Table 2. Fatty acid composition of plasma phospholipids and desaturase indices

	Boys			Girls		
	Non-obese	Obese	*p* value	Non-obese	Obese	*p* value
1st	*n*=34	*n*=4		*n*=32	*n*=7	
Saturated fatty acids						
16:0	25.1±1.2	26.1±1.4	0.1112	25.4±1.1	25.4±1.1	0.9664
18:0	14.7±0.8	15.5±1.1	0.0595	14.6±0.8	15.5±0.	0.0141
Monounsaturated fatty acids						
16:1n-7	0.7±0.3	0.7±0.3	0.8281	0.6±0.3	0.8±0.4	0.1966
18:1n-9	8.5±0.8	8.0±1.0	0.2386	8.8±0.5	8.6±1.5	0.5562
Polyunsaturated fatty acids						
18:2n-6	18.0±2.1	16.6±2.6	0.2174	19.1±1.5$^{\#}$	18.1±2.8	0.1909
20:3n-6	2.1±0.4	2.7±0.5	0.0084	2.2±0.5	2.6±0.7	0.0686
20:4n-6	9.1±1.2	8.3±0.9	0.1971	8.6±1.0	9.1±0.8	0.2799
18:3n-3	0.2±0.1	0.3±0.1	0.6117	0.2±0.1	0.2±0.1	0.8319
20:4n-3	0.1±0.1	0.2±0.2	0.0706	0.2±0.1	0.2±0.1	0.8391
20:5n-3	2.3±0.8	3.3±1.3	0.0249	1.9±0.7	1.8±0.6$^{\#}$	0.5530
22:6n-3	7.5±1.1	7.5±1.6	0.9884	6.7±1.0$^{\#}$	6.4±0.9	0.4675
SCD16	0.03±0.01	0.03±0.01	0.9105	0.02±0.01	0.03±0.01	0.1997
SCD18	0.58±0.08	0.52±0.09	0.125	0.60±0.05	0.56±0.12	0.1166
D6D	0.12±0.03	0.17±0.03	0.0081	0.12±0.03	0.15±0.06	0.0259
D5D	4.36±0.87	3.09±0.76	0.0082	4.07±0.87	3.70±1.13	0.3391
2nd	*n*=32	*n*=6		*n*=31	*n*=8	
Saturated fatty acids						
16:0	25.3±0.8	26.1±0.9	0.0268	25.7±0.9	25.8±0.7	0.6595
18:0	14.5±0.8	15.2±0.8	0.0623	14.4±0.7	15.0±0.7	0.0483
Monounsaturated fatty acids						
16:1n-7	0.9±0.2*	0.8±0.3	0.2270	0.9±0.2**	0.9±0.1	0.8829
18:1n-9	9.8±0.7**	9.6±1.0	0.4724	9.7±1.0**	9.5±0.6	0.5869
Polyunsaturated fatty acids						
18:2n-6	20.6±2.0**	19.2±1.8	0.1334	20.6±2.0**	19.6±1.3	0.2021
20:3n-6	2.3±0.5	2.9±0.7	0.0196	2.2±0.6	2.7±0.4	0.0209
20:4n-6	9.4±1.1	9.1±0.9	0.5734	9.2±1.2	9.4±0.5**	0.7126
18:3n-3	0.3±0.1*	0.3±0.1	0.5978	0.3±0.1**	0.3±0.1	0.9635
20:4n-3	0.1±0.1	0.2±0.1	0.0198	0.1±0.1	0.11±0.1	0.3208
20:5n-3	1.3±0.5**	1.4±0.6	0.6370	1.5±1.0**	1.2±0.3	0.4621
22:6n-3	6.0±1.0**	6.0±1.5	0.9672	5.8±1.2**	5.9±0.5	0.8320
SCD16	0.03±0.01*	0.03±0.01	0.1382	0.03±0.011**	0.03±0.01	0.8285
SCD18	0.68±0.06**	0.63±0.06	0.1017	0.68±0.08**	0.64±0.06	0.1877
D6D	0.11±0.03	0.15±0.05	0.0164	0.11±0.03	0.14±0.03	0.0082
D5D	4.23±0.81	3.43±1.42	0.0576	4.54±1.27*	3.55±0.58	0.0405

W/W%
1st vs. 2nd in non-obese, $^{*}p<0.05$, $^{**}p<0.01$ Mean±SD
Male vs. Female, $^{\#}p<0.05$. $^{\#\#}p<0.01$

tively with RW and WHtR ($r=-0.422$, $p=0.0083$ and $r=-0.333$, $p=0.0408$, respectively) only in boys. HOMA-R had no association with the SCD16 index or the SCD18 index in either sex.

Changes in Parameters Over 3 Years (Table 1)

The 3-year change in individual RW was −7.6± 7.6% in boys and −2.6±9.3% in girls. Of the 11 children who were obese in the first phase, 10

remained obese (4 boys and 6 girls), and an additional 2 boys and 2 girls became obese. Thus, in the second phase, 14 children (6 boys and 8 girls) were obese.

TC, LDLC and concentration of glucose in non-obese boys were decreased significantly compared to their values in the first phase. Non-obese girls showed significant increases in the concentration of TG but not TC or LDLC. Thus, in the second phase, boys had lower concentrations of TC, LDLC and TG than those in girls. One girl had hypercholesterolemia, 4 children (1 boy and 3 girls) had hypertriglyceridemia and 3 children (1 boy and 2 girls) had low concentrations of HDLC. HOMA-R and fasting insulin concentration increased in girls, and the difference between sexes was statistically significant in the second phase of the study.

Table 3. Relationship between the changes in fatty acid composition and the changes in RW

	Boys $n=38$		Girls $n=39$	
Individual 3-year change in	r	p	r	p
Saturated fatty acids				
16:0	−0.260	0.1150	0.252	0.1212
18:0	0.533	0.0006	0.042	0.7996
Monounsaturated fatty acids				
16:1n-7	0.171	0.3045	0.322	0.0458
18:1n-9	−0.222	0.1801	0.036	0.8296
Polyunsaturated fatty acids				
18:2n-6	−0.591	<0.0001	−0.293	0.0704
20:3n-6	0.463	0.0035	0.123	0.4541
20:4n-6	0.197	0.2364	−0.184	0.2632
18:3n-3	−0.059	0.7237	0.159	0.3321
20:4n-3	0.431	0.0069	−0.028	0.8673
20:5n-3	0.273	0.0977	0.159	0.3330
22:6n-3	0.409	0.0108	0.064	0.6991
SCD16	0.197	0.2351	0.307	0.0575
SCD18	−0.473	0.0061	−0.019	0.9097
D6D	0.586	0.0001	0.283	0.0811
D5D	−0.352	0.0318	−0.191	0.2431

Fatty Acid Composition in the Second Phase of the Study (Table 2)

No difference in fatty acid composition was observed between sexes in the second phase of the study. Palmitoleic acid (16:1n-7) and oleic acid (18:1n-9) contents in non-obese children were significantly higher in the second phase than in the first phase. Thus, both the SCD16 and SCD18 indices increased. Regarding n-3 PUFAs in non-obese children, the content of alpha-linolenic acid (ALA, 18:3n-3) was increased significantly and the contents of EPA (20:5n-3) and DHA (22:6n-3) were decreased significantly in both sexes. For n-6 PUFAs, the content of arachidonic acid (AA, 20:4n-6) was increased significantly only in obese girls, whereas the content of LA (18:2n-6) in non-obese children was increased significantly in both sexes. The D6D and D5D indices were unchanged during the study, except for the D5D index in non-obese girls.

In boys, the D6D and D5D indices and DGLA (20:3n-6) were correlated with RW ($r=0.569$, $p=0.0002$, $r=-0.444$, $p=0.0052$ and $r=0.433$, $p=0.0066$, respectively) and with WHtR ($r=0.640$, $p<0.0001$, $r=-0.516$, $p=0.0009$ and $r=0.404$, $p=0.0120$, respectively). HOMA-R showed a significant relationship only with DGLA ($r=0.446$, $p=0.0050$). In girls, the D6D index was correlated with RW, WHtR and HOMA-R ($r=0.391$, $p=0.0139$, $r=0.454$, $p=0.0037$ and $r=0.556$, $p<0.0001$, respectively), the D5D index was correlated with WHtR and HOMA-R ($r=-0.332$, $p=0.0392$ and $r=-0.431$, $p=0.0051$, respectively) but not with the D6D index. DGLA was correlated with RW and HOMA-R ($r=0.371$. $p=0.0200$ and $r=0.426$, $p=0.0069$, respectively) but not with the D5D index. The SCD16 index showed no significant correlation with RW, WHtR or HOMA-R in either sex. The SCD18 index had significant negative correlation with RW and WHtR ($r=-0.386$, $p=0.0167$ and $r=-0.347$, $p=0.0327$, respectively) in boys but not in girls. HOMA-R had no correlation with the SCD16 or the SCD18 index in either sex.

Association between Changes in Fatty Acid Composition and Changes in RW, WHtR and HOMA-R (Tables 3-5)

We investigated the association between changes in RW and changes in fatty acid content as well as in the desaturase indices. In girls, the changes in RW were not associated with changes in any parameter except the content of palmitoleic acid (16:1n-7). By contrast, the change in RW in boys was associated significantly with changes in fatty acid composition and desaturase indices. Increased RW was associated with increased contents of 18:0, DGLA (20:3n-6), 20:4n-3 and DHA (22:6n-3) and the D6D index, and with a decreased content of LA (18:2n-6) and the SCD18 and D5D indices.

In girls, the changes in WHtR were not associated with changes in any parameters except DGLA (20:3n-6). In boys, the change in WHtR was associated significantly with changes in 16:0, 18:0, LA

Table 4. Relationship between the changes in fatty acid composition and the changes in WHtR

Individual 3-year change in	Boys $n=38$		Girls $n=39$	
	r	p	r	p
Saturated fatty acids				
16:0	−0.336	0.0392	0.015	0.9276
18:0	0.527	0.0007	0.167	0.3089
Monounsaturated fatty acids				
16:1n-7	0.131	0.4345	0.298	0.0654
18:1n-9	−0.245	0.1388	0.131	0.4256
Polyunsaturated fatty acids				
18:2n-6	−0.476	0.0031	−0.282	0.0823
20:3n-6	0.619	<0.0001	0.362	0.0234
20:4n-6	0.203	0.2227	−0.165	0.3165
18:3n-3	−0.012	0.9440	0.114	0.4906
20:4n-3	0.433	0.0066	0.171	0.2990
20:5n-3	0.106	0.5258	0.177	0.2815
22:6n-3	0.236	0.1531	0.006	0.9695
SCD16	0.157	0.3467	0.296	0.0674
SCD18	−0.467	0.0031	0.026	0.8739
D6D	0.640	<0.0001	0.500	0.0012
D5D	−0.488	0.0019	−0.337	0.0361

Table 5. Relationship between the changes in fatty acid composition and the changes in HOMA-R

Individual 3-year change in	Boys $n=38$		Girls $n=39$	
	r	p	r	p
Saturated fatty acids				
16:0	0.130	0.4350	−0.147	0.3727
18:0	0.094	0.5734	0.306	0.0585
Monounsaturated fatty acids				
16:1n-7	0.006	0.6923	0.040	0.8076
18:1n-9	−0.084	0.6148	0.324	0.0440
Polyunsaturated fatty acids				
18:2n-6	−0.104	0.5325	−0.085	0.6081
20:3n-6	0.023	0.8502	0.236	0.1484
20:4n-6	−0.076	0.6504	−0.313	0.0526
18:3n-3	0.144	0.3873	0.249	0.1259
20:4n-3	0.079	0.6384	0.202	0.2174
20:5n-3	0.023	0.8890	0.074	0.6565
22:6n-3	0.080	0.6330	−0.019	0.9085
SCD16	0.063	0.7093	−0.034	0.8352
SCD18	−0.112	0.5045	0.115	0.4847
D6D	0.044	0.7931	0.326	0.0432
D5D	−0.095	0.5696	−0.296	0.0671

(18:2n-6), DGLA (20:3n-6) and 20:4n-3. In addition, the change in WHtR was correlated significantly to changes in the D6D and D5D indices in both boys and girls. In girls, the increases in the D6D index and oleic acid (18:1n-9) were correlated significantly to changes in HOMA-R.

Desaturase Indices Over the Period of the Study

To evaluate the tracking of desaturase indices, single regression analysis of the desaturase index and DGLA (20:3n-6) values was performed from the first and second phases of the study. Strong correlations were found for the D6D index ($r=0.431$, $p=0.0069$ in boys; $r=0.557$, $p=0.0002$ in girls), the D5D index ($r=0.554$, $p=0.0003$ in boys; $r=0.567$, $p=0.0002$ in girls), the SCD18 index ($r=0.470$, $p=0.0029$ in boys; $r=0.503$, $p=0.0011$ in girls) and DGLA (20:3n-6) ($r=0.474$ and $p=0.0026$ in boys; $r=0.513$ and $p=0.0008$ in girls). By contrast, the SCD16 index showed no significant association.

Discussion

We investigated the longitudinal changes of fatty acid composition of plasma phospholipids and the impact of body fatness and insulin resistance during early puberty in Japanese children. The pattern of change in the fatty acid composition was similar in both sexes, and body fatness was associated with longitudinal changes of D6D and D5D indices and DGLA (20:3n-6).

Body fatness is one of the determinants of fatty acid composition in serum phospholipids. In an earlier study[6], obese children showed greater contents of AA (20:4n-6) and DGLA (20:3n-6) and a higher AA (20:4n-6)/LA (18:2n-6) ratio, suggesting enhanced activity of D6D. In addition, obese children with metabolic syndrome demonstrated lower LA (18:2n-6) and higher DGLA (20:3n-6) than non-obese children and obese children without metabolic syndrome[7]. In the present study, obese children had higher DGLA (20:3n-6), a higher D6D index and lower D5D index than non-obese children both at baseline and 3 years later. Furthermore, changes in the D6D and D5D indices and DGLA (20:3n-6) were associated with changes in WHtR over 3 years; therefore, abdominal adiposity might be an important determinant of longitudinal changes in n-6 fatty acid composition of plasma phospholipids.

The present study demonstrated an increase in

MUFAs and n-6 PUFAs and a decrease in n-3 PUFAs over a 3-year period. The difference between the first and second phases of the study might be explained, in part, by changes in dietary fatty acid composition; however, endogenous fatty acid metabolism, which is modulated by desaturase activities, might be an important determinant of the plasma fatty acid composition of plasma phospholipids[16]. Furthermore, our findings of the 3-year changes in D5D and D6D indices suggest that they might also be determined by body fatness and insulin resistance. Earlier, a longitudinal study of phospholipid fatty acid composition in German children demonstrated that n-3 and n-6 PUFAs were higher and the contents of saturated fat and MUFA were lower when they were 5 years old than when they were 2 years old, and the AA (20:4n-6)/LA (18:2n-6) ratio showed no change in 3 years, although the dietary intake of fatty acid composition changed. It was also suggested that the metabolism of individual endogenous fatty acids, rather than dietary fatty acid composition, determined the longitudinal changes in plasma fatty acid profile[16].

The SCD, D5D and D6D indices are regulated by diet and hormones, which affect insulin sensitivity[22]. In our longitudinal study, we found sexual dimorphism in the relationship between changes in the D6D and D5D indices and changes in body fatness. Increased D6D index and decreased D5D index were associated with increased RW only in boys, whereas sexual dimorphism was not detected in association with changes in WHtR. During puberty, the change in body composition is markedly different between boys and girls[23]. The fat percentage decreases in boys and increases in girls; thus, increasing RW in pubertal girls does not always indicate a trend toward obesity. On the other hand, the percentage of abdominal fat, both visceral and subcutaneous, does not change with age in either boys or girls[23]; therefore, an increase in WHtR suggests a trend toward obesity in both sexes. The sexual dimorphism of the association between changes in the D6D and D5D indices and changes in body fatness could be explained by sex-specific pubertal changes in body composition.

Another novel finding of this study was that changes in the D6D and D5D indices were associated with changes in HOMA-R in girls but not in boys. During puberty, children develop transient insulin resistance in response to physiological changes, resulting in a decrease in peripheral insulin sensitivity and a compensatory increase in insulin secretion[24]. The main determinants of insulin sensitivity during this period are total body fat and central body fat in girls and total body fat and lean mass in boys[25]. The association between changes in the D6D and D5D indices and changes in HOMA-R in our study might reflect the influence of physiological insulin resistance during this period.

SCD plays a crucial role in the development of obesity and insulin resistance in animal models[26]. In some human studies, an elevated SCD index in plasma[27] and adipose tissue[28] reflects higher levels of adiposity, TG levels and insulin resistance. In this study, however, changes in the SCD16 index were not associated with changes in RW, WHtR or HOMA-R in either sex, and the change in the SCD18 index in boys was negatively associated with changes in RW and WHtR. It was difficult to interpret these findings; however, Warensjö *et al.*[14] also found that the SCD18 index obtained from the fatty acid composition of plasma phospholipids was correlated negatively with body mass index, which was compatible with our findings in boys at baseline. This might well be because other lipid fractions are appropriate for estimation of the SCD index via product/precursor ratios[29].

The present study was not designed to evaluate dietary intake, hormonal changes or pubertal stages, which are key factors of changes in body fatness and insulin resistance during early puberty; therefore, the influence of pubertal change on fatty acid composition and desaturase indices could not be evaluated. However, our results demonstrated that the association between the D6D and D5D indices and body fatness might be modified by sex, suggesting that the determinants of longitudinal changes in D6D and D5D indices are different between boys and girls. Further studies are needed to investigate the interaction between the desaturase indices and the changes in growth and sex hormones.

In conclusion, the fatty acid composition of plasma phospholipids in obese children showed an increase in DGLA (20:3n-6), an increase in the D6D index and a decrease in the D5D index. This longitudinal study demonstrated that the D6D and D5D indices and DGLA (20:3n-6) tracked strongly, and the 3-year changes in both desaturase indices and DGLA (20:3n-6) were associated with the change in WHtR; therefore, obesity, especially abdominal adiposity, is a determinant of the fatty acid composition of plasma phospholipids and its longitudinal changes during puberty.

Conflict of Interest

None.

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Abdominal adiposity is associated with fatty acid desaturase activity in boys: Implications for C-reactive protein and insulin resistance ☆

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ABSTRACT

Fatty acid composition, which is altered in patients with abdominal obesity, is influenced not only by dietary intake but also by the desaturating enzymes stearoyl-CoA desaturase (SCD), delta-6 desaturase (D6D) and delta-5 desaturase (D5D). We investigated desaturase activities and their associations with metabolic risk factors, C-reactive protein levels (CRP) and insulin resistance in Japanese children. There were 237 school children in this study; 115 were boys. The fatty acid composition of plasma phospholipids was analyzed, and the following desaturase activities were estimated: SCD (16:1n-7/16:0 and 18:1n-9/18:0), D6D (20:3n-6/18:2n-6) and D5D (20:4n-6/20:3n-6). D6D and D5D activities, but not SCD activity, were significantly associated with triglyceride levels, high-density lipoprotein cholesterol levels and insulin resistance in both sexes, and with CRP levels in boys. In addition, increased abdominal adiposity was significantly associated with increased D6D activity, and decreased D5D activity and insulin resistance in both sexes, and with increased CRP levels in boys. The n-6 polyunsaturated fatty acid desaturation pathway may be associated with metabolic risk factors, insulin resistance and increased inflammation in children with abdominal obesity, especially in boys.

1. Introduction

Childhood obesity is a worldwide epidemic, with consequences that include an increased incidence of metabolic syndrome (MetS) during childhood [1–3]. MetS, which may arise in part due to abdominal obesity [4], is defined by the clustering of several metabolic abnormalities, such as dyslipidemia, hypertension and hyperglycemia, and is associated with a higher risk of cardiovascular diseases and type 2 diabetes in later life [5]. In addition, epidemiological studies have demonstrated that metabolic risk factors, as well as abdominal obesity, were related to altered plasma fatty acid composition [6–9]. In children with MetS, an increased level of palmitoleic acid (16:1n-7) and a decreased level of arachidonic acid (AA; 20:4n-6) have been observed [10].

The fatty acid composition of serum lipids not only reflects dietary fat intake, but is also influenced by the desaturating enzymes stearoyl-CoA desaturase (SCD), delta-6 desaturase (D6D) and delta-5 desaturase (D5D) [11]. SCD is the rate-limiting enzyme in the biosynthesis of monounsaturated fatty acids (MUFAs), and D5D and D6D are key enzymes in polyunsaturated fatty acid (PUFA) metabolism, catalyzing the conversion of linoleic acid (LA; 18:2n-6) to AA and alpha-linolenic acid (ALA; 18:3n-3) to eicosapentaenoic acid (EPA; 20:5n-3) [12]. The activities of these enzymes cannot be measured easily in humans in vivo but can be estimated from the product/precursor ratios [13]. Recent studies in Japanese adults demonstrated that elevated D6D and SCD activities and reduced D5D activity were associated with MetS [14]. In addition, studies of the FADS genes, which encode D6D and D5D, showed that single nucleotide polymorphisms in this gene cluster were associated with high D6D activity and low D5D activity [15], as well as with an increase in inflammatory markers, a greater risk of coronary artery disease and an increase in fasting insulin levels [16,17]. In addition, the genetic variations of the SCD1 gene had significant associations with abdominal obesity and insulin sensitivity [18]. Altogether, these results indicate that desaturase activities can be used as biomarkers of metabolic risk factors and morbid obesity.

Furthermore, dietary fatty acids regulate the desaturases [12] and are related to the development of MetS [19]. Therefore, to better manage metabolic disturbances in obesity, determining the

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fatty acid profile of serum lipids and desaturase activities may provide an efficient guide for customizing fatty acid nutrition, as well as the composition of dietary fatty acids. However, information about desaturase activity in children is limited [20,21].

In the present study, we analyzed the fatty acid composition in plasma phospholipids and estimated desaturase activities to investigate their association with metabolic risk factors, C-reactive protein (CRP) levels and insulin resistance in Japanese children.

2. Subjects and methods

The study enrolled 237 children (115 boys and 122 girls) aged 11.5 ± 1.5 years (mean ± SD), who attended one of two schools that participated voluntarily in a school-based screening and care program for life-style related diseases. All children were free from diseases other than dyslipidemia and obesity. Each child's standing height was measured to the nearest 0.1 cm using a manual height board, and weight was determined with electronic scales to the nearest 0.1 kg in light clothes. The relative weight was determined according to the standard weight for sex, age and height using data from the Ministry of Education, Science, Sports and Culture [22]. The waist circumference was measured at the level of the umbilicus, and the waist-to-height ratio (WHtR) was calculated. Systolic blood pressure (sBP) and diastolic blood pressure (dBP) were measured in the right arm with the subjects quietly seated, using an automatic device (Nihon Colin BP-103 N, Tokyo, Japan). All blood samples were obtained from the cubital vein in the morning after an overnight fast. Total cholesterol (TC), high density lipoprotein cholesterol (HDLC) and triglyceride (TG) levels were measured by delite enzymatic methods. Plasma insulin and glucose levels were determined, and the homeostasis model of assessment ratio (HOMA-R) was obtained using Matthews' formula as an index of insulin resistance [23]. Levels of CRP were measured using a validated immunoturbidimetric method [24].

The fatty acid composition of plasma phospholipids was analyzed by gas chromatography, and the desaturase activities were estimated as follows: SCD (16:1n-7/16:0: SCD16 and 18:1n-9/18:0: SCD18), D6D (20:3n-6/18:2n-6) and D5D (20:4n-6/20:3n-6).

In this study, metabolic risk factors in children were defined as follows: (i) abdominal obesity: WHtR ≥ 0.5; (ii) dyslipidemia: TG ≥ 120 mg/dl and/or HDLC < 40 mg/dl; (iii) elevated blood pressure: sBP ≥ 125 mmHg and/or dBP ≥ 70 mmHg; and (iv) elevated level of fasting plasma glucose ≥ 100 mg/dl [25]. MetS in children was defined as having abdominal obesity as well as two or more of the metabolic risk factors, according to the criteria for Japanese children [25].

Informed consent was obtained from each child and his or her parents. The study protocol was approved by the local ethics committee, which is composed of members of the school's health education committee. This committee includes members of the local Board of Education and representatives from Nihon University Itabashi Hospital.

2.1. Statistical analysis

The data are expressed as means ± SD. Group differences were assessed using an unpaired *t*-test. The correlation coefficients between two variables were determined by single regression analysis. Stepwise multiple regression analysis was performed to identify the variables explaining D5D or D6D activity. A *P*-value of less than 0.05 was considered to be statistically significant. All statistical analyses were conducted using the statistical package JMP (v9.0; SAS Institute Inc., Cary, NC, USA).

Table 1
Characteristics of the subjects.

	Boys $n=115$	Girls $n=122$	p value
Age (years)	11.5 ± 1.5	11.4 ± 1.5	0.70
Height (cm)	148.7 ± 11.8	146.4 ± 10.7	0.13
Weight (kg)	41.6 ± 11.5	40.7 ± 12.4	0.58
Relative weight (%)	2.0 ± 16.9	1.7 ± 17.9	0.88
Waist circumference (cm)	64.2 ± 10.1	63.2 ± 9.1	0.42
Waist-to-height ratio	0.43 ± 0.06	0.43 ± 0.05	0.87
Systolic blood pressure (mmHg)	107.6 ± 10.7	106.8 ± 10.7	0.57
Diastolic blood pressure (mmHg)	59.6 ± 6.7	60.7 ± 7.8	0.23
Total cholesterol (mg/dl)	167.9 ± 23.2	176.0 ± 22.0	< 0.01
HDL cholesterol (mg/dl)	65.2 ± 13.1	65.0 ± 12.3	0.89
Triglycveride (mg/dl)	56.6 ± 32.2	61.4 ± 35.8	0.23
Glucose (mg/dl)	89.0 ± 5.1	87.4 ± 5.8	0.03
Insulin (μU/ml)	8.1 ± 5.3	11.0 ± 6.6	< 0.01
HOMA-R	1.8 ± 1.2	2.2 ± 1.5	< 0.01
CRP	0.028 ± 0.045	0.024 ± 0.028	0.45
Metabolic syndrome	2/115 (1.7%)	0/122 (0.0%)	

Values are mean ± SD.

3. Results

3.1. The prevalence of metabolic risk factors

The characteristics of the subjects are shown in Table 1. Boys had lower TC and insulin levels, lower HOMA-R and higher glucose levels than girls. No other sex differences were observed.

The prevalence of metabolic risk factors was as follows: 28 children with abdominal obesity (11.8%; 16 boys, 12 girls), 12 children with hypertriglyceridemia (5.1%; 6 boys, 6 girls), 4 children with reduced HDLC levels (1.7%; 2 boys, 2 girls), 15 children with elevated sBP (6.3%; 7 boys, 8 girls), 19 children with elevated dBP (8.0%; 6 boys, 13 girls) and 7 children with elevated fasting glucose levels (3.0%; 5 boys, 2 girls). Among the children with abdominal obesity, we found 10 children presenting with an additional risk (4 with dyslipidemia, 5 with high BP, 1 with a high fasting glucose level) and 2 children (0.8%; 2 boys) with two or more risk factors, diagnosed as MetS.

3.2. Fatty acid composition of plasma phospholipids, and desaturase activities

(Table 2) The MUFA levels (16:1n-7, 18:1n-9) and SCD activities (SCD16, SCD18) showed no sex differences. For the n-6 PUFAs, the LA level was lower in boys than in girls, whereas the levels of dihomo-γ-linoleic acid (DHGL; 20:3n-6) and AA were higher in boys. Moreover, in boys, D6D activity was significantly higher, and D5D activity tended to be lower. Among the n-3 PUFAs, the ALA level was lower in boys; however, no other sex differences were demonstrated, including docosahexaenoic acid (DHA; 22:6n-3) or EPA levels.

3.3. Relationship between metabolic risk factors, CRP levels, HOMA-R and desaturase activities

(Table 3) In boys, D6D activity had significant positive associations with WHtR, TG levels, CRP levels, sBP and dBP and a negative association with HDLC levels. Fasting glucose levels were not correlated with D6D activity; however, fasting insulin levels and HOMA-R correlated positively with D6D activity, whereas D5D activity had a significant relationship with all metabolic risk factors, CRP levels and HOMA-R. In girls, no association was demonstrated between BP, fasting glucose levels, CRP levels and desaturase activities. However, WHtR, TG and

HDLC levels and HOMA-R had significant relationships with both D6D and D5D activities. SCD activity (SCD16 or SCD18) did not correlate with any metabolic risk factors other than WHtR in either sex.

Stepwise multiple regression analysis was performed to determine the major contributors to D5D or D6D activity. Based on the results of simple regression analyses, we used WHtR, TG, HDLC and CRP levels, sBP, dBP and HOMA-R as independent variables in boys and WHtR, TG and HDLC levels and HOMA-R as independent variables in girls. In boys, WHtR and TG levels emerged as significant determinants, explaining 33.3% of the D6D activity variability and 23.4% of the D5D activity variability. In girls, only the TG level emerged as a significant determinant, explaining 26.1% of the D6D activity variability and 17.8% of the D5D activity variability.

3.4. D6D and D5D activities, HOMA-R and CRP levels in children with or without abdominal obesity

(Fig. 1) D6D and D5D activities, HOMA-R and CRP levels were compared between children with and without abdominal obesity.

Table 2
Fatty acid composition in plasma phospholipids and desaturase indices.

	Boys $n=115$	Girls $n=122$	p value
14:0	0.30 ± 0.16	0.34 ± 0.14	0.04
16:0	25.2 ± 1.1	25.1 ± 1.1	0.36
16:1n-7	0.89 ± 0.32	0.96 ± 0.49	0.23
18:0	14.6 ± 0.8	14.6 ± 0.8	0.71
18:1n-9	9.6 ± 1.0	9.4 ± 0.9	0.10
18:1n-7	1.6 ± 0.2	1.7 ± 0.2	0.30
18:2n-6	20.0 ± 2.2	20.7 ± 2.0	0.02
18:3n-6	0.19 ± 0.12	0.18 ± 0.09	0.53
18:3n-3	0.26 ± 0.08	0.30 ± 0.10	< 0.01
20:3n-6	2.5 ± 0.5	2.3 ± 0.5	< 0.01
20:4n-6	9.2 ± 1.3	8.9 ± 1.1	0.03
20:4n-3	0.13 ± 0.07	0.13 ± 0.07	0.98
20:5n-3	1.4 ± 0.7	1.5 ± 0.8	0.27
22:4n-6	0.31 ± 0.06	0.28 ± 0.06	< 0.01
22:5n-6	0.24 ± 0.08	0.22 ± 0.06	0.04
22:5n-3	1.0 ± 0.2	1.0 ± 0.2	0.54
22:6n-3	6.1 ± 1.2	6.0 ± 1.2	0.65
SCD16 activity	0.036 ± 0.013	0.038 ± 0.019	0.20
SCD18 activity	0.66 ± 0.07	0.64 ± 0.07	0.20
D6D activity	0.13 ± 0.04	0.11 ± 0.03	< 0.01
D5D activity	3.8 ± 0.9	4.0 ± 1.0	0.07

Values are mean ± SD.

The boys with abdominal obesity showed a higher D6D activity (0.18 ± 0.04), a lower D5D activity (3.0 ± 0.6), a higher HOMA-R (2.8 ± 1.6) and higher CRP levels (0.098 ± 0.072) than the boys without abdominal obesity (0.13 ± 0.03, 3.9 ± 0.9, 1.3 ± 0.7 and 0.015 ± 0.019). The girls with abdominal obesity also showed a higher D6D activity (0.16 ± 0.03), a lower D5D activity (3.1 ± 0.3) and a higher HOMA-R (4.1 ± 1.9) than the girls without abdominal obesity (0.12 ± 0.03, 4.1 ± 1.0 and 1.8 ± 1.1). However, CRP levels in girls demonstrated no significant difference between those with and without abdominal obesity (0.035 ± 0.035, and 0.023 ± 0.028, respectively). The AA levels in the children with abdominal obesity (9.2 ± 1.3, and 8.9 ± 0.8 w/w%) were not different from those in the children without abdominal obesity (9.2 ± 1.3, and 8.8 ± 1.1 w/w%) in either sex.

4. Discussion

In this study of Japanese children, we found that D6D and D5D activities as estimated from the phospholipid fatty acid profile had a significant association with individual metabolic risk factors, fasting insulin, HOMA-R, CRP levels and abdominal adiposity.

Our results for desaturase activities in children with metabolic risk factors are compatible with some previous studies. Japanese studies in middle-aged men [7] and in young women [9] demonstrated that D6D activity was positively associated with metabolic risk factors and HOMA-R, while D5D activity had a negative association. The same relationship was also shown in Koreans [26]. Hungarian children with MetS had lower D5D activities than controls [21]. Furthermore, in a long-term follow-up of more than 20 years, D5D activity at baseline predicted the development of MetS independently of lifestyle factors such as smoking, physical activity and body mass index [6]. Therefore, estimated D6D and D5D activities may be useful as biomarkers for individual metabolic risk factors. However, we found sexual dimorphism in the relationship between CRP levels and the D6D and D5D activities. Increased D6D activity and decreased D5D activity were associated with elevated CRP levels only in boys. These findings may be partly explained by the effects of sex hormones, which affect D6D and D5D activities [27] and CRP levels. Another sex difference, which was demonstrated by stepwise regression analysis, was that abdominal adiposity was the determinant of D6D and D5D activities only in boys. During puberty, body composition changes occur differently between in the sexes. Fat accumulations in most of the girls in this study may be physiological; therefore, abdominal adiposity was not a major factor affecting n-6

Table 3
Correlation coefficients between metabolic risks, HOMA-R, CRP and desaturase activities.

	Boys				Girls			
	SCD16	SCD18	D6D	D5D	SCD16	SCD18	D6D	D5D
Relative weight	0.013	−0.274**	0.464***	−0.346***	−0.064	−0.225*	0.421***	−0.291**
WHtR	−0.034	−0.308***	0.515***	−0.358***	−0.079	−0.270**	0.416***	−0.301***
SBP	0.118	0.030	0.199*	−0.199*	0.039	−0.119	0.094	−0.032
DBP	0.027	0.015	0.210*	−0.264**	−0.043	−0.075	0.082	−0.080
HDLC	0.010	0.182	−0.265**	0.332***	−0.029	0.059	−0.382***	0.224*
TG	0.161	0.068	0.498***	−0.518***	0.008	0.054	0.445***	−0.430***
Glucose	0.064	−0.045	0.166	−0.234*	−0.070	−0.042	−0.015	0.015
Insulin	−0.034	−0.135	0.378***	−0.288**	−0.008	−0.061	0.377***	−0.310***
HOMA-R	−0.028	−0.140	0.364***	−0.298**	−0.018	−0.061	0.366***	−0.302***
CRP	−0.025	−0.164	0.406***	−0.332**	0.125	−0.018	0.085	−0.172

* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

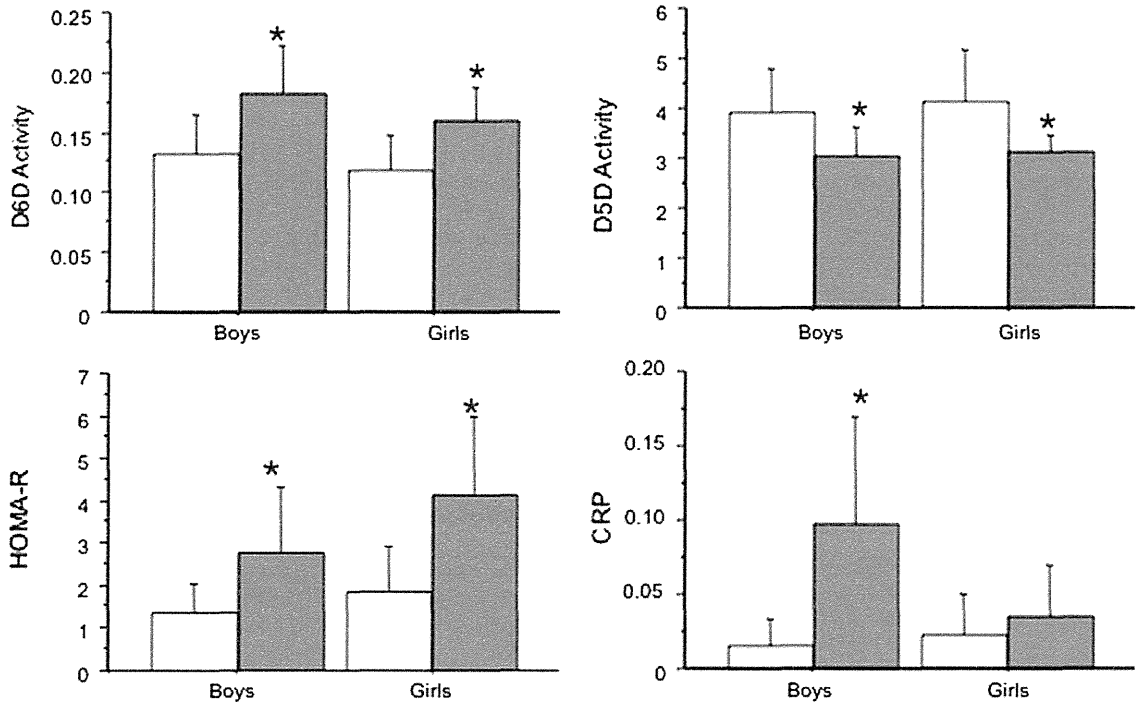

Fig. 1. Desaturase activities, HOMA-R and CRP levels in children with and without abdominal obesity. *: $p < 0.05$ vs. children without abdominal obesity by unpaired *t*-test. D6D: delta-6 desaturase, D5D: delta-5 desaturase, HOMA-R: homeostasis model of assessment ratio, CRP: C-reactive protein.

desaturating metabolism. However, we could not obtain pubertal stages or levels of sex hormones, which might provide a possible mechanism for our findings.

Some forms of obesity, especially abdominal obesity, are associated with chronic low-grade inflammation, which accelerates atherosclerosis and insulin resistance [28,29]. In addition, PUFAs are precursors of the lipid mediators known as eicosanoids, which play important roles in the regulation of inflammation. Eicosanoids are derived from PUFAs via the D6D and D5D metabolic pathways. AA is a direct precursor of inflammatory eicosanoids, and the AA content of phospholipids was most sensitive to FADS gene variants [30]. Furthermore, in patients with coronary artery disease [16], FADS gene polymorphisms were related to the AA/LA ratio and increased inflammation. Therefore, D6D and D5D activities may be predisposing factors for chronic inflammation. In our study, abdominal adiposity did not relate significantly to AA content, but was significantly associated with CRP levels in boys. Our findings, therefore, suggest that the chronic inflammation that is typical of abdominal obesity may be associated with the altered n-6 PUFA desaturating metabolism in boys.

The treatment of MetS in children is not pharmacological but instead requires lifestyle changes, such as to physical activity and diet. Total dietary fat and saturated fat are not only associated with obesity but also affect metabolic risk factors [31]. Therefore, dietary fatty acid interventions are recommended [32]. However, because of individual variability in the efficacy of dietary modification on metabolic disturbances, personalized nutrition based on genetic backgrounds has been attempted. Regarding PUFAs, Shen et al. suggested that interleukin-1beta genetic variants are associated with chronic inflammation and the risk of MetS and that genetic influences are more evident in subjects with low n-3 PUFA intake [33]. FADS gene variants also affect phospholipid fatty acid composition and inflammation [29], suggesting that individuals could require different amounts of dietary PUFAs to achieve comparable biological effects. However, identifying genetic backgrounds in clinical settings is challenging. According to our results, D6D and D5D desaturase activities may provide a guide for customizing fatty acid nutrition in place of the genetic background. A longitudinal study of fatty acid composition in children demonstrated that dietary fat has little effect on longitudinal changes in n-6 PUFAs in phospholipids, whereas tracking was observed for the AA/LA ratio [34], which represents n-6 PUFA metabolism including delta-6 and -5 desaturations. Therefore, the desaturase activities might reflect individual endogenous n-6 PUFA metabolism rather than nutritional status.

This study was not designed to obtain information about diet. Therefore, the influence of dietary fatty acid on desaturase activities, inflammation and insulin resistance could not be evaluated. However, our results demonstrated that D6D and D5D activities might be biomarkers for comorbidity of abdominal obesity. Further studies addressing the effects of dietary fatty acids on D6D and D5D activities should be conducted to evaluate them as a guide for determining nutritional fatty acid requirements.

In conclusion, n-6 PUFA metabolism is associated with abdominal adiposity, and the estimated D6D and D5D activities might be potential biomarkers for metabolic risk factors in Japanese children. In addition, the assessment of the n-6 PUFA desaturation pathway by desaturase activities could provide a new approach to establish personalized fatty acid nutrition for abdominal obesity in future studies.

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Ⅱ 基礎

小児の肥満・メタボリックシンドロームの現状と対策

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Key words:
obesity, metabolic syndrome, insulin resistance, adipokines

Current Status and Strategies for Obesity and Metabolic Syndrome in Children and Adolescents

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A new concept and definition for metabolic syndrome pronounced in 2005 in Japan elucidated the importance of abdominal obesity and insulin resistance. Until then, treatment and research for obesity might be a minor and an unsolved field in both internal medicine and pediatrics. Especially in pediatrics, we were educated and we also sent messages based on personal experience and/or information because of the paucity of evidence. Are the following messages true for recent Japanese children and adolescents?

1. Childhood and adolescent obesity has been increasing.
2. Childhood obesity will disappear after entering school.
3. Do not worry about mild obesity.
4. Childhood obesity is mainly associated with maternal obesity.
5. There is no concern about metabolic syndrome in pediatrics.
6. It is difficult to treat obesity in both the adult and pediatric population.

The author presents the current status and strategies for obesity and metabolic syndrome based on the recently obtained evidences in pediatric population.

要 旨

2005年に日本においてメタボリックシンドロームという新しい概念と診断基準が発表され，内臓肥満とインスリン抵抗性の重要性が俄かにクローズアップされた．それまで肥満を治療・研究することは，内科においても小児科においても循環器医療の中ではminorな，放置してよいカテゴリーであったと思っている．特に小児科領域ではデータが少なく，私たちはデータに基づかない個人的な経験，情報で教育され，また伝達していたように思う．私が長い間教えられてきた次の命題は現在の日本人小児にあてはまるのだろうか．

1. 小児期の肥満は増え続けている
2. 小学校に行けば肥満はなくなる
3. 軽度肥満なら心配することはない
4. 子どもの肥満は母親との関係が強い
5. 子どものメタボは気にするほどではない
6. 成人だけでなく小児期・思春期の肥満の治療は難しい

最近発表されたエビデンスに基づいて小児の肥満，メタボリックシンドロームの現状と対策を考えてみたい．

はじめに

文部科学省は学校保健統計調査報告書の中で児童生徒の身長・体重相関表を1948年から公表している．鹿児島市では1992年より肥満度40％以上（1998年からは35％以上）の小学生に対して無料の小児生活習慣病予防検診と事後処置としての相談室を続けてきた．私の病院では2005年より肥満治療を開始した．これらのデータから日本人小児の肥満・メタボリックシンドロームの現状と対策を考えてみたい．

1．小児期の肥満は増え続けている？

小児期で肥満になる時期は，全世界で胎児期，幼児期後半(4～6歳)，思春期の3時期と報告されてきた[1]．日本でもこの事実があてはまるか，学校保健統計調査報告書をもとに5～17歳の1980～2010年の肥満頻度の変化を検討した[2,3]．

肥満の程度の判定には肥満度を用いた．6，9，12，15歳の肥満頻度の横断的変化をみると，男女のどの年齢でも2000年前後に肥満頻度のピークを迎え，その後漸減している(Fig. 1)．6歳と9歳の肥満頻度の差は極めて大きいことがわかる．

Fig. 2に出生年ごと(5年ごと)のコホートの縦断的変化を示した．1990年生まれのコホートは，9歳から17歳まで一番高い肥満頻度で成長していたことがわかる．1990年は日本のバブル期(1986年11月～1991年2月)にあたる．バブル期以降はより低い肥満頻度で成長している．日本では小児の肥満頻度は減少傾向に向かっている．

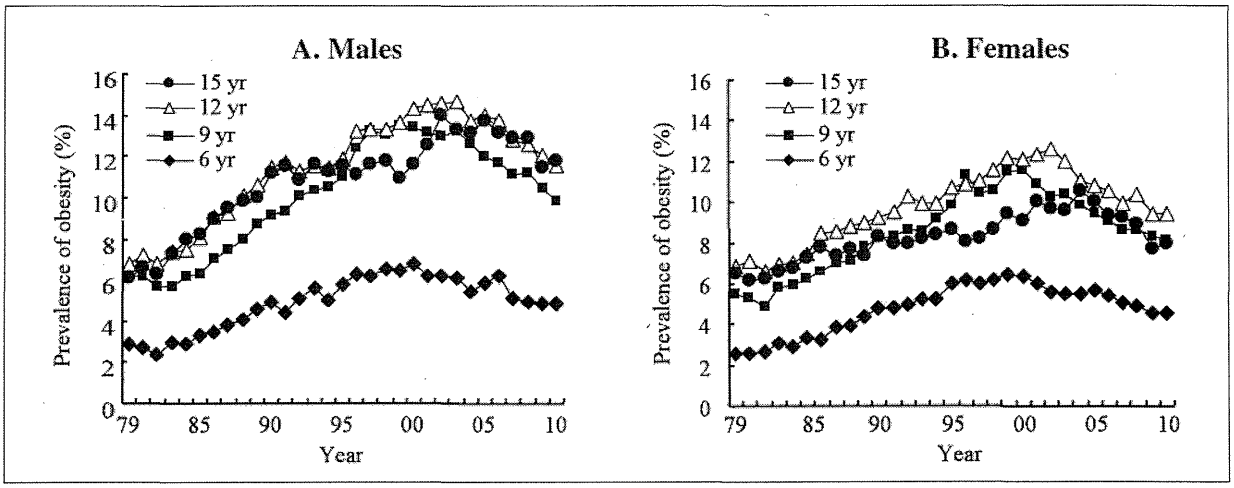

Fig. 1　Cross-sectional changes in the prevalence of obesity.
(Figure 1 in this review was rearranged from the figure in the paper now in submission[3]. Then, originality is present in the paper in submission[3])
The prevalence of obesity was highest in the late 1990s and early 2000s in both males (A) and females (B).

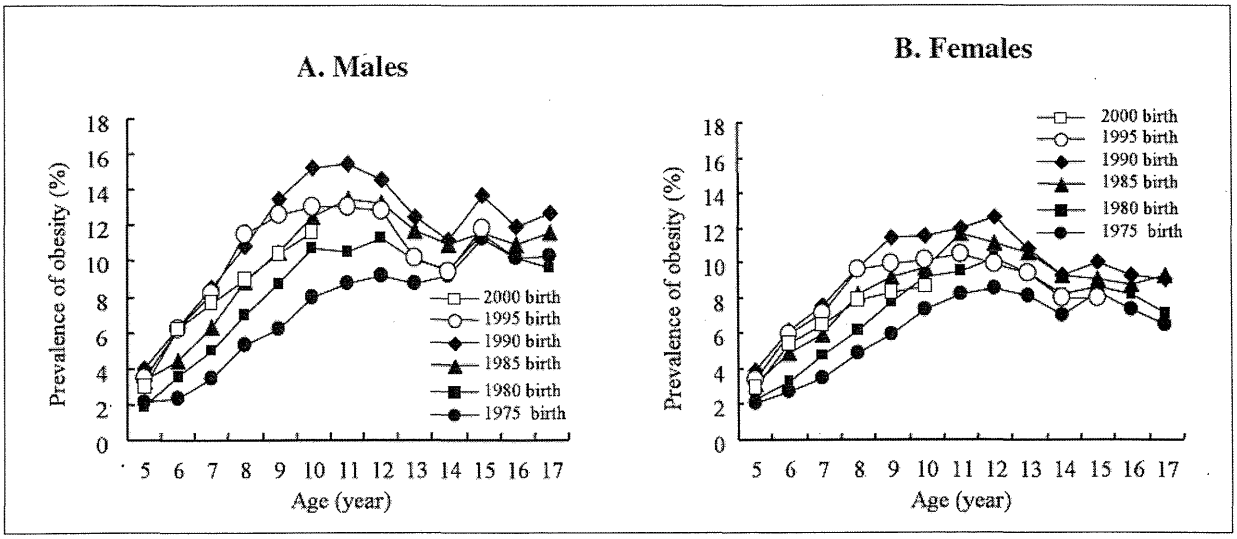

Fig. 2　Longitudinal changes in the prevalence of obesity in the 5-year interval birth cohorts at each year of age in males (A) and females (B).
(Figure 2 in this review was rearranged from the figure in the paper now in submission[3]. Then, originality is present in the paper in submission[3])
The 1990 birth cohort had the highest prevalence of obesity between ages of 9 and 17 years.

2. 小学校にいけば肥満はなくなる？

Fig. 2は別の問題も示している．小学校入学時(5～6歳になる時)男女とも頻度が急上昇し，小学校低学年の間は頻度が急上昇を続けることである．

2010年の5～17歳の肥満頻度を横断的にみると，肥満度は小学生の間は増え続け，中学校で一時減少するものの，高校生でまた増加する(Fig. 3)．16歳男子だけで全国に12万人の高度肥満が存在する．

日本での小児期・思春期の肥満予防対策の対象は小学校と高校と考えられる．特に小学校入学時から数年間の肥満の出現防止ができれば，高校卒業時の肥満頻度は10%近く減少できる．その中でも男子に対する対策は緊急課題である．

【用語の解説】

メタボリックシンドロームの源は内臓肥満とインスリン抵抗性といわれている．インスリン抵抗性を含め，いくつかの用語を解説したい．

(1)インスリン抵抗性[4]

標的細胞または標的臓器のインスリンに対する反応性が減少した状態，臨床的には高インスリン血症の状態をいう．インスリン抵抗性の存在は前糖尿病状態といえる．

(2)Homeostasis model assessment of insulin resistance(HOMA-IR)[5]

インスリン抵抗性の指標の1つである．(空腹時血糖)×(空腹時インスリン)／405で計算する．

(3)アディポネクチン[6]

脂肪細胞に特異的に発現している．抗糖尿病作用，抗動脈硬化作用，抗炎症作用を持つ．一方でTNF-αはアディポネクチンの遺伝子発現を転写レベルで抑制する．酸化ストレス，アンジオテンシンII，テストステロンなどにより抑制される．最近，心筋細胞に対する抗線維化作用も有していることが示された．肥満では，絶対的に脂肪細胞が増加しているにもかかわらずアディポネクチンの血中レベルが低下する機序については十分解明されていない．

(4)レプチン[7]

主に脂肪細胞から分泌され，脂肪細胞の肥大化によって分泌量が増加する．レプチンの作用点は視床下部に発現している受容体であり，食欲の抑制，交感神経活動を介した熱産生，褐色脂肪組織や骨格筋での糖利用促進作用を持つ．肥満状態ではレプチンの作用不全が生じ，血中濃度が上昇するにもかかわらず，濃度に見合ったレプチン作用が発揮されない(レプチン抵抗性)．

(5)肥満度

肥満度(%)｛(現在の体重÷標準体重)－1｝×100の算出に用いられる標準体重計算式は学校保健統計調査報告書をもとに10年ごとに改訂され，現在は1990年と2000年の報告書から作られた計算式が使われている．本報告では1990年版を用いた．

(6)心血管危険因子 cardiovascular risk factors

成人領域における心筋梗塞，糖尿病，脳卒中を引き起こす因子を指す．多くはメタボリックシンドローム

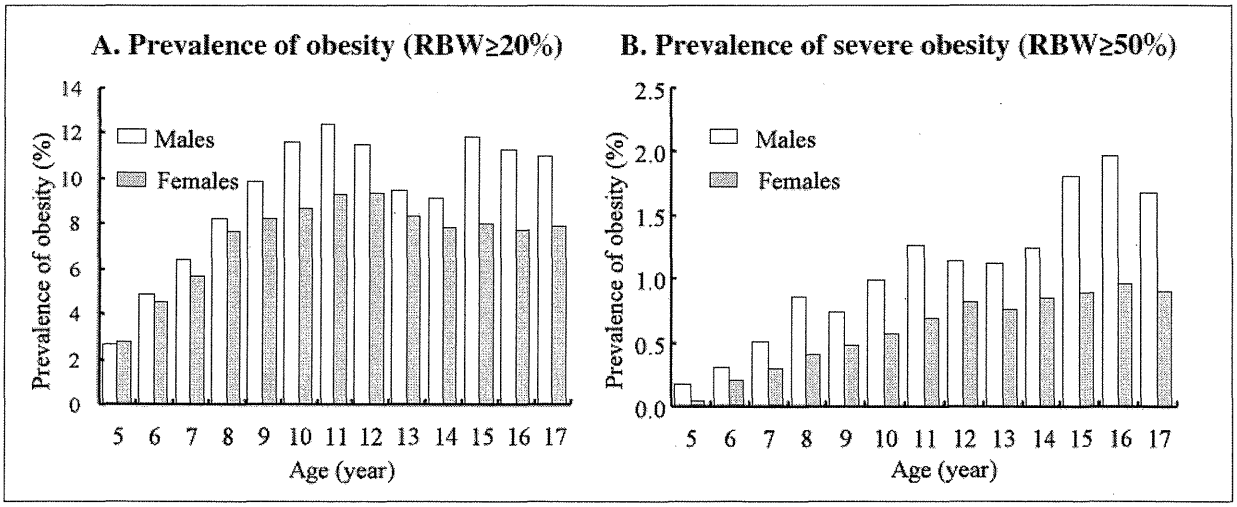

Fig. 3 Prevalence of obesity {relative body weight (RBW) ≥20%)} (A) and that of severe obesity (RBW ≥50%) (B) in males and females.
(Figure 3 in this review was rearranged from the figure in the paper now in submission[3]. Then, originality is present in the paper in submission[3])

の診断基準である内臓肥満，高血圧，高中性脂肪血症，低HDLコレステロール血症，空腹時高血糖が使用される．尿酸，ALTが採用される時もある．肥満時のALT高値に対して"脂肪肝"が使用されるが，医学論文的にはNonalcoholic Steatohepatitis (NASH)，非アルコール性脂肪性肝炎が用いられる．

3．軽度肥満なら心配することはない？

軽度肥満は心配することはない，と教えられてきた．高コレステロール血症や高中性脂血症がなければ"単純性肥満"と診断し"合併症はないけどやせたほうがいいですよ"と指導していた．これでは心配して来た母親の減量に対するmotivationはなくなる．子どものインスリン抵抗性を成人と比較検討した[8]．

男児では健常群から軽度肥満になる時と高度肥満になる時，急にHOMA-IR値が悪化する(Fig. 4A)．日本人成人の肥満は日本の肥満基準(BMIで25以上)と欧米の基準(30以上)に二分した[9]．軽度肥満男子のインスリン抵抗性は日本の肥満基準を満たす成人とほぼ同じ値である(Fig. 4B)．論文ではこの群のBMIの平均値は26.6になっている．身長が165 cmなら72.4 kg，175 cmなら81.5 kgである．

女児では肥満度が10%増すごとにインスリン抵抗性が悪化する(Fig. 4C)．軽度肥満女児のインスリン抵抗性が日本の肥満基準を満たす成人と同じ値なのは男児と同様である．中等度肥満群の女児は欧米での肥満基準を満たす成人女性と同じである(Fig. 4D)．この群のBMIの平均値は34.4となっている．身長が155 cmなら体重82.6 kg，165 cmなら93.7 kgである．

血管の病気は20～30年で形成されると考えられる．平均9歳の軽度肥満の小学生は，日本の肥満基準を満

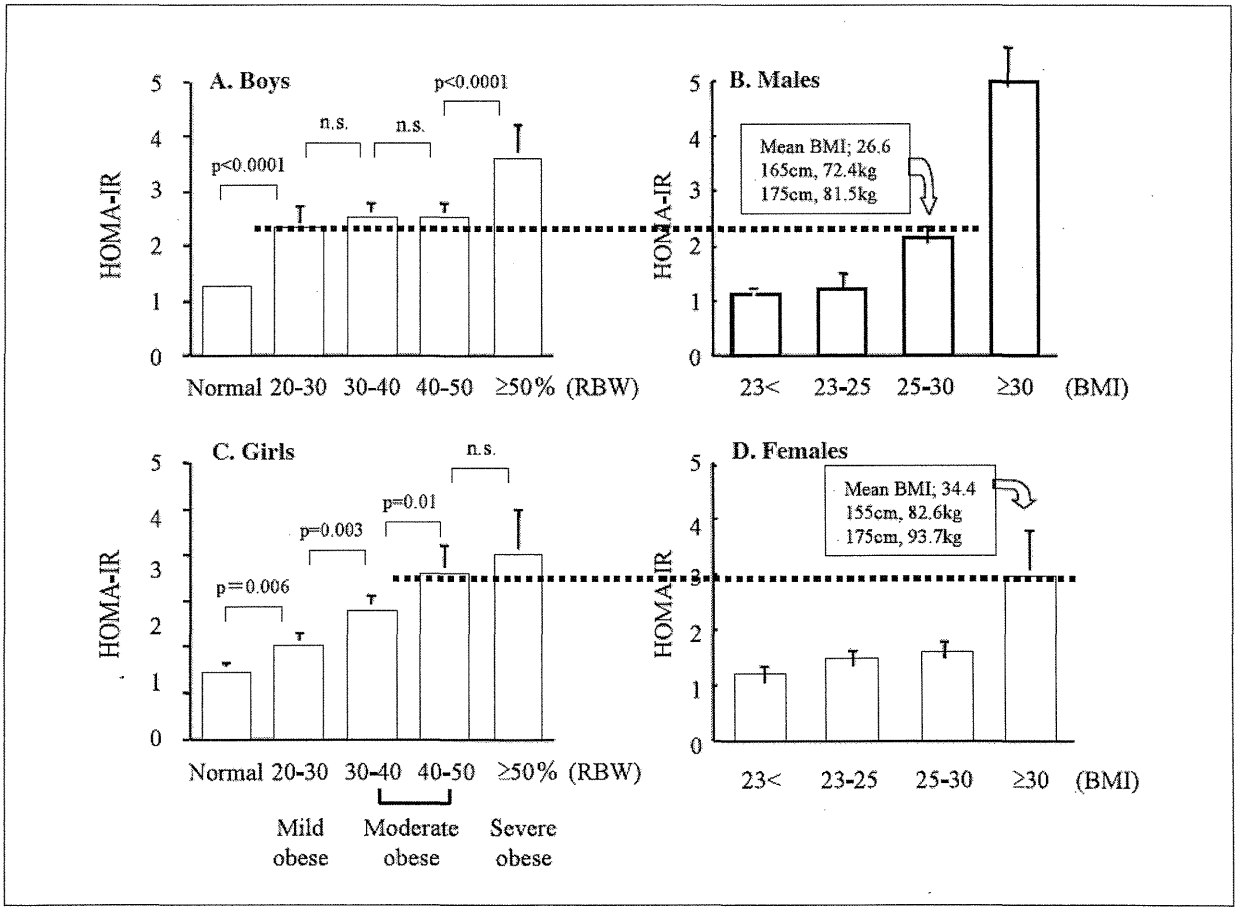

Fig. 4　Changes in HOMA-IR levels among normal and obese boys (A) and girls (C) and those among adult males (B) and females (D). (The figures a and c were rearranged from those in the reference 8)
The HOMA-IR levels in mild obese boys and girls (RBW; 20-30%) (between 6 and 12 years of age) correspond to those of obese Japanese adults (BMI; 25-30) (between 30 and 60 years of age). Importantly, the HOMA-IR levels in moderate obese girls (RBW; 40% to 50%) correspond to those of obese Japanese adults (BMI ≥30) who fulfilled the international criteria of obesity.

Table 1 Risk of presence of adolescent obesity associated with parental obesity.

	Males		Females	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Paternal obesity	2.47 (1.28, 4.77)	0.007	1.09 (0.44, 2.70)	0.86
Maternal obesity	1.74 (0.71, 4.26)	0.23	3.00 (1.13, 8.00)	0.03
Combined parental obesity	6.36 (1.86, 21.8)	0.003	2.72 (0.56, 13.2)	0.21

Parental obesity was defined as a BMI ≥25kg/m^2, based on the recommendation by The Examination Committee of Criteria for Obesity Disease for the Japanese adult population[11]. Therefore, adolescent obesity in the present study was defined using age- and sex-specific International Obesity Task Force standard corresponding to BMI cutoffs of 25 kg/m^2 at age 18 years[12].
Abbreviation; CI: confidence interval, OR: odds ratio.

たす成人のインスリン抵抗性と同じレベルで生活している．彼らは29～39歳の時に糖尿病，心筋梗塞，脳血管障害を発症することになる．中等度肥満の女児は欧米の基準を満たす成人と同じ値である．この値なら血管病を発症するのに10～20年で十分であろう．

平成20年度から40歳以上の特定健診・特定保健指導が始まった．さらに若い年齢への対応が望まれていたが，リーマンショックや今年の東北大震災・原発事故後の経済状態は悪化し続けている，私たち小児科医，小児循環器医が患児・家族・地域社会と一緒になり，限りを尽くさなければ小児期への対策は始まらないと思う．

4．子どもの肥満は母親との関係が強い？

平成18～20年度の厚生労働科学研究費で高校生ボランティアの生活習慣病検診を行い，1,358名に参加してもらった．うち，アンケートにすべて答えてもらった755名について両親のBMIと高校生のBMIとの関係を調査した[10]．Table 1の通り，男子の肥満は父の肥満と，女子の肥満は母の肥満と関係していた．母親だけでなく，父親へのアプローチも重要である．高校生において心血管危険因子出現予防の最も大きな因子は体育系部活への参加であった[10]．

5．子どものメタボは気にするほどではない？

前述した高校生ボランティアのデータで検討してみた[13]．心血管危険因子値の高校生用の基準値としては，ボランティア高校生の90パーセンタイル値を用いた．腹囲(男子≥80 cm，女子≥79 cm)，収縮期血圧(男子≥129 mmHg，女子≥119 mmHg)，拡張期血圧(男子≥75 mmHg，女子≥73 mmHg)，中性脂肪(男子≥106 mg/dl，女子≥95 mg/dl)，空腹時血糖(男子≥96 mg/dl，女子≥93 mg/dl)，HDL-cholesterol(男子＜46 mg/dl，女子＜50 mg/dl)とした．参加した健康ボランティア高校生であっても，心血管危険因子が1個増えるごとにすべての心血管危険因子値および，アディポサイトカイン値が悪化していた．代表として，収縮期血圧，中性脂肪，レプチン，アディポネクチンの値をFig. 5に示した．それぞれの心血管危険因子値に強い性差があることがわかる．心血管危険因子数と各因子値の変化，性差については小学生でも検討したが，同様であった[14]．

6．成人だけでなく小児期・思春期の肥満の治療は難しい？

肥満治療は最初の動機づけがうまくいけばそれほど困難なことではないのではないか，と考えてきた．肥満外来時，噛むことにより摂取量制限なしに減量できる，歩くことは脂肪を減少させる最良の方法である，治療初期に減量できれば，治療を継続できる，ことを理解してもらい，下記のような約束事を決め，"約束事の実行表"に○，×を記載してもらった．

1回口に入れたら20回以上噛む，休日は1万歩以上歩く，野菜をたくさん食べる，砂糖の入った飲料は飲まない．

受診回数4回以上および3カ月以上経過観察できた58名中，肥満度がわずかでも減少した人は56名(97%)，10%以上減少した人は45名(78%)，20%以上減少した人が22名(38%)である[15]．肥満治療に成功する予測因子は初回から2回目受診間での大きな肥満度減少であった．成人では5%の体重減少を成功基準としている．小児期での肥満治療は本人が治療初期に強いmotivationを持てば成功すると思う．

小児期・思春期の肥満・メタボリックシンドロームに関するデータが不足している．データに基づいた小児期・思春期肥満に対する一次・二次予防ガイドライン作成が必要である．

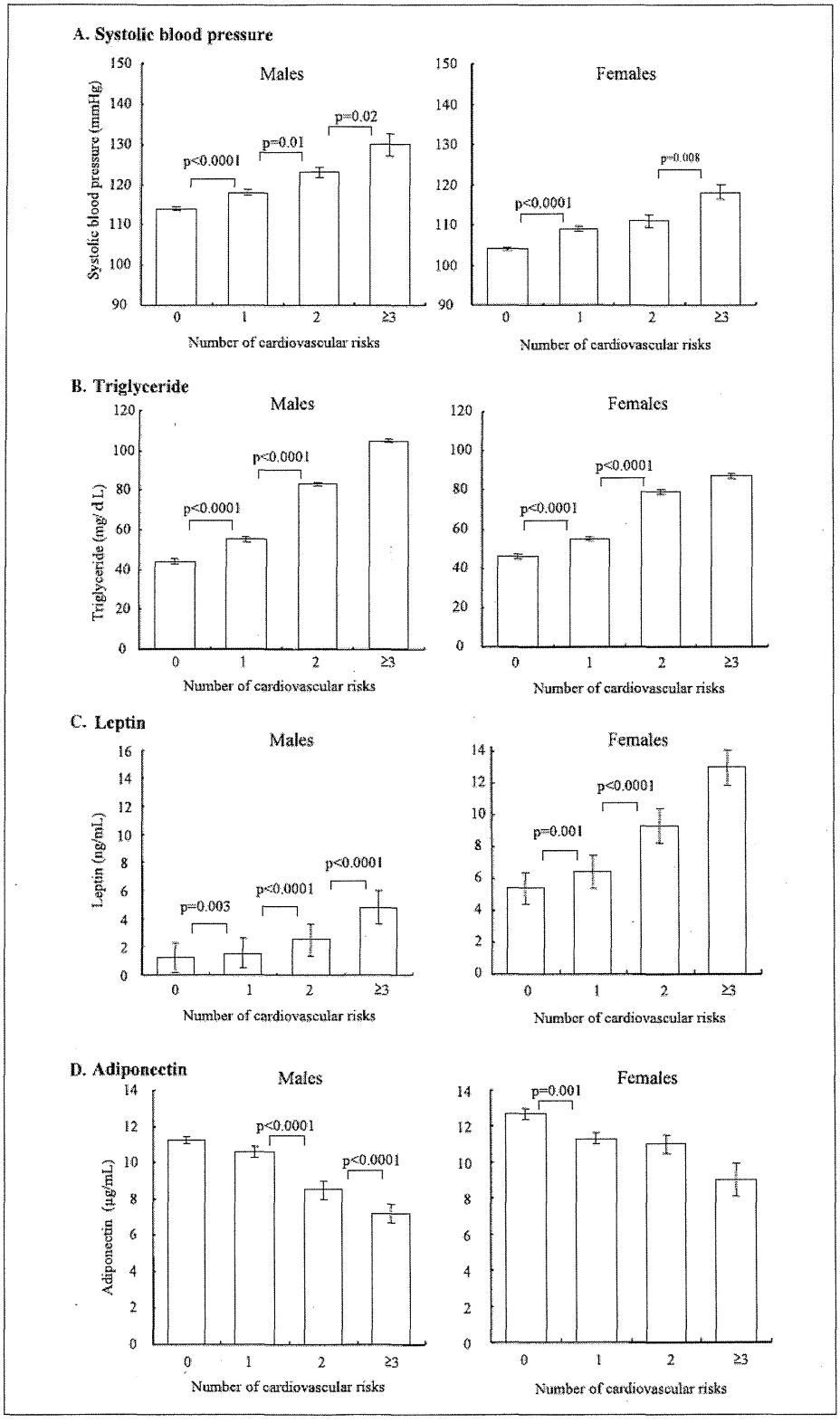

Fig. 5 Association between the total number of cardiovascular risk factors and the levels of systolic blood pressure (A), triglycerides (B), leptin (C), and adiponectin (D). Each bar shows the mean and the standard error of the mean. Statistical analysis was carried out by Tukey's multiple comparison, and *p* values were shown when the value was significant between any two successive groups.

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3．学校における生活習慣病検診の現状と歩むべき方向

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1. 小児期・思春期の肥満頻度の現状

小児期・思春期の肥満の頻度は上昇を続けている、と書かれている原著論文や総説を目にする。一部は正しく、一部は間違いである。

2010年の学校保健統計調査報告書から肥満度20%以上の頻度を5歳から17歳まで横断的にみると、小学生時代に肥満頻度が急上昇することがわかる（図1）。肥満度50%以上の高度肥満の頻度も同様に上昇するが、特に高校生男子の肥満頻度の上昇が著明である（図2）。それでは肥満頻度は各年齢で上昇を続けているのだろうか。横断的ではなく、出生年コホート毎で男子を例にとって縦断的に見てみる（図3)。1990年出生したコホートは、1975年出生コホートに比し、小学生時代に肥満頻度を急速に悪化させながら成長していったことがわかる。1990年出生コホートは日本のバブル期（1986～1991年）の最後の頃に出生したコホートである。1995年出生コホートは9歳頃より、2000年コホートは7歳頃より、1990年出生コホートより低い肥満頻度で成長している。軽度肥満以上の頻度は減少しつつある。しかし、小学生時代に肥満頻度が上昇し続けるのは現在でも同様である。

肥満頻度ではなく、肥満の重症度はどうであろうか。肥満度の98パーセンタイル値がどのように変化したかを男子でみたのが図4である。高度の肥満のレベルの変化を横断的にみたものである。図には1980年、2000年、2010年での98パーセンタイル値を図示してある。5歳から17歳まで1980年から2000年までの20年間に10%から15%も上昇している。2010年になると小・中学生では全学年で肥満度の98パーセンタイル値は5%程度減少する。ところが16、17歳の高校生男子は減少するどころか、かえって増加を続けている。

日本における小児期・思春期の肥満の問題点は、小学生時代に肥満頻度の上昇が続いていること、高校生の肥満の重症度が悪化し続けていること、にある。メタボリックシンドロームの上流に肥満、特に内臓肥満があるとすれば、介入の対象および時期はこの二つのグループの問題点の解決を目標にしていく必要があると考えられる。

2. 学校における生活習慣病検診の歩むべき方向

児童生徒の生活習慣病対策を行うためには数多くの問題が残されている。これに関しては平成25年度の「厚生労働科学研究費補助金公募要項」の新規課題で要求されている点が、的を射た内容と考えられる。そのまま転載させていただきたい。

公募課題：小児期からの生活習慣病対策及び生涯の健診等データの蓄積・伝達の在り方等に関する研究

小児期の肥満や生活習慣が、将来の循環器疾患等のリスクと関連することが報告されている。小児に対する生活習慣病スクリーニングとそれに連動した介入については、既存のエビデンスの整理や関係者のコンセンサスが得られていない。また、乳幼児健康診査、就学時健康診断、小・中・高校での学校健診のデータは、個人の手元に情報が残らないことや各段階での利活用にとどまっていること等により、子ども自身の健康管理や成人後の健康づくり等には十分に活用できていないとの指摘がある。

本研究では、学校教育担当者の負担を考慮し

図1

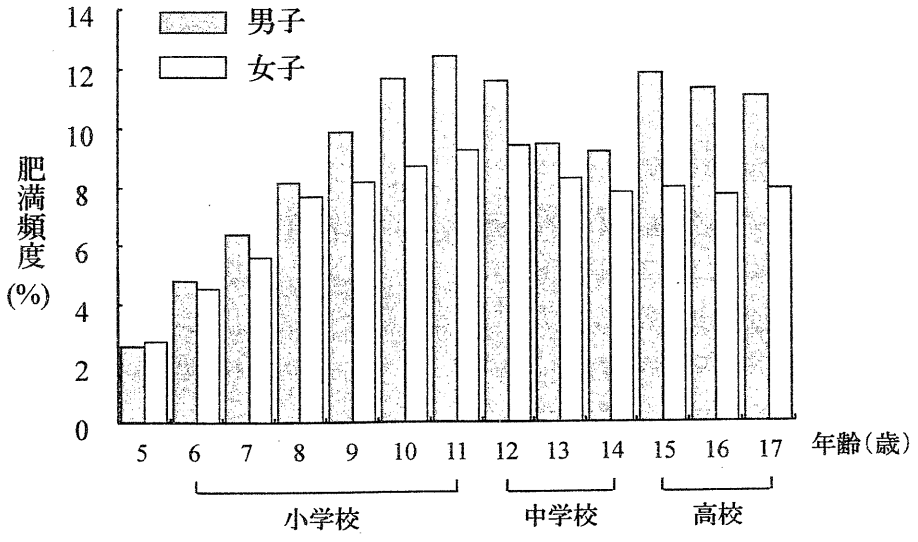

図1　2010年の5歳～17歳の男女別肥満頻度の推移　　(参考論文1より)

5歳から17歳の2010年の肥満度20%以上の頻度を示した。

□は男子、□は女子を示す。

図2

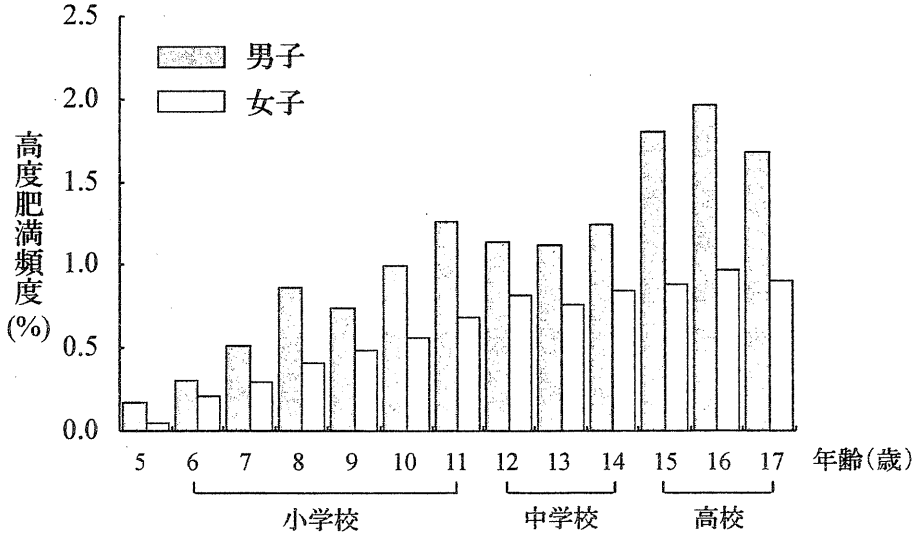

図2　2010年の5歳～17歳の男女別高度肥満頻度の推移

5歳から17歳の2010年の肥満度50%以上の頻度を示した。

□は男子、□は女子を示す

図3

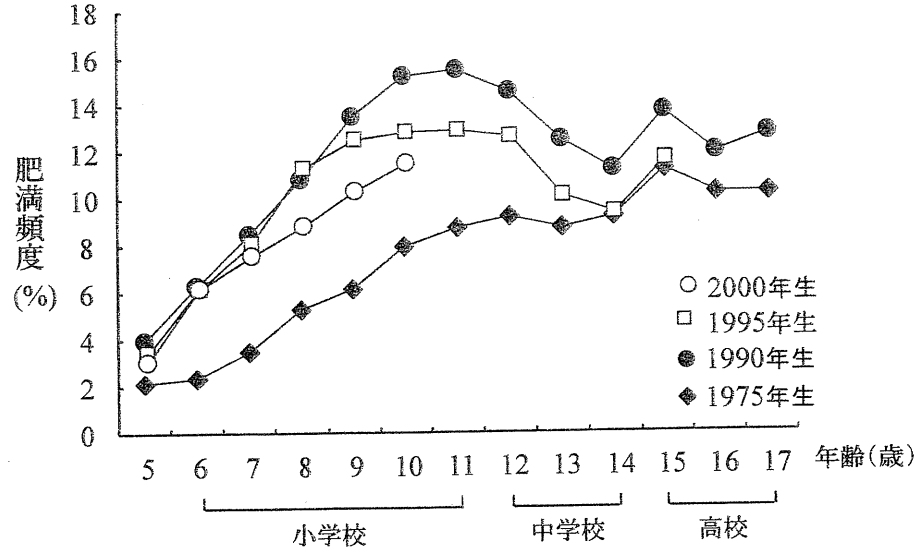

図３　1975 年～ 2000 年出生コホートの５歳から 17 歳の肥満頻度の縦断的推移
(参考論文１より改変)
内容は本文を参照。

図4

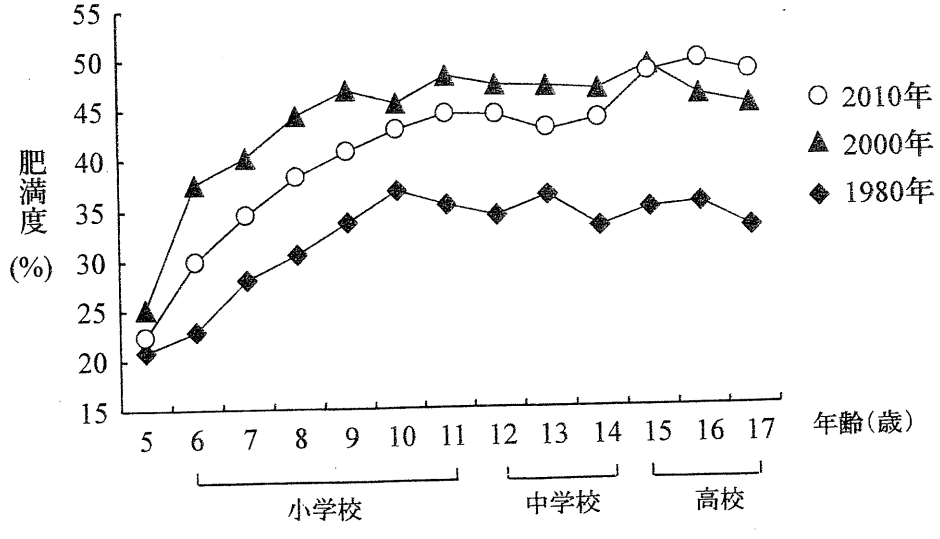

図４　肥満度の 98 パーセンタイル値の年度毎推移
内容は本文参照。