研究成果の刊行に関する一覧表

書籍

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CHAPTER

20

Impact of Sex and Lifestyle of Adolescents and Their Parents on Obesity

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INTRODUCTION

The prevalence of overweight or obese children has increased since the late twentieth century in most industrialized countries [1]. This prevalence doubled or trebled between the early 1970s and late 1990s in Australia, Brazil, Canada, Chile, Finland, France, Greece, Japan, the UK, and the USA [2]. However, recent data have shown that this increase in childhood obesity might be declining [1].

Cross-sectional analysis has shown that the prevalence of obesity has gradually decreased since the early 2000s, with the highest prevalence in the late 1990s to early 2000s in Japan [3]. Longitudinal studies have shown that the critical periods for developing obesity are in late infancy (between 5 and 6 years of age) and during the high school period in boys, and is mainly in late infancy in girls [3]. Another issue to be solved in Japan is the rapid increase in severe obesity in senior high school adolescents [4].

The development of cardiovascular disease (CVD) risk factors, including obesity, is associated with adverse behavioral patterns, such as decreased physical activity [5,6,8,9]; increased sedentary lifestyle, in particular television watching [5–10]; and unhealthy dietary habits [5,6,9]. Parental obesity is also strongly associated with CVD risk factors in children and adolescents [5,6,9].

Therefore, the present chapter aims to evaluate the effect of lifestyles of adolescents and their parents on the levels of CVD risk factors in adolescents based on data obtained from adolescent volunteers.

METHODS

Subjects

Two studies have been conducted in Japan. The first study was conducted from 2006 to 2008 and was announced through the local boards of education in three areas: Toyama, Chiba, and Kagoshima prefectures. The background of the first study has been described in detail elsewhere [9]. The study included 1358 healthy adolescent volunteers (587 males and 771 females), comprising senior high school students aged 15 to 18 years. All of the subjects gave written informed consent. The study consisted of a medical examination and a questionnaire. Volunteers were asked to complete the questionnaires before their medical examination. The questionnaire collected data on the lifestyles of both the subjects and their parents. Of the 1358 subjects, 54 participated in the study twice, and only data from the first visit were used. Of the remaining 1304 subjects, 549 did not complete the questionnaire and were excluded. Therefore, a total of 755 volunteers were included in the study (331 males and

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424 females). Subjects of both sexes included in the study had lower mean levels of several CVD risk factors than those who were excluded (data not shown), suggesting that adolescent volunteers with more healthy lifestyles were more likely to completely answer the questionnaire. We obtained permission from the ethics committee of the National Hospital Organization Kagoshima Medical Center to use and analyze the data under the condition that the confidentiality would be maintained for all subjects.

The second study was conducted from 2012 onwards. The subjects in this study were children and adolescents in kindergartens, elementary schools, and junior high schools in Japan. This ongoing study was conducted in Kagoshima, Toyama, Fukuoka, and Aichi areas, and a total of 954 children and adolescents participated during 2012. Of these, 200 adolescents aged 12–15 years in junior high schools were the final subjects of the study. All subjects in the second study also gave written informed consent. The second study was done using the same methods as the first study. Volunteers were asked to complete questionnaires before their medical examination. All subjects in the second study completed the questionnaires.

Physical and Blood Biochemistry Parameters

Height was measured to the nearest 0.1 cm and weight was measured to the nearest 0.1 kg. Body mass index (BMI) was calculated as (weight in kg)/(height in m)^2. Blood pressure was measured three times using a TM-2571 automated oscillatory system (A&D Co. Ltd, Tokyo, Japan) after subjects had rested for 10 min in a seated position, and the mean value of the second and third measurements was used. Waist circumference was measured at the umbilical level to the nearest 0.1 cm.

Blood samples were collected the morning after an overnight fast. Levels of high-density lipoprotein (HDL) cholesterol were determined using a direct quantitative assay. Triglyceride and fasting plasma glucose (FPG) levels were measured using enzymatic assays and analyzed using a JCA-BM9030 automated analyzer (JEOL Ltd, Tokyo, Japan). Insulin levels were measured using a chemiluminescence immunologic assay and an automated Lumipulse PrestoII analyzer (Fujirebio Inc., Tokyo, Japan). All assays were performed by SRL Inc, Tokyo, Japan). The homeostasis model assessment of insulin resistance (HOMA-IR) was used as a surrogate marker for insulin resistance [11], and calculated as fasting insulin (in μU/mL) × fasting glucose (in mg/dL)/405.

Levels of adiponectin, leptin, and high-sensitivity C-reactive protein (hs-CRP) were measured at the same laboratory (SRL Inc). These adipocytokines and/or inflammatory markers are hereafter collectively referred to as biomarkers. Adiponectin was measured using the Human Adiponectin ELISA kit (Otsuka Pharmaceutical Inc, Tokyo, Japan), leptin measurement was done using the Human Leptin RIA KIT (Linco Research Inc, St. Charles, MO, USA), and hs-CRP was measured using the N-Latex CRP II (Dade Behring Inc, Marburg, Germany).

Definition of Cardiovascular Disease Risk Factors, Metabolic Syndrome, and Obesity

Abdominal obesity, hypertension, elevated triglyceride levels, decreased HDL cholesterol levels, and hyperglycemia were used as CVD risk factors in the present study. The definition of CVD risk factors was based on that of the International Diabetes Federation for the ages of 10–16 years as follows [12]: triglycerides, ≥150 mg/dL; HDL cholesterol, <40 mg/dL; blood pressure, ≥130 mmHg systolic or ≥85 mmHg diastolic; and FPG, ≥100 mg/dL. Preliminary 90th percentile values in male and female junior high school adolescents for waist circumference were ≥80 cm and ≥75 cm, respectively, based on data from the participants of the present study. The definition of CVD risk factors for ages >16 years was based on that for adults as follows [13]: triglycerides, ≥150 mg/dL; HDL cholesterol, <40 mg/dL in males and <50 mg/dL in females; blood pressure, ≥130 mmHg systolic or ≥85 mmHg diastolic; and FPG, ≥100 mg/dL. Preliminary 90th percentile values in male and female high school adolescents for waist circumference were ≥80 cm based on data from the participants of the present study. The definition of metabolic syndrome was based on that of the International Diabetes Federation [12,13].

The Examination Committee of Criteria for Obesity Disease in Japan recommended a BMI ≥25 kg/m^2 as the definition of obesity in the adult Japanese population [14]. Therefore, adolescent obesity in the present study was defined using the age- and sex-specific International Obesity Task Force standard corresponding to a BMI cut-off of 25 kg/m^2 at the age of 18 years [15].

Assessment of the Lifestyles of Adolescents and Their Parents

Self-reported lifestyle parameters for all subjects included regular times of going to bed and waking up; participation in school-based extracurricular (EC) physical activities; time spent in exercise, including walking, jogging, cycling, and EC physical activities on weekdays and holidays; time spent watching a screen, including watching television, non-school-related computer use, and games on weekdays and holidays; and score for eating breakfast (1, seldom; 2, occasional; 3, regular). Age, height, weight, and the following lifestyle information for both parents were also recorded: regular times for going to bed and waking up; time spent taking exercise,

TABLE 20.1 Characteristics of Adolescents[a,b]

Characteristic	Junior High School Adolescents			Senior High School Adolescents		
	Males	Females	*P* value	Males	Females	*P* value
Number	99	101	–	337	442	–
Age (years)	14.0 (0.9)	14.0 (1.0)	0.88	16.5 (0.8)***	16.7 (0.9)***	0.01
Height (cm)	162.5 (8.4)	155.7 (5.5)	<0.001	170.5 (6.1)***	158.3 (5.3)***	<0.001
Weight (kg)	50·9 (10.7)	47.4 (6.7)	0.006	60.8 (10.3)***	51.1 (6.5)***	<0.001
Body mass index (kg/m^2)	19.1 (2.8)	19.5 (2.4)	0.32	20.9 (3.1)***	20.4 (2.3)***	0.01
Waist circumference (cm)	68.0 (8.1)	68.1 (6.5)	0.89	72.3 (8.2)***	71.2 (5.9)***	0.03
Systolic BP (mmHg)	106 (9)	100 (9)	<0.001	116 (10)***	106 (10)***	<0.001
Diastolic BP (mmHg)	58 (8)	56 (7)	0.02	63 (9)***	62 (9)***	0.02
Total cholesterol (mg/dL)	161 (23)	170 (30)	0.03	161 (28)	174 (27)	<0.001
LDL cholesterol (mg/dL)	89 (20)	97 (26)	0.02	89 (24)	96 (23)	<0.001
HDL cholesterol (mg/dL)	61 (12)	61 (11)	0.95	59 (12)	65 (13)***	<0.001
Triglycerides (mg/dL)	54 (39, 79)	63 (46, 84)	0.13	53 (41, 74)	52 (39, 69)***	0.23
FPG (mg/dL)	87 (6)	85 (5)	0.004	88 (7)	86 (6)	<0.001
Insulin (μU/mL)	7.2 (5.3, 10.7)	87 (5.7, 11.2)	0.07	6.4 (4.3, 9.1)*	7.0 (5.1, 9.5)**	0.07
HOMA-IR	1.6 (1.1, 2.3)	1.8 (1.2, 2.5)	0.16	1.4 (0.9, 2.0)	1.5 (1.1, 2.1)**	0.26
No of CV risks	0.2 (0.4)	0.2 (0.4)	0.65	0.7 (0.9)**	0.6 (0.8)	0.11
Adiponectin (μg/mL)	10.0 (4.1)	9.9 (4.6)	0.89	10.5 (4.0)	12.0 (4.6)***	<0.001
Leptin (ng/mL)	2.3 (1.8, 4.3)	7.9 (5.7, 12.8)	<0.001	1.1 (0.8, 2.2)***	6.2 (4.2, 8.6)***	<0.001
Hs-CRP (ng/mL)	82 (52, 177)	69 (25, 147)	0.053	111 (152, 268)*	58 (50, 137)*	<0.001
Birth weight (g)	3036 (533)	3014 (401)	0.74	3154 (425)*	3053 (407)	<0.001
Breast feeding (mo)	10.3 (4.3)	8.3 (4.9)	–	7.3 (5.5)***	7.8 (5.2)	0.29
Lifestyle factor						
EC activities (%)	73	47	<0.001	62	35	<0.001
Exercise (w, m)	90 (58, 120)	60 (30, 120)	0.16	120 (35, 150)	40 (10, 120)	<0.001
Exercise (h, m)	120 (30, 218)	60 (0, 180)	0.006	120 (30, 210)	30 (0, 120)	<0.001
Exercise (av, m)	90 (51, 150)	73 (25, 137)	0.04	120 (39, 167)	40 (13, 129)	<0.001
Screen (w, m)	90 (60, 150)	90 (60, 120)	0.46	120 (60, 180)	90 (60, 150)	0.70
Screen (h, m)	180 (120, 278)	180 (120, 240)	0.48	180 (120, 240)	180 (120, 240)	0.10
Screen (av, m)	118 (77, 177)	120 (77, 171)	0.92	120 (77, 184)	120 (69, 180)	0.21
Regular breakfast (%)	96%	93%	0.54	96%	92%	0.05

[a]*Data are expressed as the mean (standard deviation).* [b]*Statistical analysis was performed for each sex between junior and high school adolescents; significance levels are shown as:* $^*P<0.05$. $^{**}P<0.01$. $^{***}P<0.001$.

Variables with highly skewed distribution (triglycerides, insulin, HOMA-IR, leptin, high-sensitive CRP, exercise time, and screen time) are expressed as the mean (95% confidence interval).BP, blood pressure; CVD, cardiovascular; EC activities, extracurricular physical activities; exercise, exercise time; FPG, fasting plasma glucose; HOMA-IR, homeostasis assessment of insulin resistance; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; screen, screen time; (w, m), (weekday, minutes); (h, m), (holiday, minutes); (av, m), (average value per day, minutes).

TABLE 20.2 Characteristics of Parents[a]

Characteristics	Junior High School Adolescents		Senior High School Adolescents	
	Males	Females	Males	Females
Characteristics and lifestyle of fathers				
Age (years)	44.1 (5.4)	45.3 (6.7)	47.5 (4.6)	48.1 (5.2)
Body mass index (kg/m^2)	24.0 (3.4)	23.8 (3.2)	23.7 (3.2)	23.5 (2.6)
Exercise (av, m)	14 (0, 43)	17 (0, 51)	10 (0, 39)	17 (0, 43)
Screen (av, m)	150 (93, 197)	150 (77, 214)	129 (77, 180)	137 (94, 206)
Having a regular breakfast (%)	76	69	80	81
Smoking rate (%)	39	40	42	42
Characteristics and lifestyle of mothers				
Age (years)	44.1 (5.4)	43.5 (5.2)	44.8 (3.7)	45.4 (4.1)
Body mass index (kg/m^2)	24.0 (3.4)	22.3 (4.2)	21.7 (2.8)	21.7 (3.0)
Exercise (av, m)	0 (0, 21)	0 (0, 21)	9 (0, 30)*	15 (0, 30)[b]
Screen (av, m)	124 (75, 180)	120 (60, 184)	120 (77, 180)	137 (77, 194)
Having a regular breakfast (%)	90	89	89	89
Smoking rate (%)	6	8	11	8

[a]*Data are expressed as the mean (standard deviation).* [b]*Mothers of male and female senior high school adolescents had a longer exercise time than those of junior high school adolescents.*

Highly skewed variables in distribution (exercise time and television-watching time) were log-transformed before analysis to yield unimodal symmetry. These data are expressed as the median (interquartile ranges).Exercise (av, m), exercise time (average value per day, minute); screen (av, m), screen time (average value per day).

including walking, jogging, and cycling on weekdays and holidays; time spent watching a screen, including watching television and playing television- and/or computer-based games on weekdays and holidays; score for eating breakfast (1, seldom; 2, occasional; 3, regular); and history of smoking. Information on birth weight of the adolescents and duration of breastfeeding during infancy was obtained from the mothers.

Statistical Analysis

Data are expressed as the mean and standard deviation. Data for highly skewed variables in distribution are expressed as the median and interquartile range. Differences in mean values were examined using unpaired Student's t-tests. To determine the effect of lifestyles of adolescents and their parents on the levels of adolescent CVD risk factors, multivariate regression analyses were performed using each CVD risk level as a dependent variable, and the significant variables (P value <0.05) in previous simple regression analyses as independent variables. Highly skewed variables were log-transformed to yield unimodal symmetry, and these are indicated by ln(variable) hereafter to indicate the transformation. In regression analysis, dependent variables included BMI, waist circumference, systolic blood pressure, HDL cholesterol, ln(triglycerides), ln(insulin), ln(HOMA-IR), the number of CVD risk factors, adiponectin, ln(leptin), and ln(hs-CRP). Independent variables include age, presence or absence of participation in EC physical activities, ln(exercise time), ln(screen time), presence or absence of a regular breakfast for adolescent volunteers, age, BMI, ln(exercise time), ln(screen time), and the presence or absence of smoking habits of parents. Statistical analysis was performed using IBM SPSS Statistics version 21.0 (Tokyo, Japan). Results with a two-sided P value <0.05 were considered to be significant.

RESULTS

Characteristics of Subjects

Sex differences were present in junior and senior high school adolescent volunteers. Sex differences in height, weight, systolic and diastolic blood pressure, total cholesterol, FPG, and leptin were found in junior high school adolescents. Sex differences in age, height, weight, BMI, waist circumference, systolic and diastolic blood pressures, total cholesterol, and HDL cholesterol, FPG, insulin, adiponectin, leptin, hs-CRP, and birth weight were

TABLE 20.3 Effect of Lifestyle on Cardiovascular Risk Factors in Junior High School Adolescents by Simple Regression Analysis

	BMI	WC	SBP	HDLc	ln(TG)[a]	FPG	ln (insulin)[a]	ln (HOMA-IR)[a]	No of risk factors	AN	ln(leptin)[a]	ln (hs-CRP)[a]
Males ($n=99$)												
Age	3.66***	3.99***	2.44*	−2.36*	2.09*	–	2.18*	2.15*	–	–	–	–
EC activities[b]	−4.34***	−4.69***	−3.14**	3.73***	−2.81**	–	−2.30*	−2.16*	−2.86**	–	−4.08***	–
ln(screen time)[a]	–	–	–	–	–	–	2.63*	2.46*	–	–	–	–
ln(paternal exercise time)[a]	–	–	–	–	–	–	–	–	–	2.31*	–	–
Maternal BMI	3.19**	3.89***	–	–	–	–	–	–	–	–	3.52***	–
Females ($n=101$)												
Age	2.09*	–	–	–	–	–	–	–	–	–	–	–
EC activities[b]	−2.86**	−2.95**	–	3.60***	−2.24*	–	–	–	–	–	−5.30***	–
ln(exercise time)[a]	−3.66***	−3.49***	−2.85**	3.16**	–	–	–	–	–	–	−3.80***	–
Paternal BMI	3.21**	3.27**	–	−2.26*	–	–	–	–	2.39*	–	2.40*	–
Maternal BMI	3.10**	4.04***	–	−2.07*	–	2.08*	–	–	3.33**	–	2.42*	–

*$P<0.05$. **$P<0.01$. ***$P<0.001$. [a]*Highly skewed variables in distribution (levels of triglycerides, insulin, HOMA-IR, leptin, hs-CRP, exercise time, and screen time) were log-transformed before analysis to yield unimodal symmetry, which are indicated by ln(variable) to indicate the transformation.* [b]*Adolescents were asked whether they participated in EC activities (1, participated; 0, did not participate).*

Values are expressed as t-values obtained by simple regression analysis. Data without significance were not included in the table. –, Variables that were not significant in simple or multivariate regression analyses. AN, adiponectin (in μg/mL); BMI, body mass index (in kg/m^2); EC activities, extracurricular physical activities; exercise or screen time, average time spent (in min) per day for exercise or watching a screen; FPG, fasting plasma glucose (in mg/dL); HDLc, high-density lipoprotein cholesterol (in mg/dL); HOMA-IR, homeostasis model assessment of insulin resistance; hs-CRP, high-sensitivity C-reactive protein (in ng/mL); regular breakfast, regular breakfast consumption; SBP, systolic blood pressure (in mmHg); TG, triglycerides; WC, waist circumference.

found in senior high school adolescents (Table 20.1). Female adolescents showed a significantly lower rate of participation in EC physical activities and spent significantly less time on exercise than did male adolescents in junior and senior high school. In contrast, the amount of screen time was similar for both sexes (Table 20.1). No junior high school volunteers fulfilled the criteria of metabolic syndrome; four senior high school volunteers fulfilled the criteria.

Parental BMIs and time spent watching a screen were similar for both sexes (Table 20.2). Mothers of male and female senior high school adolescents participated in more exercise than did those of junior high school adolescents.

Effect of Lifestyle on Cardiovascular Disease Risk Factor Levels in Junior High School Adolescents

The effect of lifestyle on CVD risk factor levels determined by simple and multivariate regression analysis is shown in Tables 20.3 and 20.4. Multivariate regression analysis showed that the effect of adolescent lifestyle on BMI or waist circumference was different between sexes. In male adolescents, BMI and waist circumference were associated with maternal BMI, but not with paternal BMI. Participation in EC physical activity greatly decreased with worsening BMI and waist circumference. In female adolescents, BMI and waist circumference were associated with paternal and maternal BMI. Participation in EC physical activity was widely associated with improved CVD risk factors, except for obesity, including lowering systolic blood pressure, increasing HDL cholesterol levels, decreasing the level of ln(triglycerides), and decreasing the accumulation of CVD risk factors.

Effect of Lifestyle on Cardiovascular Disease Risk Factor Levels in Senior High School Adolescents

The effect of lifestyle on CVD risk factor levels determined by simple and multivariate regression analysis is shown in Tables 20.5 and 20.6. Multivariate regression analysis showed that the effect of adolescent lifestyle on BMI or waist circumference was sex dependent and was different between junior and senior high school adolescents. In male adolescents, higher paternal and maternal BMI were independently associated with a high BMI and

TABLE 20.4 Effect of Lifestyle on Cardiovascular Risk Factors in Junior High School Adolescents by Multivariate Regression Analysis

	BMI	WC	SBP	HDLc	ln(TG)[a]	ln(insulin)[a]	ln (HOMA-IR)[a]	No of risks	AN	ln(leptin)[a]
Males ($n=99$)										
EC activities[b]	–3.09*	–3.40**	–2.4*	2.99**	–2.14*	–	–	–2.86**	–	–3.74***
ln(screen time)[a]	–	–	–	–	–	2.68**	2.51*	–	–	–
ln(paternal exercise time)[a]	–	–	–	–	–	–	–	–	2.31*	–
Maternal BMI	2.87**	3.64***	–	–	–	–	–	–	–	3.43***
Females ($n=101$)										
EC activities	–	–	–	–	–2.24*	–	–	–	–	–3.18**
ln(exercise time)[a]	–	–	–2.85**	–	–	–	–	–	–	–
Paternal BMI	3.08**	3.03**	–	–	–	–	–	2.48*	–	–
Maternal BMI	2.65**	3.92***	–	–	–	–	–	3.17**	–	2.29*

*$P<0.05$. **$P<0.01$. ***$P<0.001$. [a]*Highly skewed variables in distribution (levels of triglycerides, insulin, HOMA-IR, leptin, hs-CRP, exercise time, and screen time) were log-transformed before analysis to yield unimodal symmetry, which are indicated by ln(variable) to indicate the transformation.* [b]*Adolescents were asked whether they participated in EC activities (1, participated; 0, did not participate).*

Values in the table are expressed as the t-value by multivariate regression analysis. Data without significance were not included in the table.

greater waist circumference. Paternal BMI had a stronger effect on male adolescent BMI and waist circumference than did maternal BMI. Having a regular breakfast was associated with a lower BMI and smaller waist circumference. Conversely, higher maternal BMI, but not higher paternal BMI, was associated with a high BMI and greater waist circumference in female adolescents.

Participation in EC physical activity had a large effect on the following risk factors in male and female senior high school adolescents: levels of HDL cholesterol, ln(triglycerides), ln(insulin), ln(HOMA-IR), adiponectin, and ln(leptin) in both sexes; and systolic blood pressure and the total number of CVD risk factors in male senior high school adolescents. Time spent watching a screen was negatively associated with HDL cholesterol levels for both sexes. Additionally, a longer time spent watching a screen was associated with high levels of ln(triglycerides) and ln(leptin) and low levels of adiponectin in female senior high school adolescents.

Concerning the association between ln(screen time) and obesity in junior and senior high school adolescents, ln(screen time) was weakly associated with a higher waist circumference (abdominal obesity) only in female senior high school adolescents. Screen time of >120 min/day was not associated with the presence of obesity, as defined by international cut offs, or with the presence of abdominal obesity defined by increased waist circumference (data not shown).

Birth weight and duration of breastfeeding were not significant for either sex (data not shown).

DISCUSSION

The present study shows that participation in school-based EC physical activities and parental BMI are strongly associated with the levels of one or more CVD risk factors in adolescents. We also show sex differences and age-specific effects on adolescent BMI and waist circumference, indicating that strategies to prevent the development of CVD risk factors in adolescents should account for sex and age.

Physical activity, especially moderate-to-vigorous physical activity, is associated with beneficial metabolic profiles [8,16]. Participating in EC activities to experience sports or liberal arts are encouraged in junior and senior high schools in Japan. In the present study, multivariate regression analysis showed that participation in EC physical activities is highly associated with improving levels of CVD risk factors in male and female adolescents. Especially in male adolescents, participating in EC physical activities is associated with improvements in many CVD risk factors, such as abdominal obesity, hypertension, low HDL cholesterol levels, and high triglyceride levels in the junior high school period, and hypertension, low HDL cholesterol levels, high triglyceride levels, and insulin resistance in the senior high school period. In female senior high school adolescents, participating in EC activities is associated with improvements in levels of CVD risk factors. The United States Department of Health and Human Services has called for an expansion of school-based EC sports

TABLE 20.5 Effect of Lifestyle on Cardiovascular Risk Factors in Senior High School Adolescents by Simple Regression Analysis

	BMI	WC	SBP	HDLc	ln(TG)[a]	FPG	ln (insulin)[a]	ln (HOMA-IR)[a]	No of risks	AN	ln (leptin)[a]	ln (hs-CRP)[a]
Males ($n=337$)												
Age	–	2.66**	–	–	–	–	–	–	–	–2.10*	–	–
EC activities[b]	–	–	–2.03*	5.29***	–4.49***	–	–3.61***	–4.50***	–4.51***	2.36*	–4.73***	–
ln(exercise time)[a]	–	–	–	3.66***	–3.67***	–	–	–3.34**	–	–	–2.68**	–
ln(screen time)[a]	–	–	2.80**	2.55**	–	–	2.27*	–	2.70**	–	2.13*	–
Regular breakfast[g]	–2.70**	–3.07**	–	–	–	–	–	–2.21*	–	–	2.88**	–
Paternal BMI	**5.32****	4.95***	–	–	–	–	2.55*	2.34*	–	–	3.29**	2.52*
ln(paternal exercise time)[a]	–	–	–	–	–2.16*	–	–	–	–	–	–	–
Maternal BMI	**3.81****	3.29***	2.14*	–	–	–	–	–	2.18*	–	–	–
ln(maternal exercise time)[a]	–	–	2.41*	–	–	–	–	–	–	–	–	–
Females ($n=442$)												
Age	–	–	–3.25**	–	–	–	–	–	–	–	–	–
EC activities	–	–	–	6.23***	–3.58***	–	–4.25***	–4.17***	–	2.63**	–6.09***	2.48*
ln(exercise time)[a]	–	–	–	3.58***	–2.35*	–	–4.22***	–4.19***	–	–	–5.10***	2.28*
ln(screen time)[a]	2.33*	2.26*	–	–2.46*	2.11*	–	–	–	–	–2.55*	2.96**	–
Regular breakfast[g]	–	–	–	–	–	–	–	–	–	–	–	–
Paternal BMI	2.08*	–	–	–	–	–	–	–	–	–	–	–
Maternal BMI	4.38***	3.03**	–	–	–	–	0.49	–	2.33*	–	–	–

*$P<0.05$. **$P<0.01$. ***$P<0.001$. [a]*Highly skewed variables in distribution (levels of triglycerides, insulin, HOMA-IR, leptin, hs-CRP, exercise time, and screen time) were log-transformed before analysis to yield unimodal symmetry, which are indicated by ln(variable) to indicate the transformation.* [b]*Adolescents were asked whether they participated in EC activities (1, participated; 0, did not participate).* [g]*Adolescents were asked whether they ate breakfast (1: seldom, 2: occasionally, or 3: regularly).*

programs to address the obesity epidemic [16,17]. The present study reinforces the premise that participation in school-based EC physical activities has a considerable impact on the levels of multiple CVD risk factors in adolescents.

Concerning the effect of parental BMI on CVD risk factors in children and adolescents, previous studies have shown a greater influence of maternal BMI than paternal BMI on childhood adiposity [18–20]. Sun et al. reported that, based on data obtained in 2002, maternal obesity was more strongly associated with adolescent obesity than was paternal obesity in 2842 males and 2911 females aged 12–13 years in Japan [21]. From data obtained in 2001, Kazumi et al. reported that adolescent BMI was associated with maternal BMI, but not with paternal BMI, in 148 male adolescents aged 18 years in Japan [22]. The present data shows sex and age differences. In junior high school, BMI in male and female adolescents was associated with maternal BMI, but paternal BMI was not associated with BMI in male adolescents. In senior high school, BMI in male adolescents was associated with paternal or maternal BMI. Importantly, paternal BMI was more strongly associated with BMI in male adolescents than was maternal BMI. BMI in female adolescents was associated with maternal BMI but not with paternal BMI. The reason for sex and age differences between adolescent and parental BMI should be further investigated to determine whether adolescent and/or parental attitudes have been changing. Nevertheless, these data suggest that approaches for adolescent obesity that focus on parents should consider the sex of the parent.

Screen time is well known as being associated with unfavorable body composition and CVD risk factors. In the present study, a longer screen time was not strongly associated with obesity. One reason for this low level of

TABLE 20.6 Effect of Lifestyle on Cardiovascular Risk Factors in Senior High School Adolescents by Multivariate Regression Analysis

	BMI	WC	SBP	HDLc	ln(TG)[a]	FPG	ln (insulin)[a]	ln (HOMA-IR)[a]	No of risks	AN	ln(leptin)	ln (hs-CRP)[#]
Males ($n=337$)												
Age	–	2.82**	–	–	–	–	–	–	–	–	–	–
EC activities[b]	–	–	−2.40*	3.64***	−2.67**	–	−4.58***	−2.95**	–	2.36*	−3.75***	–
ln(screen time)[a]	–	–	2.58*	−2.02*	–	–	–	–		–	–	–
Regular breakfast[¶]	−2.70**	−2.93**	–	–	–	–	–	–	–	–	2.03*	–
Paternal BMI	5.01***	4.62***	–	–	–	–	2.57*	2.14*	–	–	3.10**	2.47*
Maternal BMI	3.58**	2.61**	–	–	–	–	–	–	2.24*	–	–	–
ln(maternal exercise time)[a]	–	–	2.44*	–	–	–	–	–	–	–	–	–
Females ($n=442$)												
Age	–	–	−3.25**	–	–	–	–	–	–	–	–	–
EC activities	–	–	–	4.66***	−2.55**	–	−2.27*	−2.20*	–	2.60**	−3.53**	–
ln(exercise time)[a]	–	–	–	–	–	–	–	–	–	–	−2.06*	–
ln(screen time)[a]	–	1.98*	–	−2.59*	2.09*	–	–	–	–	−2.52*	3.14**	–
Maternal BMI	3.95***	2.83**	–	–	–	–	–	–	2.33*	–	–	–

*$P<0.05$. **$P<0.01$. ***$P<0.001$. [a]*Highly skewed variables in distribution (levels of triglycerides, insulin, HOMA-IR, leptin, hs-CRP, exercise time, and screen time) were log-transformed before analysis to yield unimodal symmetry, which are indicated by ln(variable) to indicate the transformation.* [b]*Adolescents were asked whether they participated in EC activities (1, participated; 0, did not participate).* [¶] *Adolescents were asked whether they ate breakfast (1: seldom, 2: occasionally, or 3: regularly).*

association may be that the present data were obtained from volunteer adolescents. However, this issue needs to be further investigated.

The present study was limited by the fact that the present data were obtained from two studies. Data were obtained from senior high school students between 2006 and 2008 and from junior high school between 2012 and 2013. Therefore, the time periods were different in each study. Another major limitation is the cross-sectional nature of the present study. Noninterventional studies on family and physical environmental factors related to health behavior (i.e. diet, physical activity, and sedentary behavior) in adolescents concluded that favorable lifestyles were associated with improved levels of CVD risk factors [6,10]. However, this may be because cross-sectional studies have commonly obtained data form adolescents and their families with favorable lifestyles for prolonged periods. Interventional studies have shown limited effectiveness in reducing the risk of obesity, particularly in the long term, or in increasing positive health behavior despite using a variety of strategies (e.g. reduction in television viewing, increasing physical activities, improving dietary choices, changing health behavior social climates, and providing recreational after school programs) [6]. For adolescents, families, and social groups, the available evidence needs to be used to determine minimal and optimal thresholds for daily sedentary time; daily exercise time by sex, age, and ethnicity; and, when possible, how thresholds differ across health outcomes or demographic status (i.e. age, gender, and ethnicity). Interventional studies are required to test the effect of improved adolescent and/or parental lifestyles on the levels of adolescent CVD risk factors. This could provide strategies for adolescents at a high risk for CVD diseases who may be resistant to ordinary procedures.

CONCLUSION

The present study shows that participation in school-based EC physical activities and parental BMI are associated with the levels of one or more CVD risk factors in adolescents. Among these, participation in EC physical activities has a profound effect on several CVD risk factors, especially for male adolescents. The influence of paternal or maternal obesity on adolescent obesity differs according to sex and age in Japan. Therefore, approaches

focusing on the parents should take into account the sex of the adolescents.

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3 思春期の生活習慣・食習慣と心血管危険因子値

小児から成人まで生活習慣・食習慣が心血管危険因子値に影響を与えることはよく知られている．しかし，心血管危険因子値に影響を与える因子は，運動時間の減少，座りがちな生活習慣の増加，栄養価の高い食材の摂取など本人の生活習慣・食習慣に限らず，保護者の生活習慣・食習慣にも影響されている[1, 2]．これらすべての因子について検討した報告はほとんどない．私たちは2006年から2008年まで厚生労働省科学研究費をいただき，高校生の生活習慣・食習慣と心血管危険因子値との関係を検討した[3]のでお示ししたい．

A 対象

思春期の生活習慣病の基準値作成を目的に，千葉，鹿児島，高岡の3地域において，健康ボランティアを募集し，研究を行った．内容は，

① 体格値，腹囲，血圧の測定
② 心血管危険因子値，アディポカインの測定
③ 生活習慣・食習慣アンケート
④ 地域により，頸動脈血管エコーまたは腹部エコー

である．3地域で1358名に参加していただいた．うち，アンケート項目にすべて回答した755名（男子331名，女子424名）を対象にした．

B 方法

1 心血管危険因子とアディポカイン

心血管危険因子としてbody mass index（BMI），腹囲，血圧，HDLコレステロール，LDLコレステロール，中性脂肪，空腹時血糖，インスリンを用いた．インスリン抵抗性のsurrogate markerとしてhomeostasis model assessment of insulin resistance（HOMA-IR）を用いた[4]．アディポカイン/炎症系因子値としてアディポネクチン，レプチン，高感度CRPを用いた．

2 生活習慣・食習慣に関するアンケート項目

高校生の就寝時間，起床時間，体育系部活動参加の有無，平日・休日の運動時間（歩行，ジョギング，サイクリング，部活を含む），TV視聴時間（TVゲームを含む），朝食摂取の有無（ほとんどない，時々食べる，毎日食べる），同胞数について調査した．保護者の生活習慣（喫煙歴を含む）についても調査した．

食事内容については半定量的調査を実施した．「日本食品成分表」[5]に基づき，エネルギー量，蛋白質，脂質，炭水化物，脂肪酸，コレステロール，食物繊維，食塩相当量等の1日摂取量を算出した．

3 統計学的解析

心血管危険因子/アディポカインを従属変数，アンケート項目値を独立変数として単回帰分析を行い，有意であったものについて重回帰分析を行った．変数のうち対数正規分布を示す変数については，対数変換後統計学的解析を行った．

C 結果

研究参加者の特徴を表1に示した．運動系部活動参加率および運動時間は男子に比し女子は有意に低かった．一方，総エネルギー摂取量は女子が有意に低く，食物繊維摂取量は女子が有意に高かった．

表1 研究参加者の特徴（文献3より改変）

	男子 (n = 337)	女子 (n = 442)	p value
年齢（歳）	16.5 (0.8)	16.7 (0.9)	0.01
身長（cm）	170.5 (6.1)	158.3 (5.3)	< 0.0001
体重（kg）	60.8 (10.3)	51.1 (6.5)	< 0.0001
Body mass index	20.9 (3.1)	20.4 (2.3)	0.01
腹囲（cm）	72.3 (8.2)	71.2 (5.9)	0.03
収縮期血圧（mmHg）	116 (10)	106 (10)	< 0.0001
拡張期血圧（mmHg）	63 (9)	62 (9)	0.02
総コレステロール（mg/dL）	161 (28)	174 (27)	< 0.0001
LDL コレステロール（mg/dL）	89 (24)	96 (23)	< 0.0001
HDL コレステロール（mg/dL）	59 (12)	65 (13)	< 0.0001
LDL/HDL 比	1.55 (0.54)	1.53 (0.50)	0.65
中性脂肪（mg/dL）*	55 (52, 58)	53 (50, 55)	0.23
空腹時血糖（mg/dL）	88 (7)	86 (6)	< 0.0001
インスリン（μU/mL）*	6.1 (5.7, 6.5)	6.7 (6.2, 7.0)	0.07
HOMA-IR*	1.33 (1.23, 1.41)	1.40 (1.31, 1.47)	0.26
心血管危険因子数	0.7 (0.9)	0.6 (0.8)	0.11
アディポネクチン（μg/mL）	10.5 (4.0)	12.0 (4.6)	< 0.0001
レプチン（ng/mL）	1.46 (1.35, 1.58)	5.94 (5.61, 6.28)	< 0.0001
高感度 CRP（ng/mL）	146 (129, 164)	96 (88, 106)	< 0.0001
出生時体重（g）	3154 (425)	3053 (407)	0.0009
母乳期間（month）	7.3 (5.5)	7.8 (5.2)	0.29
生活習慣			
運動系部活動参加率（%）	62	35	< 0.0001
運動時間（1 日平均，min）*	53 (5)	21 (7)	< 0.0001
TV 視聴時間（1 日平均，min）*	96 (2)	91 (3)	0.21
朝食の毎日摂取率（%）	96	92	0.055
食事習慣			
総エネルギー摂取量（kcal/day）	2229 (524)	1827 (455)	< 0.0001
食物繊維摂取量（g）	9.1 (3.0)	8.5 (2.9)	0.004
1000kcal 当たりの食物繊維量	4.2 (1.2)	4.7 (1.4)	< 0.0001

データは平均値（標準偏差）で表してある．

*：対数正規分布を示す変数（中性脂肪，インスリン，HOMA-IR，レプチン，高感度 CRP，運動時間，TV 視聴時間）については対数変換後，有意差検定を行った．これらの変数は平均値（95%信頼限界）で表した．

HOMA-IR: homeostasis model assessment of insulin resistance

表2　高校生および両親の生活習慣が高校生の心血管危険因子値に与える影響（文献3より改変）

	高校生の心血管危険因子値												
	BMI	Waist	SBP	HDL	LDL	ln(TG)#	FPG	ln (Insulin)#	ln (HOMA)#	No of risks	AN	ln (Leptin)#	ln (CRP)#
男子（n＝337）													
運動系部活動$	−‖	−	−2.40*	3.64***	−	−2.67**	−	−4.58***	−2.95**	−4.67***	2.36*	−3.75***	−
Ln（運動時間）#	−	−	−	−	−	−	−	−	−	−	−	−	−
ln（TV視聴時間）#	−	−	2.58*	−2.02*	−	−	−	−	−		−	−	−
毎日の朝食摂取¶	−2.70**	−3.06**	−	−	−	−	−	−	−	−	−	2.03*	−
総エネルギー摂取量	3.08**	2.96**	2.35*	−	−	−	−	−	−	−	−	−	−
Fiber/1000kcal	−	−	−	−	−	−	−2.47*	−	−	−	−	−	−
父のBMI	5.01***	4.58***	−	−	−	−	−	2.57*	2.14*	−	−	3.10**	2.47*
Ln（父の運動時間）#	−	−	−	−	−	−	−	−	−	−	−	−	−
母のBMI	3.58***	3.08**	−	−	−	−	−	−	−	−	−	−	−
Ln（母の運動時間）#	−	−	2.44*	−	−	−	−	−	−	−	−	−	−
女子（n＝442）													
運動系部活参加	−	−	−	4.66***	−	−2.55**	−	−2.27*	−2.20*	−	2.60**	−3.53***	−
ln（運動時間）#	−	−	−	−	−	−	−	−	−	−	−	−2.06*	−
ln（TV視聴時間）#	−	1.98*	−	−2.59*	−	2.09*	−	−	−	−	−2.52*	3.14**	−
総エネルギー摂取量	−	−	−	−	−2.93**	−	−	−	−	−	−	−	−
Fiber/1000kcal	−	−	−	−	−	−	−2.23*	−4.07***	−4.14***	−	−	−	2.21*
父のBMI	−	−	−	−	−	−	−	−	−	−	−	−	−
母のBMI	3.95***	2.83**	−	−	−	−	−	−	−	−	−	−	−

表内の数値は重回帰分析でのt値を示している．

‖：単回帰もしくは重回帰分析において有意でなかった変量については(−)で示してある．

AN：アディポネクチン（μg/mL），BMI：body mass index（kg/m²），CRP：高感度CRP（ng/mL），FPG：fasting plasma glucose（mg/dL），Fiber/1000kcal：1000kcal当たりの食物繊維摂取量（g），HDL：HDLコレステロール（mg/dL），HOMA：homeostasis model assessment of insulin resistance，LDL：LDLコレステロール（mg/dL），SBP：systolic blood pressure（mmHg）

*P＜0.05，**P＜0.01，***P＜0.001

#：対数正規分布を示す変数（中性脂肪，インスリン，HOMA＝IR，レプチン，高感度CRP，運動時間・TV視聴時間）については対数変換後統計学的解析を行っている．これらの変数はln（変数）として表した．

$：アンケートは運動系部活動に（1：参加している，0：参加していない）という設問にした．

¶：朝食摂取については（1：ほとんど食べない，2：時々食べる，3：毎日食べる）という設問にした．

高校生および保護者の生活・食習慣が心血管危険因子/アディポカイン値に及ぼす影響について重回帰分析の結果を表2に示した．高校生の運動系部活動への参加は男女ともに，特に男子においては心血管危険因子値に大きな影響を与えていた．男子では朝食の習慣をつけることがBMIや腹囲と有意な関係があり，女子では高い食物繊維摂取が血糖値，インスリン値，HOMA-IR値の低値と強い関係を認めた．

表3　高校生の肥満の有無に与える保護者の影響（文献3より改変）

	男子		女子	
	オッズ比（95% CI）	p値	オッズ比（95% CI）	p値
父が肥満	2.47（1.28, 4.77）	0.007	1.09（0.44, 2.70）	0.86
母が肥満	1.74（0.71, 4.26）	0.23	3.00（1.13, 8.00）	0.03
両親とも肥満	6.36（1.86, 21.8）	0.003	2.72（0.56, 13.2）	0.21

保護者の肥満は日本の基準によりBMI≧25kg/m²としてある[6]．したがって，高校生の肥満の定義はInternational Obesity Task Force standardのBMI 25kg/m²に相当する値以上としている[7]．CI：信頼限界

表4 思春期（高校生）の生活習慣病予防に関する提言―ガイドライン策定に向けて―

1. 運動習慣を身につけよう
   - 可能なら運動系部活に参加しよう
   - 運動系部活に参加していない場合は，休日に60分以上運動しよう

   平日は学校で結構運動しています．春休み，夏休み，冬休み，あるいは休日に肥満になりやすいものです．休日の運動量を増やしましょう．
2. テレビやテレビゲームから離れよう
   - 平日は1日合計50分以内，休日は1日合計100分以内に，テレビ（テレビゲームも含みます）から離れよう，テレビを消そう
3. よい食習慣を身につけよう
   - 朝食を毎日とろう
   - 食物繊維を積極的に摂取しよう
4. 腹囲が80cmを超えたら，医療機関に相談しよう

   肥満（内臓肥満）は生活習慣病の源流にあります．肥満治療や生活習慣病指導が行える医療機関を本人あるいは保護者に紹介してください．日本肥満学会「認定肥満症専門病院リスト」http://wwwsoc.nii.ac.jp/jasso/data/pdf/hplist.pdfも参考になると思います．

保護者の肥満が高校生の肥満に与える影響には性差を認め，父が肥満であると高校生が肥満であるオッズ比は男子にのみ有意に高く，母が肥満であると，高校生が肥満であるオッズ比は女子にのみ有意に高かった（表3）．

むすび

このような結果を踏まえ，表4のような提言を行っている．今後prospective studyを行い，これらにより心血管危険因子値の改善がみられるか検討を続けていきたい．

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〈吉永正夫〉

6 脂肪肝・非アルコール性脂肪性肝障害

従来から，脂肪肝（fatty liver: FL）は肥満の合併症としてよく知られている．小児期のFLの多くは無症状で，血液検査や腹部超音波検査，腹部CT検査を契機として偶然発見される場合が多い．以前は，肥満に合併するFLは減量すれば速やかに改善し予後良好と考えられてきたが，病理学的検討から，小児期でも脂肪性肝炎から肝硬変に進行する例もあることが明らかとなり，適切な介入と慎重な経過観察が必要である．FLは，メタボリックシンドロームの病態と関係が強く，日本人を含むアジア人に高頻度で発生し，近年増加傾向にあることから，特に注目されている．

A 脂肪肝・非アルコール性脂肪性肝障害・非アルコール性脂肪性肝炎の定義

近年，世界的な肥満や2型糖尿病（type 2 diabetes mellitus: T2DM）の増加に伴って，過栄養性のFLが増加している．FLとは，肝細胞内に中性脂肪が過剰に蓄積した状態を指し，組織学的には肝小葉の1/3以上に脂肪滴が沈着している場合をいう．

過栄養性FLの中には，飲酒歴がないにも関わらず，アルコール性肝障害に類似した組織像を呈す例があり，非アルコール性脂肪性肝障害（non-alcoholic fatty liver disease: NAFLD）と呼ばれている[1]．NAFLDと診断するためには，種々のウイルス性肝炎や自己免疫性肝炎，代謝疾患に伴う肝障害などを除外する必要がある．NAFLDは，単純性脂肪肝から，脂肪性肝炎，肝線維症，肝硬変までを含む幅広い概念で，FLに炎症所見や肝細胞の変成，線維化が加わった場合を非アルコール性肝炎（non-alcoholic steatohepatitis: NASH）という[2]．NASHはNAFLDの重症型であり，診断には肝生検が必要である．

B NAFLD・NASHの疫学

我が国の一般成人におけるNAFLDの頻度は約10%程度と推定されており，肥満者やT2DM者におけるNAFLDの頻度はより高率である．

小児FLについてTominagaらは，4～12歳の810名を対象として腹部超音波検査を行い，男児の3.4%，女児の1.8%にFL所見が認められ，肥満が高度な学童にFLが多かったと報告している[3]．また，Tazawaらは6～11歳の肥満小児310名を対象として，FLを反映する高ALT血症の頻度を検討し，肥満小児の約25%に高ALT血症が認められ，肥満の持続期間が長いほど高ALT血症の頻度が増加していたと報告している[4]．

NASHの診断には肝生検が必要であり，小児期NASHの頻度に関する大規模疫学調査報告はない．Kinugasaらは，肝機能障害のある肥満小児11例に肝生検を行い，単純性FLはわずか3例のみで2例は脂肪性肝炎，5例は脂肪性肝線維症，1例は肝硬変であったと報告している[5]．乾らは，30名のNAFLD小児に肝生検を施行し，うち9例（30%）はNASHであったと報告している[6]．このように，小児のNASHは想像以上に高頻度であり，肝硬変まで進行している例も散見される

ため，決して軽視できない肥満合併症である．

C NAFLD・NASHの病因・病態

NAFLDやNASHの病因として，はじめに脂肪肝が生じ，その後に脂肪性肝炎に移行するという，Two hit hypothesisが，以前から最も支持されている[7]（図1）．肥満，特に過剰な内臓脂肪蓄積は，インスリン抵抗性を惹起させ肝細胞に過剰な脂肪蓄積を招く（1st hit），その後，過酸化脂質や酸化ストレス，エンドトキシンなどの肝細胞障害因子が2nd hitとなってNASHに進展するという考え方である．

しかし近年，幼児期からすでに肥満にNAFLDを合併した例も報告されており，遺伝的素因や子宮内環境と出生後の環境のミスマッチ（いわゆるDOHaDの概念）もNAFLDやNASHの発症に関与している可能性もある[8]．

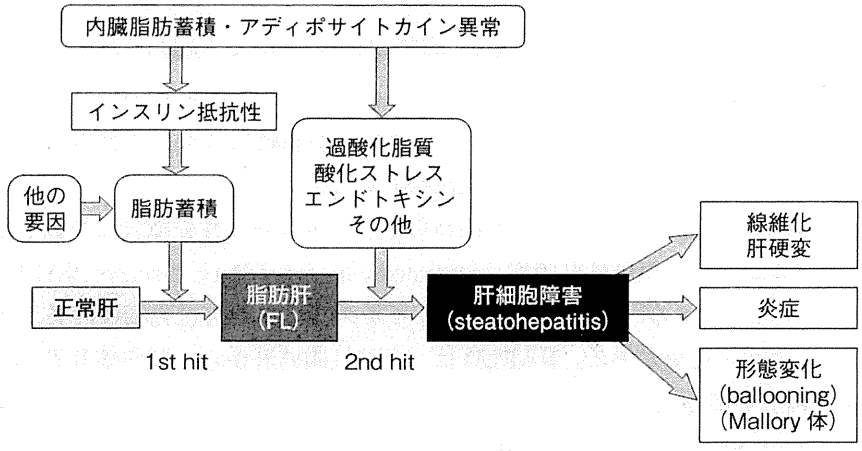

図1　NASHの病因論（Two hit hypothesis）

D NAFLDやNASHの診断

NAFLDやNASHは無症状の場合も多く，たとえ症状があっても，倦怠感や，上腹部不快感，軽度の腹痛などの非特異的な症状の場合が多い．NAFLDやNASHの合併が疑われる診察所見としては，肝臓の腫大や肝臓部分の叩打痛，頸部の黒色表皮症（achanthosis nigricans: AN）があげられる．肥満小児に認められるANは内臓脂肪蓄積に伴う高インスリン血症やインスリン抵抗性を反映しており，ANが認められる肥満小児はメタボリックシンドロームやNAFLD・NASHの合併が多い[9]．

NAFLDやNASHの診断には，アルコール摂取歴がないことと，FLをきたしうる他の肝疾患の除外が必要である．近年，思春期小児のアルコールアビュースも問題となっており，思春期以降の若年者の診察の際には20歳前でもアルコールを摂取している可能性もありうるという立場で診察に当たるべきである．また，FLの鑑別診断として，栄養障害，ウイルス感染症，代謝性疾患，自己免疫性疾患，薬剤性などに起因する肝障害を否定しなければならない[10]．表1に小児期からFLを生じうる疾患群を示す．

表1 小児期に脂肪肝を生じうる疾患群（文献10より改変）

全身性疾患/栄養障害	**代謝性疾患**
肥満，メタボリックシンドローム	シトリン欠損症
急性疾患（脱水症，重症感染症）	Wilson病
飢餓	αアンチトリプシン欠損症
クワシオルコル	ガラクトース血症
celiac病	遺伝性果糖不耐症
完全静脈栄養法に関連したもの	糖原病
その他	オルニチントランスカルバミラーゼ欠損症
	リポジストロフィー
感染症	βリポ蛋白欠損症
C型肝炎	糖尿病，他
EBウイルス感染症	
	薬剤性
自己免疫性疾患	アミオダロン
自己免疫性肝炎	メトトレキサート，L-アスパラギナーゼ
	ステロイド，ビタミンA，エタノール，他

上述したように，NAFLDやNASHの合併があっても特異的な症状に乏しいため，血液検査や画像診断でNAFLDやNASHの存在に気付かれる場合が多い．一般に，血液検査ではALT優位の肝逸脱酵素の上昇が認められる．ただし，肝硬変まで進行するとAST優位になることに留意する必要がある．腹部超音波検査では，肝臓の肥大と，肝実質の点状高エコー（bright liver），肝臓深部のエコー減衰（deep attenuation），肝内脈管の不鮮明化，肝腎コントラストの増強などの所見が，腹部CT検査では，肝実質のCT値の低下（肝臓のCT値/脾臓のCT値＜0.9）が認められる．

NAFLDの診療で一番問題となるのは，NASHに進行しているか否かの判断である．現時点では，NASHを診断する有益な血液検査指標はなく，NASHへの進行の有無を判断するには肝生検が必要である．肝生検は侵襲的な検査であるため，成人における肝生検を考慮すべき指標[11]などを参考にして個別に対応する（表2）．

NASHの診断は組織学的所見でなされる．NASHは進行性であるため活動性と進行度の診断にBruntの分類が汎用されている．最近，小児期NASHの中には，成人NASHと組織学的に異なるパターンを呈する者が多いことが明らかとなった[12]（表3）．“Pediatric type”のNASHは，肥満が高度な有色人種の男児に多いと報告されている．

表2 肝生検を考慮すべき症例（文献11より改変）

① ALTが高値（100IU/L以上）で増悪傾向にある
② NASHの危険因子を有する
（内臓脂肪蓄積，糖代謝異常，脂質異常症，高血圧，メタボリックシンドローム，高カロリー輸液，小腸手術後，急激な体重減少・飢餓など）
③ 肝硬変への進行が疑われる
（肝機能低下，AST＞ALT，血小板減少，線維化マーカーの上昇）
④ 食事運動療法で改善が認められない
⑤ 脂肪肝を生じる他疾患（特に代謝性疾患との鑑別）との鑑別が困難

表3　小児期 NASH の組織像の相違点

	Pediatric-type NASH	Adult-type NASH
小児における頻度	多い	少ない
脂肪変性	強い	弱い
炎症性細胞浸潤	門脈域が主体	小葉内が主体
肝細胞の ballooning	認めない	認める
線維化	認めないかあっても門脈域	類洞周辺か小葉中心周囲
肝硬変	あり	あり

E NAFLD や NASH の予後

成人の NASH は進行性で，肝線維化から肝硬変へ，さらには肝細胞癌が発症する場合があることが報告されている．小児期 NASH の予後はまだ明らかになっていない点も多いが，肝硬変を呈する例が報告されており，小児期 NASH も進行性であると考えられる．むしろ，小児期に NASH を発症した者は，肥満の治療成績が芳しくないことや NASH の病態が成人発症例よりも長期的に継続する可能性が高いことを考慮すると，成人の NASH より予後が悪い可能性も否定できない．乾らは，小児の NAFLD 例は，治療途中で脱落する者や再燃する者が 93% を占めており，社会的予後はきわめて悪いと報告している[6]．

F NAFLD や NASH の治療

肥満に伴う NAFLD や NASH の治療の第一段階は，肥満の是正である．小児肥満治療の原則は，正常な成長発達を妨げることなく，肥満に伴う合併症や肥満の程度を改善させることである．したがって，強いエネルギー制限は行わず，性別年齢別の推定エネルギー必要量の 90% 程度のエネルギー制限を行う．三大栄養素のバランスは，糖尿病食に準じ，単純糖質や高果糖コーンシロップに代表される異性化糖を制限し，グリセミックインデックスの小さい複合糖質の摂取を勧める．NAFLD や NASH を合併する肥満小児の多くは身体活動が不十分である．適度な運動は，ストレス解消や，インスリン感受性の改善効果があるため，運動系部活動や地域のスポーツ活動に参加するようにアドバイスする．さらに肥満改善には，生活リズムの適正化がきわめて重要であり，夜更かしをしないようにして，起床したら朝日を浴びて必ず朝食を摂取するように指導する．指導が奏効して肥満が改善すると，血液検査における肝逸脱酵素の上昇や画像診断における FL 所見は改善する場合が多いが，高度肥満例や，肥満の経過が長期にわたる思春期の肥満例は，肥満治療の成績が悪いため NAFLD や NASH も改善しにくい．

NAFLD や NASH に対する薬物用法としては，ビタミン E やビタミン C などの抗酸化薬や，ウルソデオキシコール酸，ポリエンホスファチジルコリンなどの肝庇護剤が用いられる場合もある[13]．成人 NASH に対してはメトホルミンやチアゾリジン誘導体などのインスリン抵抗性改善薬が使用されている．表 4 に小児期の NASH や NAFLD に対する薬剤を示す．FL に保険適用があるのはポリエンホスファチジルコリンのみである点に注意を要する．小児ではビタミン E やメトホルミンが使用される場合が多く，我々も T2DM に合併した NAFLD にメトホルミンが著効した

表4 小児期 NAFLD・NASH の薬物療法

	薬剤名	商品名	用量
インスリン抵抗性改善薬	メトホルミン	メルビン錠（1 錠 200mg）	2〜3 錠　分 2〜3
	チオゾラジン誘導体	アクトス錠（1 錠 15mg）	1〜2 錠　分 1
抗酸化薬	ビタミン E	ユベラ錠（1 錠 50mg）	3〜6 錠　分 2〜3
	ビタミン C	シナール配合顆粒（1 包 200mg）	3〜9 包　分 1〜3
肝庇護剤	ウルソデオキシコール酸	ウルソ錠（1 錠 100mg）	3〜6 錠　分 3
	ポリエンホスファチジルコリン	EPL カプセル（1Cap 250mg）	3〜6 錠　分 3
漢方薬	大柴胡湯	ツムラ大柴胡湯エキス顆粒	7.5g　分 2〜3　食前

例を経験しているが，メトホルミンの有効性に関する大規模臨床試験は現在施行中である[14]．

むすび

FL は，小児肥満によくみられる合併症である．NAFLD は，メタボリックシンドロームの病態を反映している点が重要で，一部は小児期から NASH や肝硬変に移行するため予後は楽観できない．

現在の NAFND・NASH 診療の問題点は，NASH 診断のために有益な検査法が肝生検以外にないことや，大規模疫学調査結果に裏付けされた有効な治療法が明らかになっていないことである．現状では，NASH・NAFLD の温床となる肥満やメタボリックシンドロームそのものの予防対策がきわめて重要なことは論を待たないが，メタボリックシンドロームの病態を有し肥満治療に抵抗する肝障害が持続する例では，NASH の有無や進行度を評価するために肝生検を考慮すべきである．

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