015)

Hyeongyeong Choi

*Department of Medicine  
The Graduate School of Yonsei University*

(Directed by Professor Sang-Baek Koh)

## I . Background

Hepatic disorder is a major concern in Korea and many other countries. Since the liver is a primary organ involved in biotransformation of food and drugs, hepatic disorders are very often. The determination of various liver enzymes in serum is used to evaluate the functional status of the liver. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activities in serum are the most frequently used indicators for evaluation of liver dysfunction.<sup>1-2</sup> The increase in these liver enzymes can be caused by viruses, bacterial infections, alcohol or toxic substances,

excessive accumulation of fat or heavy metals, and abnormal immune responses.<sup>3</sup>

In addition, recent studies suggest that there is a relationship between liver health and specific occupations, especially shift work. Shift work has become universal throughout the world. At least 15% of workers are engaged in shift work in the European Union<sup>4</sup> and United States<sup>5</sup> and estimated 10.2 - 14.5 % of wage earners in Korea (1.27 - 1.97 million people) perform night shift work.<sup>6-7</sup> Shift work is an important and well-known health hazard in the modern workplace. Unlike day workers, shift workers are exposed to light at night and can interfere with sleep and circadian rhythms.<sup>8</sup> And it can cause various health problems. Shift work is known to be related with chronic diseases such as cardiovascular diseases, diabetes mellitus, metabolic syndrome, and breast cancer.<sup>9</sup> Interestingly, abnormal liver function is widespread among many occupations including shift work. Although inconclusive, several studies have shown that shift work is associated with abnormal level of liver enzymes.<sup>10-13</sup>

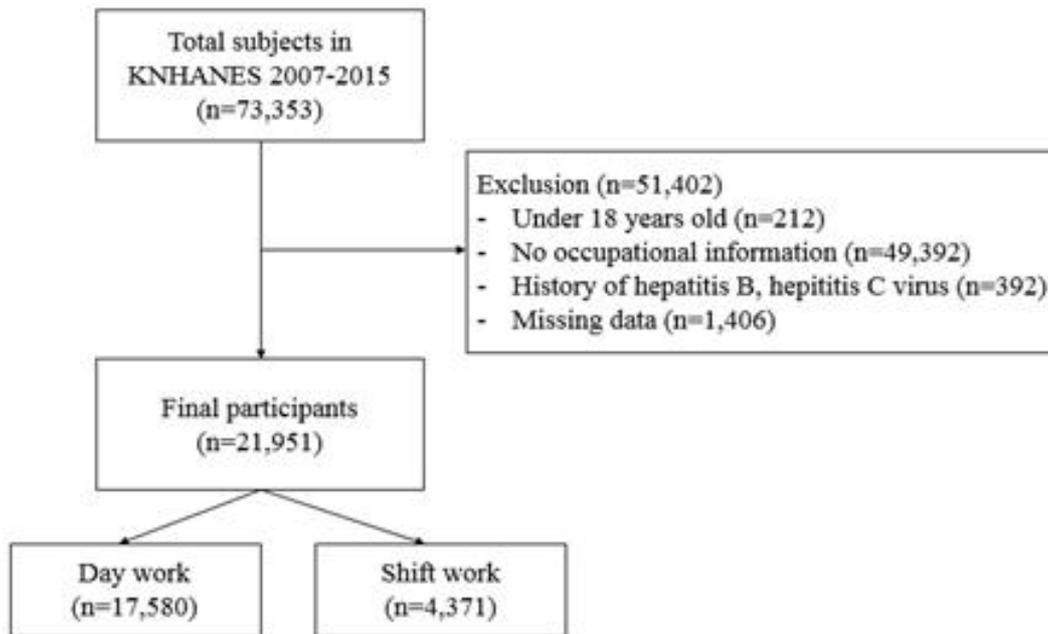
The aim of the present study was to investigate the relationship between shift work and abnormal level of liver enzymes, utilizing data from the Korea National Health and Nutrition Examination Survey (KNHANES).

## II. Methods

### A. Participants

This study used aggregated data from the 2007 - 2009, 2010 - 2012, and 2013 - 2015 cycles of the KNHANES. The KNHANES is a national cross-sectional survey gathered annually by the Korea Centers for Disease Control and Prevention (KCDC), and is designed according to multistage stratified and cluster sampling. The data includes health questionnaire and blood test results. Participants who were at least 18 years old, and who had occupational information were included in this study. Individuals who had Hepatitis B and Hepatitis C were excluded from the analysis. In addition, individuals with missing values for major variables and covariates were also excluded. Finally, 51,402 were excluded from the analysis and a total of 21,951 participants were included in the analysis (Figure 1).

Fig. 1. A flow of the study design.



## **B. Shift work and Day work**

In KNHANES, work groups were divided as follows. "Do you usually work during the day time (between 6 a.m. and 6 p.m.)? Or are you working in another time?". Participants who answered "Usually work during the day time (between 6 a.m. and 6 p.m.)" were classified as day workers, and other participants who answered "fixed-evening shift (between 2 p.m. and 24:00), fixed-night shift (between 9 p.m. and 8 a.m. next day), regular day and night rotating shift, 24-hours rotating shift, split shift (working two shifts in one day), irregular rotating shift, and others" were classified as shift workers.

## **C. Definition of abnormal level of liver enzymes**

According to the standard reference limit, abnormal serum level of aspartate aminotransferase (abnormal AST) was defined as  $AST > 40$  IU/L, and abnormal serum level of alanine aminotransferase (abnormal ALT) was defined as  $ALT > 35$  IU/L.<sup>14</sup>

## **D. Covariates**

Age, sex, smoking status, drinking status, hours of sleep, body mass index (BMI), physical activity and history of disease (hypertension,

diabetes mellitus and dyslipidemia) were included as potential confounding variables. Information regarding demographic and social factors was obtained using a standardized questionnaire in health interviews. Age was divided into 6 groups: 18-29 years, 30-39 years, 40-49 years, 50-59 years, 60-69 years and above 70 years. Smoking status was divided into non-smokers, ex-smokers, and current smokers. Drinking status was divided into non-drinkers, social-drinkers, and binge-drinkers. Social drinkers are categorized as drinking less than 5 units of alcohol per time, and binge drinkers are categorized as drinking 5 or more units of alcohol per time.<sup>15</sup> Hours of sleep were categorized into three groups (<7 hours, 7 - 9 hours and >9 hours per night) according to appropriate sleep durations recommended by the National Sleep Foundation.<sup>16</sup> BMI was calculated by dividing body weight by height squared (kg/m<sup>2</sup>). As for physical activity, the subjects were grouped according to whether they performed exercise over 10 minutes that are more strenuous than usual activities or not.

## E. Statistical analysis

The t-test and the chi-square test were used to examine the general characteristics of the study population with regarding to the abnormal level of liver enzymes. Relationship between the shift work and abnormal level of liver enzymes was examined using multiple logistic regression after stratification for gender. To reflect the impact of each variable, age, smoking status, drinking status, and physical activity were adjusted in

model 1, and hours of sleep, BMI, and history of disease were additionally adjusted in model 2. The statistical analyses were performed using SPSS version 23.0 to take into account sample weights and complex sample design effects.

### III. Results

#### A. General characteristics

The general characteristics of participants are shown in Table 1. From a total of 21,951 participants included in the final analysis, 11,288 (51.4%) were male and 10,663 (48.6%) were female. In the mean age, shift workers were younger than day workers in both male and female. The proportion of day workers was higher in both male and female workers. In patterns of shift work schedule, the proportion of fixed-evening shift was the highest in both male and female shift workers. Among lifestyle factors, the smoking rate and the proportion of sleeping less than 7 hours were higher in shift workers and the proportion of binge drinker in female shift workers was higher compared with female day workers.

Table 1. General characteristics of the subjects.

Variable	Male			Female		
	Day work	Shift work	p-value	Day work	Shift work	p-value
Total(N <sup>a</sup> )	8954	2334		8626	2037	
Shift work patterns	fixed-evening shift	795(34.06)		1318(64.70)		
	fixed-night shift	427(18.29)		232(11.39)		
	regular day and night rotating shift	450(19.28)		181(8.89)		
	24-hours rotating shift	312(13.37)		65(3.19)		
	split shift	135(5.78)		113(5.55)		
	irregular rotating shift	215(9.21)		128(6.28)		
Age (years)	48.04±14.43	44.24±15.74	<0.01*	46.82±14.87	41.65±14.35	<0.01*
Age group	18-29	965(10.78)	503(21.55)	1,314(15.23)	519(25.48)	
	30-39	1,850(20.66)	483(20.69)	1,591(18.44)	370(18.16)	
	40-49	2,002(22.36)	458(19.62)	1,932(22.40)	481(23.61)	
	50-59	2010(17.81)	394(16.88)	1,938(22.47)	448(21.99)	<0.01†
	60-69	1,420(15.86)	373(15.98)	1,177(13.64)	167(8.20)	
	≥70	707(7.90)	123(5.27)	674(7.81)	52(2.55)	
Smoking Status	Non-Smoker	1,747(19.51)	515(22.07)	7,721(89.51)	1,694(83.16)	
	Ex-Smoker	3,347(37.38)	604(25.88)	406(4.71)	87(4.27)	<0.01†
	Current Smoker	3,860(43.11)	1,215(52.06)	499(5.78)	256(12.57)	
Drinking Status	Non-Drinker	1,177(13.14)	286(12.25)	2,568(29.77)	481(23.61)	
	Social-Drinker	2,958(33.04)	750(32.13)	4,667(54.10)	1,059(51.99)	<0.01†
	Binge-Drinker	4,819(53.82)	1,298(56.61)	1,391(16.13)	497(24.40)	
Hours of sleep	<7	3,804(33.70)	1,017(43.57)	3,632(42.11)	887(43.54)	
	7-9	4,649(51.92)	1,152(49.36)	4,424(51.29)	945(46.39)	<0.01†
	>9	501(5.60)	165(7.07)	570(6.61)	205(10.06)	
BMI (kg/m <sup>2</sup> )	<23	205(2.29)	54(2.31)	521(6.04)	156(7.66)	
	23-25	5,345(59.69)	1,403(60.11)	5,747(66.62)	1,376(67.55)	<0.01†
	≥25	3,404(38.02)	877(37.57)	2,358(27.34)	505(24.79)	

Physical activity	No	1,597(17.84)	293(12.55)	<0.01†	1,908(22.12)	383(18.80)	<0.01†
	Yes	7,357(82.16)	2,041(87.45)		6,718(77.88)	1,654(81.20)	
Hypertension	No	7,258(81.06)	1,956(83.80)	<0.01†	7,235(83.87)	1,817(89.20)	<0.01†
	Yes	1,696(18.94)	378(16.20)		1,391(16.13)	220(10.80)	
Diabetes Mellitus	No	8,272(92.38)	2,186(93.66)	0.03†	8,216(95.25)	1,974(96.91)	<0.01†
	Yes	682(7.62)	148(6.34)		410(4.75)	63(3.09)	
Dyslipidemia	No	8,090(90.35)	2,146(91.95)	0.01†	7,766(90.03)	1,869(91.75)	0.01†
	Yes	864(9.65)	188(8.05)		860(9.97)	168(8.25)	
AST (IU/L)		24.77±14.65	23.85±11.88	<0.01*	20.03±8.51	19.81±8.51	0.29*
AST status	Normal	8,350(93.25)	2,203(94.39)	0.05†	8,439(97.83)	1,986(97.50)	0.35†
	Abnormal	604(6.75)	131(5.61)		187(2.17)	51(2.50)	
ALT (IU/L)		26.64±21.94	25.87±18.01	0.12*	17.25±12.86	17.01±12.51	0.44*
ALT status	Normal	7,304(81.57)	1,895(81.19)	0.67†	8,195(95.00)	1,921(94.31)	0.19†
	Abnormal	1,650(18.43)	439(18.81)		431(5.00)	116(5.69)	

<sup>a</sup> unweighted count

Data are shown as N<sup>a</sup> (estimated percentage) for categorical variables and as mean ± standard error for continuous variables.

\* : p-value by independent two sample t-test

† : p-value by chi-square test

## **B. Odds ratios of abnormal AST and abnormal ALT according to shift work**

Association between shift work and abnormal AST, and between shift work and abnormal ALT by multiple logistic regression analysis are shown in Table 2. For male, the odds ratios (ORs) of abnormal AST and abnormal ALT in shift workers were found to be low, but the difference was not significant. For female, the OR of abnormal ALT in shift workers was 1.19 (95% CI 0.92 - 1.54) compared with day workers. After adjusting for age, smoking status, drinking status, and physical activity, the OR of abnormal ALT was significantly higher with OR 1.30 (95% CI 1.00 - 1.69). After additionally adjusting for hours of sleep, BMI, and history of disease, the same results were obtained 1.31 (95% CI 1.00-1.71).

Table 2. Crude and adjusted odds ratio for abnormal AST and abnormal ALT by shift work in male and female subjects.

		Abnormal AST		Abnormal ALT	
		Male	Female	Male	Female
<b>Crude OR</b> <b>(95% CI)</b>	Day work	Reference	Reference	Reference	Reference
	Shift work	0.81 (0.65-1.02)	1.20 (0.83-1.72)	0.99 (0.87-1.14)	1.19 (0.92-1.54)
<b>Model 1</b>	Day work	Reference	Reference	Reference	Reference
	Shift work	0.85 (0.68-1.06)	1.30 (0.90-1.87)	0.95 (0.83-1.09)	1.30 (1.00-1.69)
<b>Model 2</b>	Day work	Reference	Reference	Reference	Reference
	Shift work	0.85 (0.68-1.07)	1.30 (0.90-1.87)	0.96 (0.84-1.11)	1.31 (1.00-1.71)

OR, odds ratio; CI, confidence interval.

Model 1: Adjusted by age, smoking status, drinking status, physical activity.

Model 2: Model 1+hours of sleep, BMI, hypertension, diabetes mellitus, dyslipidemia

### C. Odds ratios of abnormal AST and abnormal ALT according to work patterns

The work patterns were divided into 7 groups of day work, fixed-evening shift, fixed-night shift, regular day and night rotating shift, 24-hours rotating shift, split shift (working two shifts in one day), and irregular rotating shift (Table 3). The ORs of abnormal AST and abnormal ALT for all patterns of shift work compared with day work were not significantly higher in analysis stratified by sex.

Table 3. Crude and adjusted odds ratio for abnormal AST and abnormal ALT by shift work patterns male and female subjects.

	Abnormal AST		Abnormal ALT		
	Male	Female	Male	Female	
<b>Crude OR (95% CI)</b>	day work	Reference	Reference	Reference	Reference
	fixed-evening shift	0.85(0.63-1.15)	0.88(0.54-1.42)	1.08(0.90-1.30)	1.20(0.85-1.69)
	fixed-night shift	1.13(0.67-1.89)	1.68(0.71-3.98)	1.02(0.73-1.43)	1.35(0.76-2.39)
	regular day and night rotating shift	0.89(0.52-1.53)	1.31(0.53-3.27)	1.07(0.77-1.50)	0.74(0.36-1.54)
	24-hours rotating shift	0.91(0.45-1.86)	0.17(0.02-1.23)	1.01(0.64-1.58)	0.49(0.22-1.11)
	split shift	1.78(0.88-3.58)	1.22(0.27-5.44)	1.48(0.92-2.38)	0.96(0.36-2.58)
	irregular rotating shift	0.69(0.36-1.35)	1.46(0.46-4.67)	1.12(0.73-1.71)	1.59(0.79-3.19)
<b>Model 1</b>	day work	Reference	Reference	Reference	Reference
	fixed-evening shift	0.86(0.63-1.16)	0.91(0.56-1.47)	1.06(0.88-1.28)	1.24(0.88-1.74)
	fixed-night shift	1.11(0.66-1.87)	1.74(0.73-4.17)	0.98(0.70-1.37)	1.39(0.78-2.47)
	regular day and night rotating shift	0.92(0.53-1.59)	1.29(0.52-3.21)	1.04(0.75-1.46)	0.75(0.36-1.54)
	24-hours rotating shift	0.89(0.43-1.81)	0.18(0.03-1.30)	1.00(0.64-1.57)	0.50(0.22-1.15)
	split shift	1.74(0.85-3.54)	1.41(0.32-6.31)	1.46(0.90-2.37)	1.06(0.40-2.84)
	irregular rotating shift	0.75(0.38-1.47)	1.67(0.52-5.39)	1.10(0.72-1.69)	1.76(0.88-3.56)
<b>Model 2</b>	day work	Reference	Reference	Reference	Reference
	fixed-evening shift	0.86(0.63-1.17)	0.92(0.56-1.49)	1.06(0.87-1.30)	1.27(0.91-1.78)
	fixed-night shift	1.11(0.66-1.87)	1.75(0.74-4.15)	1.00(0.72-1.38)	1.40(0.80-2.46)
	regular day and night rotating shift	0.92(0.53-1.60)	1.33(0.53-3.34)	1.07(0.76-1.51)	0.77(0.36-1.61)
	24-hours rotating shift	0.91(0.44-1.86)	0.18(0.03-1.35)	1.07(0.69-1.67)	0.53(0.23-1.22)
	split shift	1.74(0.86-3.55)	1.39(0.31-6.21)	1.47(0.89-2.43)	1.03(0.38-2.77)
	irregular rotating shift	0.69(0.35-1.36)	1.67(0.53-5.24)	0.97(0.61-1.54)	1.77(0.85-3.68)

OR, odds ratio; CI, confidence interval.

Model 1: Adjusted by age, smoking status, drinking status, physical activity.

Model 2: Model 1+hours of sleep, BMI, hypertension, diabetes mellitus, dyslipidemia

## IV. Discussion

This study analyzed relationship between shift work and abnormal level of liver enzymes in Koreans, using large-scale survey data. Gender difference on the association between shift work and abnormal liver enzymes was shown in this study. The results of the current study showed that shift work was associated with abnormal ALT in female workers (adjusted OR: 1.31, 95% CI 1.00–1.71). The association between shift work and abnormal AST in female was shown as the OR 1.30 (95% CI 0.90 - 1.87), but not statistically significant. However, there was no significant association between shift work and abnormal liver enzymes among male workers. When patterns of shift work were divided into subgroups, there were no significant differences between all patterns of shift work and risk of abnormal liver enzymes stratified by gender.

Abnormal liver function, usually indicated by liver enzyme abnormalities is common among workers in many occupations, which involve shift work.<sup>10,11,13</sup> The circadian clock system is the main factor in the association between shift work and the abnormal level of liver enzymes. Circadian clock system consists of a central clock located in the suprachiasmatic nucleus in the hypothalamus and peripheral clocks in peripheral tissues. Peripheral clocks in the liver play a fundamental role in maintaining liver homeostasis, including the regulation of energy metabolism and the expression of enzymes regulating the absorption and metabolism of xenobiotics.<sup>17</sup> Many experimental animal studies and clinical trials revealed

that significant genes, proteins and enzymes levels in livers are controlled by circadian rhythms to a great extent.<sup>18-20</sup> Also, there is still more evidence to support that the disruption of circadian rhythm is a crucial molecular mechanism in the pathogenesis from organic injury to fibrosis.<sup>21-24</sup> Shift work causes circadian disorganization between workers' activity and the normal rhythm of the liver. Such disorganization might exacerbate liver diseases, including fatty liver, cholestasis, hepatitis, cirrhosis and liver cancer, and these diseases can in turn disrupt the circadian clock system.<sup>17</sup>

Several previous studies have shown that shift work affects the risk of liver disorder. A 5-year retrospective cohort study by Lin et al. evaluated the impact of shift work on liver health and concluded that night shift work hindered the normalization of ALT.<sup>12</sup> In another study, it was found that persistent rotating shift work exposure significantly aggravates the development of abnormal ALT among employees with preexisting sonographic fatty liver.<sup>11</sup> A prospective cohort study by Wang F et al. examined the relationship between night shift work and abnormal ALT showed that compared with day workers, current night shift workers had a higher risk of abnormal ALT (OR: 1.19, 95% CI 1.00-1.42) after adjusting confounding factors. And an increasing trend ( $p=0.031$ ) of abnormal ALT risk was observed in night shift workers without non-alcoholic fatty liver, the prevalence of abnormal ALT increased from 9.7% to 13.3% as the number of night shift work years increased.<sup>13</sup>

In our study, we expected that shift work, which interferes circadian rhythms, would be related to abnormal level of liver enzymes, and the results showed a significant association between shift work and abnormal

ALT among female workers. This result partially supported previous studies which reported the positive association of abnormal ALT.<sup>10,11,13</sup> There was no significant association between shift work and abnormal AST. It may have occurred as a characteristic difference between ALT and AST. ALT is a highly specific marker of liver pathology, restricted to the cytosolic component of the hepatocytes. However, AST is less liver specific, as it is released by damage to the liver, and also to the heart, skeletal muscle, kidney, brain, pancreas, and erythrocytes.<sup>25-26</sup>

In addition, there was no significant association between shift work and abnormal level of liver enzymes among male workers. The reasons for this finding are not clear. The published data on the liver function of shift workers are limited, and no research of gender specific differences between liver functions and shift work was found. However, there are several possible factors for this gender difference. While disturbance of circadian rhythm is the most important factor of abnormal liver enzymes in shift workers, shift work related factors such as insulin resistance<sup>27-31</sup>, sleep disorder<sup>32-33</sup> and poor eating habits<sup>34</sup> can also affect liver disorders indicated by abnormal liver enzymes. In the Swedish study, although insulin resistance was not possible to estimated, it was found that the prevalence of subjects with impaired glucose tolerance was higher among women than men, and the proportion with impaired glucose tolerance among shift working women was significantly higher than among corresponding day working women.<sup>35</sup> Marquie et al. examined the effects shift work experience on sleep, it was found that female shift workers report more sleep problems and more use of hypnotics to fall asleep than male shift

workers.<sup>36</sup> In addition, according to two studies of sleep and insulin resistance, it was reported that short sleep duration or sleep disturbance may lead to the development of insulin resistance in women only, supporting a possible gender difference.<sup>37-38</sup> Lastly, in a study of industrial workers who work day and night shifts in Korea, the eating habits and nutrient intake of the female night workers was the worst.<sup>39</sup> Therefore, another biological factor may play a role in the association between shift work and risk of abnormal liver enzymes in women. Further research is needed to reveal the potential gender difference underlying this association.

This study did not find significant differences between patterns of shift work and abnormal liver enzymes when shift work were divided into 6 groups. Previous studies have reported that the duration and pattern of the shift work appear to have different biological effects on humans.<sup>40-42</sup> However, the pattern of shift work cannot always be categorized clearly, and workers are not permanently engaged in the same pattern of shift work. We could not get precise information on the duration of each pattern, extra work and other possible differences between the shift groups, which could have helped us better interpret the results. This is a limitation of our study and more studies should be conducted between the type of shift work and the risk of liver enzyme abnormalities.

This study has some limitations. First, as the KNHANES is a cross-sectional study, only relation between shift work and abnormal level of liver enzymes could be established, not causal relationships. Second, there was no information about the duration of the shift work, so we could not investigate the dose response relationship with shift work and liver

enzymes. Lastly, we could not get detailed information on the possible differences between shift patterns.

Despite these limitations, the strengths of this study are the use of a nationally representative large scale survey, and data was analyzed after stratification for gender considering multiple variables such as age, smoking status, drinking status, hours of sleep, BMI, physical activity. Additionally, to our knowledge, this is the first study that shows gender differences between abnormal ALT and shift work, though there are previous studies reported that shift work is associated with abnormal level of liver enzymes.<sup>10-12</sup>

## V. Conclusion

There was a relationship between shift work and abnormal ALT in female workers. This study provides limited support for the hypothesis that shift work is related to liver enzyme abnormality, but offers some evidence in favor of the idea that shift work affects female workers more than males on abnormal ALT. Therefore, the results of this study are regarded as preliminary and further studies are needed to define the relationship between shift work and abnormal liver enzymes to be carried out as well as the gender difference in the association.

## References

1. Contreras-Zentella, M. L., Hernández-Muñoz, R. Is liver enzyme release really associated with cell necrosis induced by oxidant stress? *Oxidative Medicine and Cellular Longevity*. 2016.
2. Johansson, L. E., Lindblad, U., Larsson, C. A., Råstam, L., Ridderstråle, M. Polymorphisms in the adiponutrin gene are associated with increased insulin secretion and obesity. *European journal of endocrinology*. 2008;159(5):577-583.
3. Deepa K. Ingawale, Satish K. Mandlik, Suresh R. Naik. Models of hepatotoxicity and the underlying cellular, biochemical and immunological mechanism (s): a critical discussion. *Environmental toxicology and pharmacology*. 2014;37(1): 118-133.
4. Eurofound. Sixth European Working Conditions Survey - Overview Report. In: Publications Office of the European Union Luxembourg; 2016.
5. Alterman T, Luckhaupt SE, Dahlhamer JM, Ward BW, Calvert GM. Prevalence rates of work organization characteristics among workers in the US: data from the 2010 National Health Interview Survey. *Am J Ind Med*. 2013;56(6):647-59.
6. Kim HJ, Moon SH. Report of management for working time and shift work in Korea. Korea: Ministry of Employment and Labor; 2011. p. 19-34. Korean.
7. Moon SH, Lee BJ, Kim SJ, Kim HC. Relationship between thyroid stimulating hormone and night shift work. *Ann Occup Environ Med*. 2016 Oct 6;28:53.

8. Arendt J. Shift work: coping with the biological clock. *Occup Med (Lond)*. 2010;60(1):10-20.
9. Wang X, Armstrong M, Cairns B, Key T, Travis R. Shift work and chronic disease: the epidemiological evidence. *Occup Med*. 2011;61:78-89.
10. Nakamura K, Motohashi Y, Kikuchi S, et al. Liver transferase activity in healthy Japanese employees aged 18-39 years. *Ind Health*. 1998;36:218-22.
11. Lin YC, Chen PC. Persistent rotating shift work exposure is a tough second hit contributing to abnormal liver function among on-site workers having sonographic fatty liver. *Asia Pac J Public Health*. 2015;27:NP1765-74.
12. Lin YC, Hsieh IC, Chen PC. Long-term day-and-night rotating shift work poses a barrier to the normalization of alanine transaminase. *Chronobiol Int*. 2014;31:487-95.
13. Wang F, Zhang L, Wu S, et al. Night shift work and abnormal liver function: is non-alcohol fatty liver a necessary mediator? *Occup Environ Med*. 2019;76:83-89.
14. Ministry of Health and Welfare of Korea. Health examination implementation guidelines(Korean):No.2016-252. [http://www.takehealth.or.kr/bbs/board.php?board=TB\\_rule&load=read&page=1&no=28&md=&sk=&ik=&sa=](http://www.takehealth.or.kr/bbs/board.php?board=TB_rule&load=read&page=1&no=28&md=&sk=&ik=&sa=).
15. U.S. Department of Health and Human Services and U.S. Department of Agriculture. 2015 - 2020 Dietary Guidelines for Americans. 8th Edition. December 2015. Available at <http://health.gov/dietaryguidelines/2015/guidelines/>.

16. M. Hirshkowitz et al. National Sleep Foundation's updated sleep duration recommendations: final report. *Sleep Health*. 2015;1:233-243.
17. Tahara Y, Shibata S. Circadian rhythms of liver physiology and disease: experimental and clinical evidence. *Nat Rev Gastroenterol Hepatol*. 2016 Apr;13(4):217-26.
18. Reddy AB, Karp NA, Maywood ES, Sage EA, Deery M, O'Neill JS, Wong GK, Chesham J, Odell M, Lilley KS, Kyriacou CP, Hastings MH. Circadian orchestration of the hepatic proteome. *Curr Biol*. 2006;16:1107-1115.
19. Davidson AJ, Castanon-Cervantes O, Stephan FK. Daily oscillations in liver function: diurnal vs circadian rhythmicity. *Liver Int*. 2004;24:179-186.
20. Reddy AB, Maywood ES, Karp NA, King VM, Inoue Y, Gonzalez FJ, Lilley KS, Kyriacou CP, Hastings MH. Glucocorticoid signaling synchronizes the liver circadian transcriptome. *Hepatology*. 2007;45:1478-1488.
21. Pekovic-Vaughan V, Gibbs J, Yoshitane H, Yang N, Pathiranaige D, Guo B, Sagami A, Taguchi K, Bechtold D, Loudon A. The circadian clock regulates rhythmic activation of the NRF2/glutathione-mediated antioxidant defense pathway to modulate pulmonary fibrosis. *Genes Dev*. 2014;28:548-560.
22. Touw D, Knox A, Smyth A. Population pharmacokinetics of tobramycin administered thrice daily and once daily in children and adults with cystic fibrosis. *J Cyst Fibros*. 2007;6:327-333.
23. Chen P, Kakan X, Wang S, Dong W, Jia A, Cai C, Zhang J. Deletion

- of clock gene *Per2* exacerbates cholestatic liver injury and fibrosis in mice. *Exp Toxicol Pathol.* 2013;65:427-432.
24. Zhou D, Wang Y., Chen L, Jia L, Yuan J, Sun M, et al. Evolving roles of circadian rhythms in liver homeostasis and pathology. *Oncotarget.* 2016;23:8625-8639.
25. M.C. Kew. Serum aminotransferase concentration as evidence of hepatocellular damage. *Lancet.* 2000;355:591-592.
26. Goessling W, Massaro JM, Vasan RS, D'Agostino RB Sr, Ellison RC, Fox CS. Aminotransferase levels and 20-year risk of metabolic syndrome, diabetes, and cardiovascular disease. *Gastroenterology.* 2008;135:1935-1944.
27. Ghamar-Chehreh ME, Amini M, Khedmat H, et al. Elevated alanine aminotransferase activity is not associated with dyslipidemias, but related to insulin resistance and higher disease grades in non-diabetic non-alcoholic fatty liver disease. *Asian Pac J Trop Biomed.* 2012;2(9):702-706.
28. Méndez-Sánchez N, Arrese M, Zamora-Valde's D, Uribe M. Current concepts in the pathogenesis of nonalcoholic fatty liver disease. *Liver Int.* 2007;27:423-433.
29. Ahima RS. Insulin resistance: cause or consequence of nonalcoholic steatohepatitis? *Gastroenterology.* 2007;132:444-446.
30. Agarwal N, Sharma BC. Insulin resistance and clinical aspects of non-alcoholic steatohepatitis (NASH). *Hepatol Res.* 2005;33:92-96.
31. Nagaya, T., Yoshida, H., Takahashi, H. et al. Markers of insulin resistance in day and shift workers aged 30 - 59 years. *Int Arch Occup*

- Environ Health. 2002;75:562.
32. Hsieh SD, Muto T, Murase T, Tsuji H, Arase Y. Association of short sleep duration with obesity, diabetes, fatty liver and behavioral factors in Japanese men. *Intern Med.* 2011;50(21):2499-502.
  33. Kim CW, Yun KE, Jung HS, Chang Y, Choi ES, Kwon MJ, et al. Sleep duration and quality in relation to non-alcoholic fatty liver disease in middle-aged workers and their spouses. *J Hepatol.* 2016;59:351-357.
  34. Turek, Fred W, Allada, Ravi. Liver has rhythm. *Hepatology.* 2002;35(4):743-745.
  35. Karlsson B, Knutsson A, Lindahl B. Is there an association between shift work and having a metabolic syndrome? Results from a population based study of 27,485 people. *Occup Environ Med.* 2001;58:747-752.
  36. Marquie JC, Foret J. Sleep, age, and shiftwork experience. *J Sleep Res.* 1999;8:297-304.
  37. Liu R, Zee PC, Chervin RD, Arguelles LM, Birne J, Zhang S, et al. Short sleep duration is associated with insulin resistance independent of adiposity in Chinese adult twins. *Sleep Med.* 2011;12:914-919.
  38. Suarez EC. Self-reported symptoms of sleep disturbance and inflammation, coagulation, insulin resistance and psychosocial distress: evidence for gender disparity. *Brain Behav Immun.* 2008;22:960-968.
  39. Park YO, Choi IS, Lee SS, Oh SH. A study of the eating habits and nutrient intake of industrial workers who work day and night shifts. *Korean J Community Nutrition.* 2002;7(5):615-627.
  40. Smith L, Folkard S, Tucker P, Macdonald I. Work shift duration: a review comparing eight hour and 12 hour shift systems. *Occup Environ*

Med. 1998;55:217-229.

41. Tucker P, Smith L, Macdonald I, Folkard S. Effects of direction of rotation in continuous and discontinuous 8 hour shift systems. *Occup Environ Med.* 2000;57:678-684.
42. Kawada T, Otsuka T, Inagaki H, Wakayama Y, Katsumata M, Li Q, Li YJ. A cross-sectional study on the shift work and metabolic syndrome in Japanese male workers. *Aging Male.* 2010;13:174-8.

## 국 문 요 약

한국인 근로자에서 교대근무와 간수치의 관련성 :  
국민건강영양조사 (2007-2015)를 이용한 단면연구

<지도교수 고상백>

연세대학교 대학원 의학과

최 현 경

**배경** : 주간근무와 달리 교대근무는 일주기 리듬에 영향을 미칠 수 있고, 심혈관질환, 당뇨병, 대사증후군 및 유방암과 같은 다양한 건강문제를 일으킬 수 있다. 교대근무의 건강영향에 대한 많은 연구가 이루어졌으나, 교대근무와 간 건강 사이의 관계를 조사한 연구는 많지 않다. 이 연구는 교대근무와 비정상 간수치 사이의 관련성을 평가하고자 하였다.

**대상 및 방법** : 본 연구는 2007 - 2009, 2010 - 2012, 2013 - 2015년 국민건강영양조사 자료를 이용한 단면 조사 연구이다. 직업력, 혈청 내 아스파르테이트 아미노전이효소(AST), 알라닌 아미노전이효소(ALT)수치, 연령, 성별, 흡연상태, 음주상태, 수면시간, 체질량지수, 신체활동 및 과거력 자료를 이용하였다. 그룹 간 일반적 특성은 Chi-square test 및 t-test를 사용하였으며, 교대근무와 비정상 간수치 사이의 관계를 평가하기 위해 Multiple logistic regression을 사용하였다. 통계분석은 연도별 가중치를 적용하여 SPSS version 23을 사용하였다.

**결과** : 연령, 성별, 흡연상태, 음주상태, 수면시간, 체질량지수, 신체활동 및 과거력을 보정한 후 주간근무자에 비해 여성 교대근무자에서 비정상 ALT에 대한 오즈비가 1.31 (95% CI 1.00-1.71)로 유의한 결과를 보였다. 교대 근무 패턴별로 나누어 분석하였을 때 비정상 간수치에 대한 오즈비는 유의한 결과를 보이지 않았다.

**결론** : 본 연구의 결과는 교대근무가 비정상 간수치와 관련이 있다는 가설을 제한적으로 뒷받침하였다. 또한 교대근무가 남성보다 여성 교대근무자에게 비정상 ALT에 영향을 미친다는 결과를 제시하였다. 교대근무와 비정상 간수치와의 관련성과 그 성별에 따른 차이에 대한 추가적인 연구가 필요하다.

---

핵심되는 말: 교대근무, 비정상 간수치, 아스파르테이트 아미노전이효소, 알라닌 아미노전이효소, 국민건강영양조사