Childhood Non-Alcoholic Steatohepatitis and Risk of Complications Develop in Adulthood: Korean National Health Insurance Data 2002 to 2021

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ABSTRACT

Childhood Non-Alcoholic Steatohepatitis and Risk of Complications Develop in Adulthood: Korean National Health Insurance Data 2002 to 2021

Introduction

The prevalence of nonalcoholic fatty liver disease (NAFLD) is increasing worldwide. Several studies show complications of nonalcoholic steatohepatitis (NASH) in children and adult. NAFLD is known to cause many complications, it is very important to identify and manage NAFLD as soon as possible. Failure to manage NAFLD can result in many complications such as diabetes mellitus, hyperlipidemia, hypertension, and cardiovascular disease. Moreover, increased medical costs cause social problems. However, longitudinally observing from children to adults are scarce. The aim of this study was to determine risk of complications occurring in adulthood due to childhood NASH, compared to population without NASH.

Material and Methods

Matched cohort study was conducted among 12,894 children and adolescents aged between 7 and 18 years who were registered with the Korean National Health Insurance Service Data from 2002 to 2021. The analysis of complications was conducted for a minimum of 1 year to a maximum of 10 years, starting from the age of 19 years or more. NASH patients were defined those who had diagnosis code K75.8 once and without the complication disease of interest in age below 19 years old. The control group was defined as non-NASH population without the complication disease of interest until below age of 19. NASH patients and non-NASH population were matched and analyzed by ratio of 1:5. Among 12,894 NASH patients and 921,141 non-NASH patients, we analyzed the frequency of complications occurring from age 19 or older. In addition, we analyzed the medical costs incurred by each group, and in order to more accurately determine the impact of NASH, the identical analysis was conducted on patients who had diagnosis code K75.8 twice or more.

Results

NASH group had a higher hazard ratio (HR) of complications than the non-NASH group when patients become age of 19 or older. Liver fibrosis and cirrhosis had highest HR of 4.76 [95% confidence interval (CI) = 3.57-6.36], hypertensive disease had HR of 2.59 [95% CI = 2.38-2.83], HR of hyperlipidemia was 1.73 [95% CI = 1.64-1.83], and HR of diabetes was 1.98 [95% CI = 1.81-2.16]. In addition, cancer HR was 1.91 [95% CI = 1.71-2.14] and mental disease HR was 1.40 [95% CI = 1.33-1.47]. Through the same analysis, patients with NASH diagnosis more than twice were analyzed, and it was confirmed that HR was higher than the results for patients with one visit. Liver fibrosis and cirrhosis had highest HR of 5.93 [95% CI = 4.16-8.44], hypertensive disease had HR of 3.17 [95% CI = 2.82-3.55], HR of diabetes was 2.59 [95% CI = 2.29-2.93], and HR of cancer was 2.19 [95% CI = 1.89-2.55].

Additionally, regarding cerebrovascular disease, the total medical cost of the NASH group was 40,759,320 Korean Won (KRW), which was higher than the 9,942,578 KRW in the non-NASH group (p<0.0001). The cost incurred due to liver fibrosis disease was confirmed to be 33,112,011 KRW, which is higher than the non-NASH group's 17,367,077 KRW (p<0.0001). In addition, it was confirmed that patients in the NASH group consumed more medical costs than patients in the non-NASH group for other diseases.

Conclusion

Children with NASH, the increased risk of various complications occurs when the patient is over 19 years old than non-NASH population. The risk of complications was higher in the NASH group, and the costs incurred were also higher in the NASH group. When the NASH group was defined as two or more visits, it was confirmed that the risk increased further. In this study, result provides evidence for the need for more active management than when NASH occurs in childhood. The government and society need policies to be aware of the risks of pediatric NASH and to intervene and manage it more actively.

Key words : children, nonalcoholic steatohepatitis, complication, adult, policy

1. INTRODUCTION

Recently, the prevalence of patients with non-alcoholic fatty liver disease (NAFLD) is increasing worldwide.[1] Although NAFLD was thought to be a major disease in adults, the number of children and adolescents with NAFLD is also increasing.[2] Furthermore, according to the Korean National Nutrition Survey, about 8% of pediatric patients are expected to have NAFLD, and up to 34% of obese patients.[3-5] NAFLD encompasses a broad range of liver pathology, from simple fat accumulation in the liver to non-alcoholic steatohepatitis (NASH) and liver cirrhosis.[6, 7] Since NAFLD does not remain asymptomatic, even cirrhosis can occur. Moreover, NAFLD has a close relationship with other metabolic diseases; hence, efforts to identify and manage it are ongoing.[8, 9] NAFLD can cause many complications such as diabetes mellitus, hyperlipidemia, and hypertension; therefore, it is important to identify and manage it as soon as possible.[10, 11, 12] Moreover, NAFLD is known to cause social problems, rather than just personal problems, as medical costs increase.[13, 14] Complications from NAFLD result in high medical costs, causing an inability to lead a proper social life as an adult due to complications that occurred in childhood.[15, 16] If NAFLD occurs at a young age, it becomes difficult to live a normal social life as an adult due to the various complications that accompany it.[17] When NAFLD occurs in women, it can cause polycystic ovary syndrome and affect reproductive health, causing gestational diabetes mellitus during pregnancy, which can lead to problems in the next generation. Additionally, NAFLD continues even after menopause, and the longer a person has NAFLD, the more complications may occur.[18] Men can also suffer from sexual dysfunction and infertility; hence, NAFLD does not self-resolve but also causes problems in the next generation. Therefore, it is better to prevent complications before they occur rather than treat them after; however, this is not easy in many situations.[19]

For example, the intrauterine environment is an important cause of NAFLD. Both small-for-gestational-age and large-for-gestation-age infants have a high probability of developing NAFLD in childhood and adolescense.[20] A child's microbiome and breastfeeding status are also known to affect the development of NAFLD.[21] NAFLD can also occur due to genetic problems and a high intake of fructose or ultra-processed foods.[22] One study found that the number of patients with NAFLD has increased worldwide due to coronavirus disease (COVID)-19 infection.[23] Although COVID-19 infection may have directly affected the liver, it may also have occurred due to the decrease in physical activity from COVID-19.[24] Some studies have shown that the number of patients with

NAFLD increases with increased use of mobile devices, increased intake of westernized diets, and decreased activity levels.[25] Consequently, due to this milieu, the number of children with NAFLD and its accompanying complications is increasing.

NASH is associated with many risks and complications; however, it has received insufficient attention. When patients contract diseases such as diabetes, hypertension, cancer, and mental illness, which are commonly known, most people are afraid and worry about their future. However, when it comes to NASH, most parents say it is because children like to eat food or because they do not like exercise.[26] Furthermore, many parents think liver enzyme levels are a little high, showing a lack of awareness. This is because the diagnosis of NASH has only recently become known; hence, there is insufficient research to strongly counsel parents. Several studies have shown the importance of managing patients with NAFLD and predicting complications; however, most studies distinguish between children and adults. Consequently, longitudinal observational studies of NAFLD from childhood to adulthood are scarce. Moreover, patients with simple steatosis and normal liver enzymes in NAFLD are rarely found using disease codes. Hence, this study aimed to determine the risk of complications occurring in adulthood due to childhood NASH compared with a population without NASH.

2. MATERIALS AND METHODS

2.1. DATA SOURCE

In this study, we used the National Health Insurance Service (NHIS) database of South Korea for analysis. Korean NHIS database consists of information on a unique anonymous identification number for each patient, age, gender, diagnosis code according to the International Classification of Disease (ICD-10), and medical costs. Researchers can request a customized database for academic research purposes. Detailed information about the database can be accessed through the Health Insurance Data Service homepage (http://nhiss.nhis.or.kr).

This study was approved by the institutional review board of Wonju Severance Christian Hospital, Yonsei University Wonju College of Medicine, Wonju, South Korea (approval number: CR322341).

2.2. STUDY POPULATION

We conducted a matched-cohort study using the Korean NHIS database among age under 19 years old between January 1, 2002 and December 31, 2016. Patients with NASH were defined as those with the diagnosis code “K75.8” once and total 53,017 patients were identified. NASH patients who had diagnosis code before age of 7, and born after 2002 or who died before age 19 were excluded. As a result of these criteria, 40,123 cases were excluded and 12,894 cases were finally anaylzed.

The control group was defined as the non-NASH population without NASH diagnostic code until 19 years of age between January 1, 2002 and December 31, 2016. Total 1,060,340 population were selected with age and sex matching with NASH group, and finally 921,141 population were selected by excluding population who had born after 2002 or died before age 19.

The complications were analyzed only from the age of 19 years or more up to 10 years due to possibility of bias. Hence, the analysis was conducted from a minimum of 1 year to a maximum of 10 years, starting from the age of 19 years or more. The cases with complications that developed under the age of 19 years were excluded from both groups, and the final ratio of the NASH to non-NASH group was 1:5. (Table 1)

2.3. OUTCOMES

Each complication was compared only if it occurred at 19 years of age or more. Circulatory system disease was defined as the presence of either: ischemic heart disease (code I20-I25); cerebrovascular disease (I60-I69); disease of arteries, arterioles, and capillaries (I70-I79); or hypertensive disease (I10–I15). Metabolic disease was defined as either diabetes (E11-E14) or hyperlipidemia (E78.0-E78.5). Cancer was defined by the disease codes (C00–C97). Mental and behavioral disorders were defined as those with disease codes (F00–F99). Liver fibrosis and cirrhosis were defined as disease codes (K74). (Figure 1) An identical analysis was performed for the patients who visited the hospital more than twice for additional analysis. Moreover, the total medical costs were analyzed for the amounts incurred from the age of 19 years or more.

2.4. COVARIATES

Covariates included demographic characteristics including age and sex. Data for children were limited, therefore, no additional covariates were used for analysis.

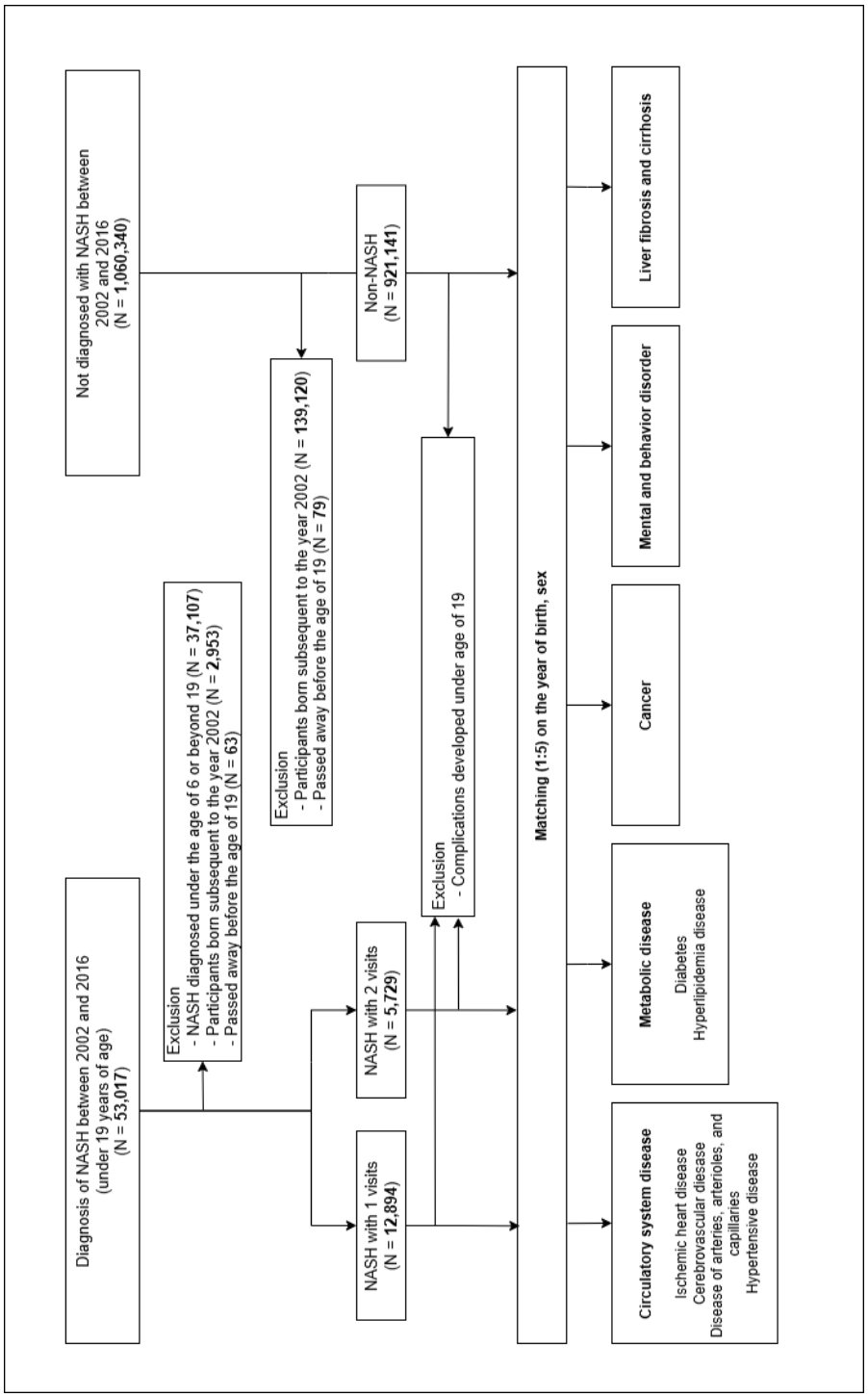


Figure 1. Flow chart of study design. NASH, nonalcoholic steatohepatitis.

2.5. STATISTICAL ANALYSIS

Categorical data were presented as numbers with corresponding percentages and subjected to comparison using either Pearson's chi-squared tests or Fisher's exact tests. For continuous data, represented as mean (standard deviation), we utilized independent t-tests depending on their distribution. Additionally, matching and analysis between NASH patients and a non-NASH population at a ratio of 1:5 based on age and sex was done. During this matching process, individuals with specific disease codes were excluded from the analysis. Cox proportional hazard regression analysis was used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for each variable. All reported p-values were two-sided, and p-values <0.05 were considered statistically significant. SAS system for Windows, version 9.4 (SAS Institute Inc., Cary, NC, USA), and R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria) were used for statistical analyses.

3. RESULTS

3.1. BASIC CHARACTERISTICS OF ENROLLED POPULATION

Table 1. described enrolled NASH and Non-NASH populations. Patients with NASH (with a diagnosis code K75.8 once and without complications of the disease of interest) between the age of 7 and 18 years were assigned to the NASH with 1 visit group (n=12,894) and an age- and sex-matched non-NASH (without NASH or complications of the disease of interest before the age of 19 years) group was selected as the control. Patients with NASH (with a diagnositic code K75.8 twice or more and without complications of the disease of interest) were assigned to the NASH with 2 vistis group (n=5,729).

Table 1. Basic characteristics of enrolled population

Variable	NASH with 1 visit (n = 12,894)	NASH with 2 visits (n = 5,729)	Non-NASH (n = 921,141)
Age at diagnosis of NASH, mean (SD), year	14.7 (2.8)	14.8 (2.7)	
Sex, n (%) of patients			
Male	8,304 (64.4)	3,924 (68.5)	577,341 (62.7)
Female	4,590 (35.6)	1,805 (31.5)	343,800 (37.3)

NASH, nonalcoholic steatohepatitis; SD, standard deviation

3.2. RISK OF CIRCULATORY SYSTEM DISEASE WITH NASH

Table 2. describes the analysis of 11,028 patients diagnosed with NASH and their subsequent risk of developing circulatory system disease at 19 years of age or more. The prevalence of hypertensive disease in patients with NASH was 6.9% (n=791) compared with 2.7% (n=1,506) in the non-NASH group (p<0.0001). The risk of ischemic heart disease was 4.2% (n=466), cerebrovascular disease 2.1% (n=233), and disease of vessels was 5.9% (n=649), which were more common in the NASH group than in the non-NASH group (p<0.0001). The highest medical cost was seen in patients with NASH complicated with cerebrovascular disease, at 40,759,320 KRW, compared with the non-NASH group at 9,942,587 KRW (p<0.0001).

Table 3. shows an identical analysis for patients with two or more visits for NASH diagnosis. The risk of hypertensive disease increased to 9.1% (n=428), and the risk of ischemic heart disease increased to 4.6% (n=214) (p<0.0001). The risks of cerebrovascular disease and diseases of the arteries, arterioles, and capillaries were 2.2% (n=102) and 6.1% (n=287), respectively (p<0.0001).

Table 2. Risk of Circulatory System Disease in NASH patients with one visit

Variable	NASH with one visit		p-value
	NASH (n = 11,028)	Non-NASH (n = 55,140)	
Age at diagnosis of NASH, mean (SD), year	14.7 (2.8)		
Sex, n (%) of patients			1.000
Male	7,068 (64.1)	35,340 (64.1)	
Female	3,960 (35.9)	19,800 (35.9)	
Hypertensive disease, n (%) of patients	761 (6.9)	1,506 (2.7)	<0.0001
Follow-up duration, mean (SD), days	1,265.2 (977.5)	1,428.8 (1052.4)	0.0004
Age at diagnosis, mean (SD), year	21.97 (2.7)	22.39 (2.9)	0.0008
Sex, n (%) of male patients	612 (80.4)	1178 (78.2)	0.2490
Total medical costs, mean (SD), KRW	13,797,332 (22,716,441)	9,578,355 (27,579,082)	<0.0001
Ischemic Heart Disease, n (%) of patients	466 (4.2)	1428 (2.6)	<0.0001
Follow-up duration, mean (SD), days	1,620.7 (1006.9)	1,535.6 (1007.9)	0.7811
Age at diagnosis, mean (SD), year	22.62 (2.7)	22.66 (2.7)	0.7500
Sex, n (%) of male patients	300 (64.4)	868 (60.8)	0.1659
Total medical costs, mean (SD), KRW	13,725,945 (24,500,677)	8,038,169 (10,970,546)	<0.0001
Cerebrovascular disease, n (%) of patients	233 (2.1)	732 (1.3)	<0.0001
Follow-up duration, mean (SD), days	1,543.8 (986.5)	1,585.5 (978.5)	0.8645
Age at diagnosis, mean (SD), year	22.7 (2.7)	22.82 (2.7)	0.5543
Sex, n (%) of male patients	136 (58.4)	456 (62.3)	0.2838
Total medical costs, mean (SD), KRW	40,759,320 (37,507,000)	9,942,578 (15,152,701)	<0.0001
Diseases of arteries, arterioles and capillaries, n (%) of patients	649 (5.9)	2290 (4.2)	<0.0001
Follow-up duration, mean (SD), days	1,429.2 (959.1)	1,556.3 (970.2)	0.0031
Age at diagnosis, mean (SD), year	22.39 (2.6)	22.74 (2.6)	0.0023
Sex, n (%) of male patients	357 (55.0)	1268 (55.4)	0.8694
Total medical costs, mean (SD), KRW	11,778,720 (18,917,795)	6,727,500 (8,617,834)	<0.0001

NASH, nonalcoholic steatohepatitis; SD, standard deviation; KRW, Korean won

Table 3. Risk of Circulatory System Disease in NASH patients with two visits

Variable	NASH with two visits		p-value
	NASH (n = 4,705)	Non-NASH (n = 23,525)	
Age at diagnosis of NASH, mean (SD), year	14.8 (2.7)		
Sex, n (%) of patients			1.000
Male	3,220 (68.4)	16,100 (68.4)	
Female	1,485 (31.6)	7,425 (31.6)	
Hypertensive disease, n (%) of patients	428 (9.1)	654 (2.8)	<0.0001
Follow-up duration, mean (SD), days	1,192.9 (963.6)	1,347.1 (1013.9)	0.0128
Age at diagnosis, mean (SD), year	21.78 (2.6)	22.16 (2.8)	0.0234
Sex, n (%) of male patients	355 (82.9)	534 (81.7)	0.5871
Total medical costs, mean (SD), KRW	14,542,651 (24,468,717)	10,218,807 (38,531,076)	<0.0001
Ischemic Heart Disease, n (%) of patients	214 (4.6)	598 (2.5)	<0.0001
Follow-up duration, mean (SD), days	1,443.5 (977.6)	1,487.5 (964.5)	0.5679
Age at diagnosis, mean (SD), year	22.41 (2.7)	22.54 (2.6)	0.5527
Sex, n (%) of male patients	145 (67.8)	396 (66.2)	0.6825
Total medical costs, mean (SD), KRW	13,820,580 (22,215,402)	8,729,220 (14,196,461)	<0.0001
Cerebrovascular disease, n (%) of patients	102 (2.2)	307 (1.3)	<0.0001
Follow-up duration, mean (SD), days	1,334.5 (921.3)	1,458.4 (896.5)	0.2305
Age at diagnosis, mean (SD), year	22.14 (2.5)	22.48 (2.4)	0.2299
Sex, n (%) of male patients	64 (62.8)	208 (67.8)	0.3532
Total medical costs, mean (SD), KRW	16,823,562 (27,584,884)	8,658,514 (10,046,343)	<0.0001
Diseases of arteries, arterioles and capillaries, n (%) of patients	287 (6.1)	909 (3.9)	<0.0001
Follow-up duration, mean (SD), days	1,330.5 (927.3)	1,453.1 (950.7)	0.0557
Age at diagnosis, mean (SD), year	22.14 (2.5)	22.47 (2.6)	0.0576
Sex, n (%) of male patients	173 (60.3)	551 (60.6)	0.9188
Total medical costs, mean (SD), KRW	13,773,736 (25,286,868)	6,729,701 (7,542,839)	<0.0001

NASH, nonalcoholic steatohepatitis; SD, standard deviation; KRW, Korean won

3.3. RISK OF DIABETES MELLITUS AND HYPERLIPIDEMIA WITH NASH

The risk of diabetes and hyperlipidemia occurring at 19 years of age or more was compared and analyzed in the NASH (n=6,046) and non-NASH (n=30,230) groups (Table 4.). The results showed that diabetes mellitus occurred in 11.4% (n=691) of patients with NASH compared with only 6.0% (n=1, 808) of patients without NASH. Hyperlipidemia was confirmed in 27.6% (n=1,670) of patients in the NASH group, compared with only 17.4% (n=5,258) in the non-NASH group. The highest medical cost was 11,410,962 KRW in patients with NASH complicated by hyperlipidemia, compared with 7,461,632 KRW in the non-NASH group (p<0.0001).

Table 5. shows an identical analysis for patients with diabetes and hyperlipidemia with two or more visits with a NASH diagnosis. The risk of diabetes increased to 14.6% (n=319) and that of hyperlipidemia increased to 31.6% (n=692), which was confirmed to have increased significantly compared with the one-visit cases (p<0.0001). The total medical costs also increased to 12,605,741 KRW for hyperlipidemia in patients with NASH.

Table 4. Risk of Metabolic Disease in NASH patients with one visit

Variable	NASH with one visit		p-value
	NASH (n = 6,046)	Non-NASH (n = 30,230)	
Age at diagnosis of NASH, mean (SD), year	14.6 (2.9)		
Sex, n (%) of patients			1.000
Male	3,810 (63.0)	19,050 (63.0)	
Female	2,236 (37.0)	11,180 (37.0)	
Diabetes, n (%) of patients	691 (11.4)	1,808 (6.0)	<0.0001
Follow-up duration, mean (SD), days	1,544 (1034.8)	1,715.8 (1015.8)	0.0002
Age at diagnosis, mean (SD), year	22.71 (2.8)	23.19 (2.8)	0.0001
Sex, n (%) of male patients	428 (61.9)	1045 (57.8)	0.0598
Total medical costs, mean (SD), KRW	2,309,563 (22,413,106)	8,684,892 (19,615,597)	0.0002
Hyperlipidemia, n (%) of patients	1,670 (27.6)	5,258 (17.4)	<0.0001
Follow-up duration, mean (SD), days	1,396.2 (1006.4)	1,606.7 (1004.2)	<0.0001
Age at diagnosis, mean (SD), year	22.33 (2.7)	22.9 (2.7)	<0.0001
Sex, n (%) of male patients	1,011 (60.5)	2,982 (56.7)	0.0059
Total medical costs, mean (SD), KRW	11,410,962 (22,066,592)	7,461,632 (15,205,626)	<0.0001

NASH, nonalcoholic steatohepatitis; SD, standard deviation; KRW, Korean won

Table 5. Risk of Metabolic Disease in NASH patients with two visits

Variable	NASH with two visits		p-value
	NASH (n = 2,189)	Non-NASH (n = 10,945)	
Age at diagnosis of NASH, mean (SD), year	14.8 (2.8)		
Sex, n (%) of patients			1.000
Male	1,474 (67.3)	7,370 (67.3)	
Female	715 (32.7)	3,575 (32.7)	
Diabetes, n (%) of patients	319 (14.6)	621 (5.7)	<0.0001
Follow-up duration, mean (SD), days	1,449.6 (1,021.5)	1,708 (1,016.6)	0.0002
Age at diagnosis, mean (SD), year	22.46 (2.8)	23.15 (2.8)	0.0003
Sex, n (%) of male patients	216 (67.7)	392 (63.1)	0.1635
Total medical costs, mean (SD), KRW	14,208,286 (29,475,532)	7,720,235 (9,985,801)	0.0002
Hyperlipidemia, n (%) of patients	692 (31.6)	1,848 (16.9)	<0.0001
Follow-up duration, mean (SD), days	1,300.2 (1007.1)	1,584.8 (988.8)	<0.0001
Age at diagnosis, mean (SD), year	22.08 (2.7)	22.83 (2.7)	<0.0001
Sex, n (%) of male patients	456 (65.9)	1109 (60.0)	0.0066
Total medical costs, mean (SD), KRW	12,605,741 (26,876,890)	7,173,631 (11,647,549)	<0.0001

NASH, nonalcoholic steatohepatitis; SD, standard deviation; KRW, Korean won

3.4. RISK OF CANCER WITH NASH

The risk of cancer at 19 years of age or more were compared among the NASH (n=12,354) and non-NASH (n=61,770) groups. In the NASH group, cancer developed in 3.4% (n=418) of patients, whereas in the non-NASH group, it developed in 1.8% (n=1,108). The total medical cost incurred was 21,590,656 KRW in patients with NASH compared with 11,566,836 KRW in the non-NASH population (p<0.0001). (Table 6.)

Table 7. shows an identical analysis of cancer in patients with two or more visits with a NASH diagnosis. Cancer risk increased by 4.1% (n=219). The total medical cost incurred when a patient with NASH developed cancer increased to 24,086,998 KRW compared with 11,097,681 KRW in the non-NASH group (p<0.0001).

Table 6. Risk of Cancer in NASH patients with one visit

Variable	NASH with one visit		p-value
	NASH (n = 12,354)	**Non-NASH (n = 61,770)**	
Age at diagnosis of NASH, mean (SD), year	14.7 (2.8)		
Sex, n (%) of patients			1.000
Male	7,960 (64.4)	39,800 (64.4)	
Female	4,394 (35.6)	21,970 (35.6)	
Cancer, n (%) of patients	418 (3.4)	1,108 (1.8)	<0.0001
Follow-up duration, mean (SD), days	1,430.2 (982.6)	1,663 (1,018.4)	0.0001
Age at diagnosis, mean (SD), year	22.43 (2.7)	23.03 (2.8)	<0.0001
Sex, n (%) of male patients	219 (52.4)	434 (39.2)	<0.0001
Total medical costs, mean (SD), KRW	21,590,656 (45,234,993)	11,566,836 (19,339,188)	<0.0001

NASH, nonalcoholic steatohepatitis; SD, standard deviation; KRW, Korean won

Table 7. Risk of Cancer in NASH patients with two visits

Variable	NASH with two visits		p-value
	NASH (n = 5,374)	Non-NASH (n = 26,870)	
Age at diagnosis of NASH, mean (SD), year	14.8 (2.7)		
Sex, n (%) of patients			1.000
Male	3,681 (68.5)	18,405 (68.5)	
Female	1,693 (31.5)	8,465 (31.5)	
Cancer, n (%) of patients	219 (4.1)	461 (1.7)	<0.0001
Follow-up duration, mean (SD), days	1,352.8 (987.6)	1,623.2 (1,013.9)	0.0011
Age at diagnosis, mean (SD), year	22.22 (2.7)	22.93 (2.7)	0.0016
Sex, n (%) of male patients	131 (59.8)	213 (46.2)	0.0009
Total medical costs, mean (SD), KRW	24,086,998 (50,443,897)	11,097,681 (18,407,168)	0.0003

NASH, nonalcoholic steatohepatitis; SD, standard deviation; KRW, Korean won

3.5. RISK OF MENTAL AND BEHAVIORAL DISORDER WITH NASH

The NASH and non-NASH groups were compared to determine the effect of NASH in children on mental and behavioral disorders when children were 19 years of age or more. Table 8. shows the risk of mental and behavioral disorders in the NASH (n=8,256) and non-NASH (n=41,280) groups. In the NASH group, 23.4% (n=1,934) cases were confirmed to have mental and behavioral disorders, and in the non-NASH group, 17.7% (n=7,298) cases were confirmed. The total medical costs for complications of mental and behavioral disorders were 10,463,902 KRW in patients with NASH compared with 6,312,775 KRW in the non-NASH population (p<0.0001).

Table 9. shows an identical analysis of mental and behavioral disorders in patients with two or more visits with a NASH diagnosis. The risk of mental and behavioral disorders was 22.5% (n=790) in patients with NASH compared with 16.9% (n=2,966) in the non-NASH group (p<0.0001). Furthermore, the total medical costs increased to 12,391,754 KRW for mental and behavioral disorders in patients with NASH compared with 6,285,960 KRW in the non-NASH group (p<0.0001).

Table 8. Risk of Mental and Behavioral Disease in NASH patients with one visit

Variable	NASH with one visit		p-value
	NASH (n = 8,256)	Non-NASH (n = 41,280)	
Age at diagnosis of NASH, mean (SD), year	14.6 (2.8)		
Sex, n (%) of patients			1.000
Male	5,402 (65.4)	27,010 (65.4)	
Female	2,854 (34.6)	14,270 (34.6)	
Mental and Behavioral Disorders, n (%) of patients	1,934 (23.4)	7,298 (17.7)	<0.0001
Follow-up duration, mean (SD), days	1,298.5 (935.3)	1,354.6 (943.9)	0.0199
Age at diagnosis, mean (SD), year	22.06 (2.5)	22.21 (2.6)	0.0239
Sex, n (%) of male patients	1,099 (56.8)	4,129 (56.6)	0.8448
Total medical costs, mean (SD), KRW	10,463,902 (20,426,649)	6,312,775 (10,654,797)	<0.0001

NASH, nonalcoholic steatohepatitis; SD, standard deviation; KRW, Korean won

Table 9. Risk of Mental and Behavioral Disease in NASH patients with two visits

Variable	NASH with 2 visits		p-value
	NASH (n = 3,505)	**Non-NASH (n = 17,525)**	
Age at diagnosis of NASH, mean (SD), year	14.7 (2.7)		
Sex, n (%) of patients			1.000
Male	2,462 (70.2)	12,310 (70.2)	
Female	1,043 (29.8)	5,215 (29.8)	
Mental and Behavioral Disorders, n (%) of patients	790 (22.5)	2,966 (16.9)	<0.0001
Follow-up duration, mean (SD), days	1,213.7 (909.4)	1,307.9 (933.3)	0.0113
Age at diagnosis, mean (SD), year	21.83 (2.5)	22.09 (2.6)	0.0132
Sex, n (%) of male patients	492 (62.3)	1,846 (62.2)	0.9836
Total medical costs, mean (SD), KRW	12,391,754 (23,972,131)	6,285,960 (11,678,392)	<0.0001

NASH, nonalcoholic steatohepatitis; SD, standard deviation; KRW, Korean won

3.7. RISK OF LIVER FIBROSIS AND CIRRHOSIS WITH NASH

The risk of liver fibrosis and cirrhosis occurring at 19 years of age or more was compared and analyzed in the NASH (n=12,780) and non-NASH (n=63,900) groups (Table 10). In the NASH group, 0.7% were confirmed to have liver disease, whereas in the non-NASH group, 0.15% were confirmed to have liver disease. The total medical costs for the complications of liver fibrosis and cirrhosis were 33,112,011 KRW in patients with NASH and 17,367,077 KRW in the non-NASH population.

Table 11. shows an identical analysis for liver fibrosis and cirrhosis in patients with two or more visits with a diagnosis of NASH. The risk of liver fibrosis and cirrhosis was 1.12%. Furthermore, the total medical costs increased to 40,435,828 KRW for liver fibrosis and cirrhosis in patients with NASH compared with 15,267,357 KRW in those without (p<0.0001).

Table 10. Risk of liver fibrosis and cirrhosis in NASH patients with one visit

Variable	NASH with one visit		p-value
	NASH (n = 12,780)	**Non-NASH (n = 63,900)**	
Age at diagnosis of NASH, mean (SD), year	14.7 (2.8)		
Sex, n (%) of patients			1.000
Male	8,222 (64.3)	41,110 (64.3)	
Female	4,558 (35.7)	22,790 (35.7)	
Liver fibrosis and cirrhosis, n (%) of patients	90 (0.7)	95 (0.2)	<0.0001
Follow-up duration, mean (SD), days	1,414.9 (1012.4)	1,489.7 (1029.3)	0.6191
Age at diagnosis, mean (SD), year	22.36 (2.7)	22.53 (2.8)	0.6759
Sex, n (%) of male patients	63 (70.0)	59 (62.1)	0.2574
Total medical costs, mean (SD), KRW	33,112,011 (67,614,469)	17,367,077 (37,136,771)	0.0496

NASH, nonalcoholic steatohepatitis; SD, standard deviation; KRW, Korean won

Table 11. Risk of liver fibrosis and cirrhosis in NASH patients with two visits

Variable	NASH with 2 visits		p-value
	NASH (n = 5,646)	**Non-NASH (n = 28,230)**	
Age at diagnosis of NASH, mean (SD), year	14.7 (2.7)		
Sex, n (%) of patients			1.000
Male	3,867 (68.5)	19,335 (68.5)	
Female	1,779 (31.5)	8,895 (31.5)	
Liver fibrosis and cirrhosis, n (%) of patients	63 (1.1)	44 (0.2)	<0.0001
Follow-up duration, mean (SD), days	1,262.3 (932.3)	1525.6 (1078.6)	0.1808
Age at diagnosis, mean (SD), year	21.94 (2.5)	226136 (3.0)	0.2083
Sex, n (%) of male patients	43 (68.3)	27 (61.4)	0.4609
Total medical costs, mean (SD), KRW	40,435,828 (78,294,179)	15,267,357 (32,329,556)	0.0246

NASH, nonalcoholic steatohepatitis; SD, standard deviation; KRW, Korean won

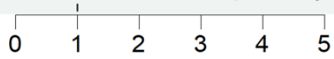
3.7. RISK OF VARIOUS COMPLICATIONS WITH NASH

Figure 2. shows the HRs for each disease in the NASH and non-NASH groups at 19 years of age or more. For all complications, the NASH group had a higher HR than the non-NASH group. Liver fibrosis and cirrhosis had the highest HR of 4.76 (95% CI: 3.57-6.36), hypertensive disease had a HR of 2.59 (95% CI: 2.38-2.83), hyperlipidemia had a HR of 1.73 (95% CI: 1.64-1.83), diabetes had a HR of 1.98 (95% CI: 1.81-2.16), cancer had a HR of 1.91 (95% CI: 1.71-2.14), and mental and behavioral disease had a HR of 1.40 (95% CI: 1.33-1.47).

Furthermore, we found that the HR for all complications was higher in patients who visited twice rather than once with the diagnosis of NASH, with a HR of 5.93 (95% CI: 4.16-8.44) for liver fibrosis and cirrhosis, 3.17 (95% CI: 2.82-3.55) for hypertensive disease, 1.98 (95% CI: 1.83-2.15) for hyperlipidemia, 2.59 (95% CI: 2.29-2.93) for diabetes, and 2.19 (95% CI: 1.89-2.55) for cancer. Figure 3. shows that the NASH with one-visit group has a higher risk of complications than the non-NASH group over the age of 19 years. Moreover, Figure 4. shows that the difference between the two groups was steeper than that shown in Figure 3. (p<0.0001).

A

Clinical events	Non-NASH	NASH	HR (95% CI)
Hypertensive disease	1506 / 55140	761 / 11028	2.59 (2.38 to 2.83)
Ischemic Heart Disease	1428 / 55140	466 / 11028	1.65 (1.49 to 1.83)
Cerebrovascular disease	732 / 55140	233 / 11028	1.60 (1.38 to 1.86)
Diseases of arteries, arterioles and capillaries	2290 / 55140	649 / 11028	1.44 (1.32 to 1.57)
Diabetes	1808 / 30230	691 / 6046	1.98 (1.81 to 2.16)
Hyperlipidemia	5258 / 30230	1670 / 6046	1.73 (1.64 to 1.83)
Cancer	1108 / 61770	418 / 12354	1.91 (1.71 to 2.14)
Mental and Behavioural disorders	7298 / 41280	1934 / 8256	1.40 (1.33 to 1.47)
liver fibrosis	95 / 63900	90 / 12780	4.76 (3.57 to 6.36)



B

Clinical events	Non-NASH	NASH	HR (95% CI)
Hypertensive disease	654 / 23525	428 / 4705	3.17 (2.82 to 3.55)
Ischemic Heart Disease	598 / 23525	214 / 4705	1.80 (1.55 to 2.09)
Cerebrovascular disease	307 / 23525	102 / 4705	1.66 (1.34 to 2.05)
Diseases of arteries, arterioles and capillaries	909 / 23525	287 / 4705	1.63 (1.44 to 1.85)
Diabetes	621 / 10945	319 / 2189	2.59 (2.29 to 2.93)
Hyperlipidemia	1848 / 10945	692 / 2189	1.98 (1.83 to 2.15)
Cancer	461 / 26870	219 / 5374	2.19 (1.89 to 2.55)
Mental and Behavioural disorders	2966 / 17525	790 / 3505	1.40 (1.30 to 1.51)
liver fibrosis	44 / 28230	63 / 5646	5.93 (4.16 to 8.44)

Figure 2. Hazard ratio of complications in NASH and non-NASH population after 19 years old. A. NASH with one visit, B. NASH with two visits. NASH, nonalcoholic steatohepatitis; CI, confidencial interval

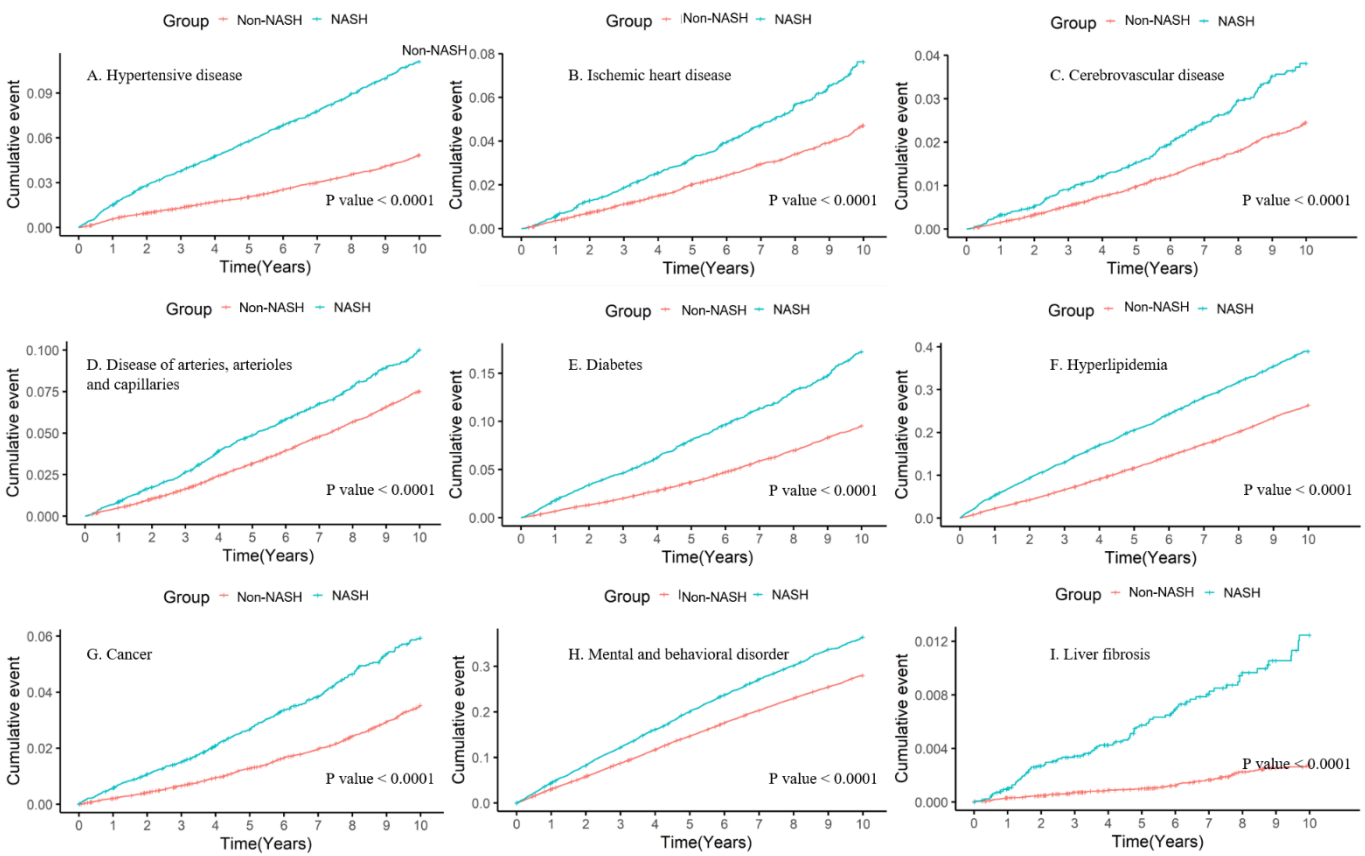


Figure 3. Kaplan–Meier curves for developing complications of NASH with one visit and non-NASH population age of 19 or older. A. hypertensive disease; B. ischemic heart disease; C. cerebrovascular disease; D. diseases of arteries, arterioles and capillaries; E. diabetes; F. hyperlipidemia; G. cancer; H. mental and behavior disorder; I. liver fibrosis and cirrhosis

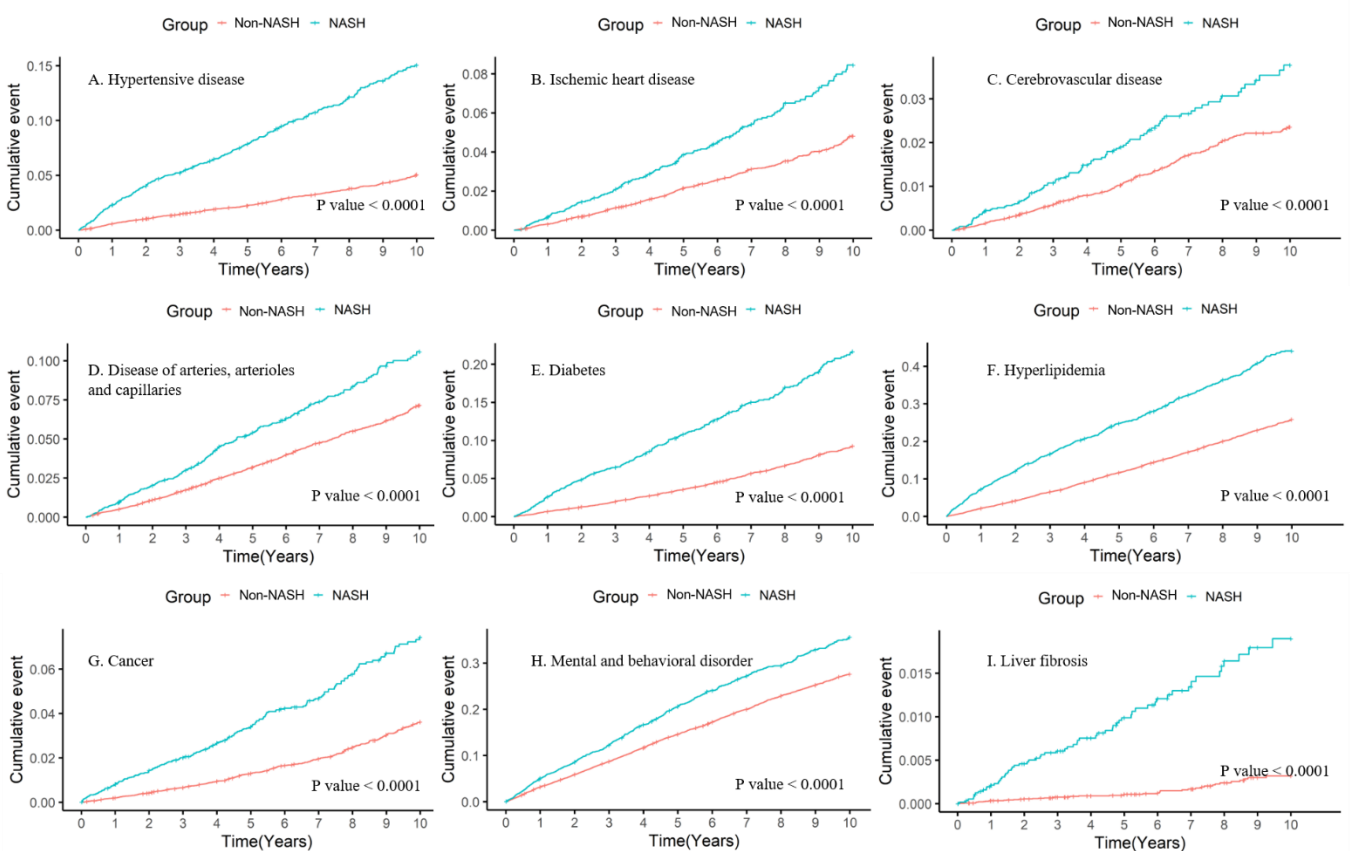


Figure 4. Kaplan–Meier curves for developing complications of NASH with two visits and non-NASH population age of 19 or older. A. hypertensive disease; B. ischemic heart disease; C. cerebrovascular disease; D. diseases of arteries, arterioles and capillaries; E. diabetes; F. hyperlipidemia; G. cancer; H. mental and behavior disorder; I. liver fibrosis and cirrhosis

4. DISCUSSION

As various factors such as the environment and food intake have changed over the years, the number of patients with NASH has also increased, resulting in an increase in NASH complications requiring management[27] With time, an increasing number of children are being diagnosed with NASH, consequently resulting in an increase in the incidence of complications. Zhang et al. found that the incidence of NAFLD and NASH among children, adolescents, and young adults has increased to 29.49 million globally.[2] A similar NAFLD prevalence was reported among Korean children and adolescents between 2010 and 2015.[3]

Cardiovascular disease, type 2 diabetes mellitus, sleep disorders, and osteoporosis have been suggested as complications arising in children with NAFLD.[28, 29] Teng et al. reported that the global prevalence of adult NAFLD is 32%.[30] The resulting complications include chronic kidney disease, cancer, psychological dysfunction, gastroesophageal reflux, and obstructive sleep apnea syndrome.[31]

Simon et al. reported that biopsy-proven NAFLD in 718 children and young adults was associated with increased long-term mortality compared with healthy controls, with an HR of 5.88.[32] Similarly, in the present study, we found an increased HR of cancer and cardiovascular disease when NASH occurred at a young age.

Several studies have described the longitudinal disease course in children.[33] Hassan et al. reviewed 18 children with NAFLD for 2.3 years, and Kuntz et al. showed the disease course of 58 children for 1.8 years.[34, 35] However, despite this high and increasing prevalence and its dangerous complications, there have been no large-scale studies describing the disease course of childhood NASH in adults.

Although this study did not attempt to determine the exact incidence, the number of children and adolescents diagnosed with NASH is increasing. These patients have not only increased in number, but also developed various complications in over the age of 19 years. In this study, we found that NASH in childhood has a HR of 2.59 for hypertension, and an HR of 1.98 for diabetes mellitus. Moreover, we also found that cancer and mental and behavioral disease have high HRs of 1.91 and 1.40, respectively. Although the number of patients was small, those diagnosed with liver fibrosis or cirrhosis had a high HR of 4.76. Additional analysis by defining patients with NASH as those

with two NASH disease codes showed that the HR for hypertension increased to 3.17, for diabetes mellitus to 2.59, for cancer to 2.19, and for liver fibrosis and cirrhosis to 5.93.

Multiple NASH disease codes could mean that the NASH diagnosis was more certain or that patients visited the hospital due to a lack of NASH control. Depending on the doctor's treatment style, some cases may be diagnosed after only one visit; however, in most cases, patients require two or more visits and are treated until NASH improves. Considering this situation, our results showed that patients with definite childhood NASH are at a high risk of complications over the age of 19 years. In addition, not only complications, but also medical costs incurred due to NASH are higher than those in patients without NASH. Moreover, for patients who visited more than twice, medical expenses nearly doubled compared with the results listed in the table. In some cases, such as those in this study, patients may have NASH without complications until adulthood. However, we found that even in such cases, many complications may occur when the patient becomes an adult. Therefore, patients and caregivers should actively manage NASH even if patients do not have other complications at a young age. We found that NASH not only results in more disease complications in patients, but also increases medical costs, increasing the burden on patients and the government.

This study has a few limitations. First, the patients were identified using NASH diagnostic codes, and the correct number of patients could not be predicted. In the International Classification of Diseases 10th Revision, “K75.8” is classified as another specified inflammatory liver disease and NASH; hence, there is a possibility that other diagnoses such as hepatitis may be used instead of NASH. Moreover, in some cases the diagnosis is included owing to insurance issues; therefore, caution may be needed while interpreting the results. Additionally, there may have been an underestimation of disease incidence because of poor evaluation, which could have led to more severe complications than currently predicted. Second, because the HR for complications increases more when the NASH diagnosis code is set at two visits compared with one, the HR may be higher if there are more visits. Consequently, the HR may be even higher than currently presented; hence, the HR may have been underestimated. Third, there is no guarantee that the biopsy was proven directly in the patient, and because NASH was confirmed and complications were identified based only on the diagnosis, the risk mentioned may not be accurate. Fourth, the number of patients with liver fibrosis and cirrhosis was small. This may have occurred because, rather than filling in the diagnosis code for fibrosis and cirrhosis, additional complications were often included due to insurance issues. Fifth, diabetes and hypertension are diseases that can be more easily diagnosed if

patients visit hospitals frequently. Therefore, the HR may be higher than that of ischemic heart disease or cerebrovascular disease. However, despite these limitations, this is highly valuable study because, to the best of our knowledge, this is first study to longitudinally observe children with NASH using large-scale data to determine the complications and medical costs that occur in adulthood.

5. CONCLUSION

In children with NASH, the risk of developing various complications is higher when they turn 19 years of age or older, compared with the non-NASH population. This suggests the need for more active management of NASH in children. Hence, the government and society may need to implement policies to increase awareness of the risks of childhood NASH and to intervene and manage it more actively.

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Abstract in Korean

소아 비알코올지방간염 및 성인기에 발병하는 합병증 위험: 국민건강보험공단 데이터 2002-2021

아이들을 건강하게 자라게 도와서 성인이 되었을 때 건강하게 지낼 수 있게 하는 것은 매우 중요하다. 최근 전 세계적으로 비알코올지방간염 환자의 유병률이 증가하고 있다. 여러 연구에서 단편적으로 소아의 비알코올지방간염의 합병증을 일으키는 것으로 보고되었다. 가능한 한 빨리 비알코올지방간염을 확인하고 관리하는 것이 매우 중요합니다. 하지만 아직 비알코올지방간염을 소아부터 성인까지 종단적으로 관찰한 경우는 없는 실정이다. 이에 본 연구에서는 소아에서 발생한 비알코올지방간염 환자와 비알코올지방간염이 없는 소아 인구와 비교하여 성인에서 발생할 수 있는 합병증의 위험을 확인하였다.

2002년부터 2021년까지 국민건강보험공단 자료에 등록된 7세부터 18세의 12,894명의 소아청소년 환자를 대상으로 연구를 실시하였다. 질환군은 K75.8의 진단 코드를 1회라도 입력된 환자로 정의하였으며 대조군은 성인이 될 때까지 비알코올지방간염이 없는 그룹으로 모집단을 정의하였다. 대조군은 총 921,141명이 선정 되었으며 질환군과 대조군을 1:5 비율로 매칭하여 성인이 되었을 때 발생하는 합병증을 분석하였다.

비알코올지방간염 그룹은 환자가 19세 이상일 때 질환이 없는 그룹에 비해 여러 합병증이 발생할 위험비가 높았다. 고혈압질환이 2.59 [95% 신뢰구간 = 2.38-2.83]로 확인되었고 고지혈증은 1.73 [95% 신뢰구간 = 1.64-1.83], 당뇨병은 1.98[95% 신뢰구간=1.81-2.16]로 나타났다. 또한 암은 1.91 [95% 신뢰구간=1.71-2.14], 정신질환은 1.40 [95% 신뢰구간=1.33-1.47]으로 나타났으며 간섬유화와 간경변증의 경우는 4.76 [95% 신뢰구간=3.57-6.36]으로 확인되었다. 동일한 분석을 통해 비알코올지방간염 진단명이 2회 이상 기입된 환자를

분석한 결과 1회 기입된 환자보다 합병증의 위험도가 높은 것을 확인하였다.

뇌혈관질환의 경우 비알코올지방간염 그룹의 의료비용은 40,759,320원으로 대조군 그룹의 비용 9,942,578원보다 높았다(p<0.0001). 간섬유화와 간경변증으로 인한 의료비용은 33,112,011원으로 대조군 그룹의 17,367,077원보다 높았다(p<0.0001). 그 외의 다른 합병증에서도 비알코올지방간염 그룹이 대조군 그룹보다 의료비를 더 지출하는 것으로 확인됐다.

비알코올지방간염을 앓고 있는 환자는 그렇지 않은 환자보다 성인이 되었을 때 많은 합병증이 발생할 위험비가 높은 것을 확인하였다. 합병증 발생 위험이 비알코올지방간염 그룹에서 높았고, 발생한 의료 비용도 비알코올지방간염 그룹에서 높았다. 비알코올지방간염으로 2회 이상 방문할 경우 위험도는 더욱 높아지는 것으로 확인됐다. 이는 소아기에 발생한 비알코올지방간염이 보다 적극적인 관리가 필요하다는 증거를 제공한다. 정부와 사회는 소아 비알코올지방간염의 위험성을 인지하고 보다 적극적으로 개입하고 관리하기 위한 정책이 필요하다.

핵심되는 말: 소아, 비알코올지방간염, 합병증, 성인, 정책