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Original Article

Validation of auxological reference values for Japanese children with Noonan syndrome and comparison with growth in children with Turner syndrome

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Abstract. We recently published growth references for Japanese individuals with Noonan syndrome (NS). However, it is uncertain whether these references can be used to evaluate the longitudinal growth of children with NS. In addition, these charts did not include detailed values suitable for clinical practice, and they did not include weight-for-height (WFH) charts. In the present study, we validated the references and established new WFH charts for children with NS. In addition, we investigated the growth patterns of these children by comparing them with those of children with Turner syndrome (TS), as well as with those of the normal population. To validate our reference values, we enrolled 32 subjects from our previous study with data available at both a younger (≤ 5 yr) and an older age (≥ 15 yr). We then investigated longitudinal changes in NS-specific standard deviation scores (SDSs) for height in these subjects. There was no significant difference between the initial and later SDSs (mean difference: –0.12, 95% confidence interval: –0.26–0.023, $P = 0.10$), suggesting that the references could be applied in clinical practice. We also confirmed that the growth patterns of children with NS in each index are significantly different from those of children with TS. In conclusion, we confirmed auxological reference values for Japanese children with NS.

Key words: Noonan syndrome, growth chart, growth pattern, validation, Turner syndrome

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Introduction

Noonan syndrome (NS) is a relatively common disease, affecting approximately 1 in 1,000–2,500 live births (1–3). It is characterized by short stature, dysmorphic facial features, congenital heart disease, and other comorbidities (1, 4). The growth patterns of individuals with NS are different from those of the normal population. For this reason, NS-specific growth charts are essential to NS care. We recently constructed growth reference charts based on height, weight, and body mass index (BMI) for Japanese individuals with NS (5). However, it is uncertain whether these references can be used to evaluate the longitudinal growth of patients with NS. Moreover, the references did not include a weight-for-height (WFH) chart, nor did they provide practical values for each index, although they did provide the Lambda-Mu-Sigma (LMS) values every 6 mo. Furthermore, in a clinical setting, physicians often evaluate the measurements of patients with NS by comparing them to reference values from the normal population; these have recently been modified (6). Therefore, before our published charts can be applied to clinical practice, it will be necessary to confirm their applicability and ascertain practical values for each index.

NS and Turner syndrome (TS) share similar phenotypes, including short stature, congenital heart disease, early feeding difficulties, and lymphatic vessel abnormalities, although their etiologies are entirely different (1, 7), and the postnatal growth patterns of NS are not the same as those of TS. Nonetheless, the two syndromes are sometimes compared in terms of growth or response to GH (8, 9). To allow an accurate comparison of the effects of GH treatment between the two syndromes, it will be necessary to understand the difference in growth patterns between them. However, few studies have investigated this difference, and none have done so in the Japanese population.

In the present study, we used longitudinal height data to investigate whether our recently published NS height references are applicable in clinical practice. We then established WFH charts for NS children and provided auxological reference values for height, weight, BMI, and WFH for Japanese individuals with NS. These values can be used in clinical practice. Finally, we studied the growth patterns of children with NS by comparing them to those of children with TS, as well as with those of children in the normal population.

Methods

The longitudinal measurements used to investigate the applicability of height references were derived from our previous study (5). We sampled subjects for whom data were available in both the younger (1–5 yr) and older (≥ 15 yr) age groups, because we wanted to know whether the published height references could be used over the whole course of growth. In total, 32 subjects (17 boys, 15 girls) were selected for this purpose. We calculated the standard deviation score (SDS) of each measurement in these subjects using the NS height references (5); we then investigated longitudinal changes in height SDS values by comparing the difference between the initial and later SDSs. The initial SDS refers to the earliest available data of each subject (mean age: 2.1 ± 1.2 yr), and the later values refer to their last available data (mean age: 17.4 ± 1.4 yr); 11.6% of the subjects had height data available in the younger age group, while 38.3% had data available in the older age group. The comparisons described above were assessed by paired t-test using JMP 12 (SAS Institute Inc., Cary, NC), and P-values < 0.05 were considered statistically significant.

To establish WFH charts for children with NS, we reanalyzed the population from our previous study (5). Therein, we conducted a nationwide survey by collaborating with three academic societies in Japan (The Japan Society of Pediatric Genetics, The Japanese Society of Pediatric Cardiology and Cardiac Surgery, and The Japanese Society for Pediatric Endocrinology). We obtained the data of 356 subjects —from 20 hospitals— who had been clinically diagnosed with NS and whose birth year was not earlier than 1970, with consideration for the secular height trend in Japan (10). After excluding 48 subjects because of missing auxological data (26 subjects), complications that affected growth

(5 subjects), or extreme longitudinal growth aberrations that lay more than three SDSs from the population mean (17 subjects), we analyzed the remaining 308 subjects (159 boys, 149 girls).

To establish the WFH charts, we used the LMS method (11), which assumes that the data can be transformed to normality using a suitable power transformation (L), and that the distribution can be summarized in terms of the median (M) and coefficient of variation (S). Using penalized likelihood, three curves (L, M, and S) can be fitted as cubic splines using non-linear regression, and the extent of smoothing is controlled by equivalent degrees of freedom. The values of L, M, and S were constrained to change smoothly with age, and the fitted values were used to construct any required centile curves. The fitting and smoothing were performed using lmsChartMaker Pro ver. 2.3 (Medical Research Council, London, UK). The SD score (Z-score) of each measurement (y-value) could be calculated from the L, M, and S curves using the following equation: $Z = [(y/M)^{L-1}] / (L \times S)$, and if L = 0, $Z = \ln (y/M)/S$.

To compare growth patterns among individuals with NS, individuals with TS, and normal individuals, we used the median values of each index in subjects with NS (5), subjects with TS (12), and the normal population (6, 13). First, we calculated these values every month using the LMS values for each index. Thereafter, the median values of subjects with NS and with TS were transformed into SDSs on the basis of the standard for the normal population (6, 13).

This study was approved by the National Center for Child Health and Development Ethics Committee (approval number: 2012-562), as well as by the Ethics Committees of all other institutes participating in this study.

Results

There was no significant difference between the initial and later NS-specific height SDS values (mean difference: –0.12, 95% confidence interval (CI): –0.26–0.023, $P = 0.10$). When the same analysis was performed within each sex, neither revealed significant differences (mean difference in boys: –0.11, 95% CI: –0.37–0.13, $P = 0.34$; mean difference in girls: –0.12, 95% CI: –0.27–0.027, $P = 0.10$).

To establish the WFH charts, we used 3,249 height measurements (1,674 in boys, 1,575 in girls) and 3,111 weight measurements (1,564 in boys, 1,547 in girls), after excluding 23 height measurements and 19 weight measurements derived from three outliers. The centile curves were smoothed to the data using the LMS method. There was an appreciable skewness, and the age-varying power transformations were therefore adjusted.

To provide auxological reference values of height, weight, BMI, and WFH for clinical practice among Japanese individuals with NS, we reanalyzed these references and calculated the median ± 2 SD value for each index. Table 1 shows the mean and SD height values by both sex and age. Tables 2 and 3 present the median ± 2 SD weight and BMI values, respectively, by both sex and age. Table 4 exhibits the median ± 2 SD value for WFH by both sex and height. Supplementary Tables 1, 2, and 3 (online only) provide LMS values for weight, BMI, and WFH, respectively. Practical growth charts superimposed onto those of the normal population (6) are shown in Supplementary Fig. 1 (online only), while practical growth charts for BMI and WFH are depicted in Supplementary Figs. 2 and 3 (online only), respectively.

Figures 1a, 1b, and 1c show the growth patterns of patients with NS and TS in terms of height, weight, and BMI, respectively, by presenting the median SDSs of each index within the normal population by both sex and age. Growth patterns of height in children with NS were different from those in children with TS. Specifically, height SDS in individuals with NS declined, mainly in infancy, and remained stable throughout childhood. Notably, the decline in height SDS during infancy in girls with NS

Table 1. Mean and standard deviation (SD) values of height in Japanese children with Noonan syndrome

Male						Female					
Age (year)	Mean (cm)	SD (cm)	Age (year)	Mean (cm)	SD (cm)	Age (year)	Mean (cm)	SD (cm)	Age (year)	Mean (cm)	SD (cm)
0.00	48.46	2.43	9.25	117.58	5.81	0.00	48.01	2.87	9.25	116.94	6.25
0.08	50.67	2.48	9.50	118.88	5.93	0.08	50.21	2.94	9.50	118.16	6.35
0.17	52.92	2.52	9.75	120.23	6.07	0.17	52.38	3.01	9.75	119.41	6.46
0.25	55.22	2.57	10.00	121.60	6.20	0.25	54.50	3.07	10.00	120.70	6.57
0.33	57.46	2.61	10.25	122.98	6.34	0.33	56.53	3.12	10.25	122.03	6.67
0.42	59.51	2.66	10.50	124.34	6.49	0.42	58.42	3.16	10.50	123.40	6.78
0.50	61.37	2.70	10.75	125.67	6.64	0.50	60.16	3.20	10.75	124.78	6.88
0.58	63.03	2.75	11.00	126.94	6.80	0.58	61.72	3.23	11.00	126.16	6.97
0.67	64.49	2.81	11.25	128.17	6.97	0.67	63.14	3.26	11.25	127.54	7.05
0.75	65.77	2.86	11.50	129.35	7.15	0.75	64.42	3.28	11.50	128.90	7.13
0.83	66.89	2.92	11.75	130.49	7.34	0.83	65.60	3.31	11.75	130.23	7.18
0.92	67.88	2.98	12.00	131.61	7.53	0.92	66.69	3.33	12.00	131.51	7.22
1.00	68.79	3.04	12.25	132.73	7.73	1.00	67.71	3.36	12.25	132.74	7.25
1.25	71.25	3.18	12.50	133.86	7.93	1.25	70.47	3.47	12.50	133.93	7.27
1.50	73.58	3.29	12.75	135.00	8.11	1.50	72.95	3.59	12.75	135.07	7.27
1.75	75.78	3.38	13.00	136.16	8.29	1.75	75.15	3.71	13.00	136.15	7.27
2.00	77.84	3.45	13.25	137.38	8.45	2.00	77.06	3.82	13.25	137.19	7.25
2.25	79.74	3.50	13.50	138.66	8.60	2.25	78.80	3.92	13.50	138.18	7.23
2.50	81.53	3.55	13.75	140.02	8.73	2.50	80.44	4.02	13.75	139.13	7.21
2.75	83.23	3.61	14.00	141.45	8.85	2.75	82.01	4.10	14.00	140.03	7.18
3.00	84.83	3.66	14.25	142.91	8.94	3.00	83.53	4.18	14.25	140.88	7.15
3.25	86.41	3.72	14.50	144.36	9.00	3.25	85.01	4.26	14.50	141.67	7.12
3.50	87.97	3.78	14.75	145.77	9.03	3.50	86.47	4.34	14.75	142.40	7.09
3.75	89.50	3.84	15.00	147.11	9.02	3.75	87.94	4.42	15.00	143.07	7.06
4.00	90.95	3.89	15.25	148.34	8.97	4.00	89.41	4.49	15.25	143.66	7.03
4.25	92.33	3.93	15.50	149.45	8.90	4.25	90.90	4.57	15.50	144.19	7.00
4.50	93.69	3.96	15.75	150.46	8.80	4.50	92.40	4.65	15.75	144.65	6.98
4.75	95.06	3.98	16.00	151.35	8.68	4.75	93.88	4.73	16.00	145.05	6.96
5.00	96.46	4.02	16.25	152.14	8.56	5.00	95.34	4.80	16.25	145.38	6.94
5.25	97.92	4.07	16.50	152.83	8.44	5.25	96.80	4.88	16.50	145.65	6.92
5.50	99.37	4.13	16.75	153.45	8.31	5.50	98.24	4.96	16.75	145.87	6.91
5.75	100.78	4.20	17.00	154.00	8.20	5.75	99.67	5.04	17.00	146.03	6.90
6.00	102.15	4.27	17.25	154.48	8.10	6.00	101.10	5.12	17.25	146.14	6.90
6.25	103.54	4.37	17.50	154.90	8.00	6.25	102.50	5.21	17.50	146.22	6.89
6.50	104.93	4.49	17.75	155.27	7.92	6.50	103.87	5.29	17.75	146.26	6.89
6.75	106.26	4.62	18.00	155.60	7.84	6.75	105.21	5.38	18.00	146.27	6.89
7.00	107.54	4.75	18.25	155.90	7.77	7.00	106.50	5.46	18.25	146.28	6.89
7.25	108.78	4.89	18.50	156.17	7.71	7.25	107.74	5.55	18.50	146.31	6.89
7.50	109.96	5.02	18.75	156.42	7.65	7.50	108.92	5.63	18.75	146.36	6.88
7.75	111.06	5.14	19.00	156.65	7.59	7.75	110.06	5.71	19.00	146.42	6.88
8.00	112.11	5.25	19.25	156.86	7.54	8.00	111.18	5.79	19.25	146.50	6.87
8.25	113.13	5.36	19.50	157.03	7.50	8.25	112.29	5.88	19.50	146.59	6.87
8.50	114.16	5.47	19.75	157.18	7.46	8.50	113.41	5.97	19.75	146.68	6.86
8.75	115.22	5.57	20.00	157.33	7.43	8.75	114.56	6.06	20.00	146.78	6.86
9.00	116.36	5.69				9.00	115.74	6.15			

Table 2. Median ± 2 SD values of weight in Japanese children with Noonan syndrome

Male						Female					
Age (year)	–2SD (kg)	–1SD (kg)	Median (kg)	+1SD (kg)	+2SD (kg)	Age (year)	–2SD (kg)	–1SD (kg)	Median (kg)	+1SD (kg)	+2SD (kg)
0.00	2.05	2.61	3.11	3.59	4.03	0.00	1.94	2.56	3.09	3.57	4.00
0.25	3.23	3.92	4.61	5.29	5.97	0.25	2.91	3.76	4.49	5.15	5.75
0.50	4.29	5.07	5.88	6.74	7.64	0.50	3.81	4.82	5.71	6.51	7.26
0.75	5.10	5.91	6.80	7.77	8.84	0.75	4.45	5.55	6.53	7.43	8.26
1.00	5.71	6.53	7.47	8.52	9.71	1.00	4.95	6.12	7.16	8.12	9.01
1.50	6.62	7.47	8.46	9.63	11.03	1.50	5.77	7.03	8.17	9.23	10.23
2.00	7.42	8.29	9.34	10.62	12.19	2.00	6.56	7.91	9.15	10.31	11.40
2.50	8.19	9.10	10.20	11.58	13.34	2.50	7.41	8.84	10.17	11.44	12.64
3.00	8.93	9.86	11.03	12.50	14.45	3.00	8.27	9.77	11.19	12.55	13.87
3.50	9.64	10.61	11.82	13.40	15.55	3.50	9.00	10.55	12.04	13.49	14.90
4.00	10.33	11.33	12.60	14.29	16.66	4.00	9.64	11.23	12.78	14.30	15.80
4.50	11.00	12.03	13.36	15.15	17.76	4.50	10.25	11.88	13.49	15.09	16.68
5.00	11.66	12.73	14.12	16.04	18.91	5.00	10.86	12.52	14.19	15.87	17.55
5.50	12.33	13.44	14.90	16.95	20.14	5.50	11.44	13.15	14.88	16.64	18.42
6.00	12.99	14.14	15.67	17.87	21.40	6.00	12.01	13.75	15.55	17.39	19.28
6.50	13.62	14.81	16.42	18.76	22.66	6.50	12.58	14.38	16.24	18.18	20.18
7.00	14.21	15.45	17.13	19.62	23.91	7.00	13.19	15.03	16.98	19.02	21.15
7.50	14.79	16.08	17.84	20.48	25.19	7.50	13.82	15.72	17.75	19.91	22.20
8.00	15.39	16.72	18.57	21.38	26.57	8.00	14.46	16.44	18.57	20.86	23.32
8.50	16.03	17.43	19.37	22.39	28.15	8.50	15.15	17.21	19.45	21.90	24.56
9.00	16.74	18.22	20.29	23.56	30.04	9.00	15.92	18.06	20.44	23.08	25.99
9.50	17.53	19.11	21.35	24.93	32.33	9.50	16.70	18.95	21.49	24.34	27.54
10.00	18.38	20.09	22.53	26.49	35.06	10.00	17.50	19.88	22.59	25.68	29.22
10.50	19.27	21.13	23.81	28.24	38.24	10.50	18.35	20.87	23.78	27.16	31.08
11.00	20.15	22.19	25.15	30.13	41.79	11.00	19.25	21.93	25.07	28.77	33.13
11.50	21.03	23.27	26.56	32.14	45.58	11.50	20.21	23.08	26.48	30.52	35.38
12.00	21.92	24.40	28.05	34.30	49.44	12.00	21.25	24.32	27.99	32.41	37.78
12.50	22.84	25.58	29.65	36.61	53.17	12.50	22.35	25.63	29.57	34.35	40.23
13.00	23.79	26.85	31.38	39.06	56.56	13.00	23.49	26.96	31.16	36.28	42.60
13.50	24.79	28.22	33.26	41.64	59.52	13.50	24.67	28.33	32.75	38.16	44.84
14.00	25.82	29.66	35.24	44.25	61.98	14.00	25.91	29.75	34.38	40.04	47.01
14.50	26.79	31.07	37.19	46.71	63.86	14.50	27.26	31.28	36.12	42.00	49.22
15.00	27.63	32.36	38.98	48.87	65.19	15.00	28.66	32.86	37.89	43.98	51.41
15.50	28.32	33.51	40.58	50.69	66.10	15.50	29.99	34.33	39.53	45.80	53.43
16.00	28.89	34.52	41.99	52.21	66.74	16.00	31.18	35.65	40.99	47.42	55.22
16.50	29.35	35.42	43.25	53.50	67.20	16.50	32.21	36.77	42.23	48.80	56.78
17.00	29.75	36.26	44.40	54.64	67.59	17.00	33.07	37.71	43.26	49.96	58.10
17.50	30.09	37.06	45.49	55.69	67.97	17.50	33.77	38.47	44.11	50.91	59.20
18.00	30.39	37.83	46.55	56.67	68.35	18.00	34.33	39.08	44.78	51.67	60.08
18.50	30.66	38.60	47.58	57.62	68.76	18.50	34.76	39.55	45.30	52.26	60.77
19.00	30.88	39.36	48.59	58.55	69.20	19.00	35.08	39.90	45.69	52.70	61.29
19.50	31.06	40.11	49.60	59.47	69.67	19.50	35.33	40.17	45.98	53.03	61.68
20.00	31.17	40.87	50.61	60.38	70.19	20.00	35.51	40.36	46.20	53.28	61.97

Table 3. Median ± 2 SD values of body mass index in Japanese children with Noonan syndrome

Male						Female					
Age (year)	–2SD (kg/m²)	–1SD (kg/m²)	Median (kg/m²)	+1SD (kg/m²)	+2SD (kg/m²)	Age (year)	–2SD (kg/m²)	–1SD (kg/m²)	Median (kg/m²)	+1SD (kg/m²)	+2SD (kg/m²)
0.00	10.51	11.79	13.13	14.54	16.02	0.00	10.65	12.23	13.80	15.37	16.93
0.25	12.14	13.44	14.86	16.43	18.14	0.25	11.36	12.91	14.49	16.12	17.77
0.50	12.76	14.03	15.45	17.05	18.85	0.50	11.80	13.33	14.91	16.56	18.27
0.75	13.00	14.23	15.63	17.22	19.04	0.75	12.11	13.60	15.17	16.83	18.57
1.00	13.09	14.28	15.65	17.21	19.03	1.00	12.31	13.77	15.33	16.99	18.75
1.50	13.15	14.27	15.56	17.08	18.86	1.50	12.57	13.97	15.48	17.12	18.90
2.00	13.19	14.26	15.51	16.97	18.71	2.00	12.74	14.08	15.55	17.17	18.95
2.50	13.23	14.26	15.47	16.89	18.60	2.50	12.88	14.17	15.60	17.19	18.97
3.00	13.23	14.24	15.41	16.80	18.48	3.00	12.99	14.23	15.63	17.20	18.98
3.50	13.21	14.19	15.34	16.70	18.35	3.50	13.07	14.27	15.64	17.19	18.96
4.00	13.17	14.13	15.26	16.60	18.22	4.00	13.11	14.28	15.61	17.14	18.91
4.50	13.13	14.07	15.18	16.51	18.11	4.50	13.11	14.25	15.56	17.07	18.83
5.00	13.09	14.03	15.13	16.43	18.03	5.00	13.08	14.20	15.48	16.98	18.73
5.50	13.06	13.99	15.08	16.38	17.96	5.50	13.03	14.13	15.40	16.88	18.62
6.00	13.04	13.96	15.04	16.34	17.92	6.00	12.97	14.06	15.31	16.78	18.53
6.50	13.02	13.94	15.02	16.32	17.91	6.50	12.92	13.99	15.24	16.71	18.46
7.00	13.01	13.93	15.02	16.33	17.93	7.00	12.88	13.94	15.19	16.66	18.43
7.50	13.01	13.94	15.04	16.36	17.98	7.50	12.86	13.92	15.17	16.65	18.44
8.00	13.03	13.97	15.09	16.43	18.08	8.00	12.86	13.93	15.19	16.69	18.50
8.50	13.07	14.03	15.16	16.52	18.22	8.50	12.89	13.97	15.24	16.76	18.62
9.00	13.13	14.10	15.25	16.65	18.39	9.00	12.95	14.04	15.33	16.88	18.78
9.50	13.19	14.18	15.36	16.80	18.59	9.50	13.03	14.13	15.45	17.04	18.99
10.00	13.27	14.28	15.49	16.96	18.81	10.00	13.13	14.26	15.60	17.23	19.25
10.50	13.35	14.39	15.63	17.14	19.06	10.50	13.25	14.40	15.78	17.46	19.54
11.00	13.44	14.50	15.77	17.34	19.32	11.00	13.39	14.58	16.00	17.73	19.88
11.50	13.54	14.62	15.93	17.54	19.60	11.50	13.56	14.78	16.24	18.02	20.26
12.00	13.64	14.75	16.09	17.76	19.89	12.00	13.75	15.00	16.50	18.35	20.68
12.50	13.74	14.87	16.25	17.98	20.19	12.50	13.95	15.23	16.79	18.71	21.14
13.00	13.84	15.00	16.42	18.20	20.50	13.00	14.17	15.49	17.10	19.09	21.62
13.50	13.93	15.13	16.59	18.42	20.80	13.50	14.40	15.76	17.42	19.49	22.14
14.00	14.03	15.25	16.75	18.64	21.11	14.00	14.64	16.04	17.76	19.91	22.67
14.50	14.12	15.37	16.91	18.86	21.42	14.50	14.89	16.34	18.11	20.34	23.23
15.00	14.22	15.49	17.07	19.08	21.73	15.00	15.14	16.63	18.47	20.79	23.80
15.50	14.31	15.61	17.23	19.29	22.03	15.50	15.40	16.94	18.84	21.24	24.38
16.00	14.39	15.73	17.38	19.50	22.33	16.00	15.66	17.24	19.20	21.69	24.97
16.50	14.48	15.84	17.54	19.71	22.64	16.50	15.91	17.54	19.57	22.15	25.57
17.00	14.57	15.95	17.69	19.92	22.93	17.00	16.16	17.84	19.93	22.61	26.17
17.50	14.65	16.06	17.83	20.13	23.23	17.50	16.41	18.14	20.29	23.06	26.77
18.00	14.73	16.17	17.98	20.33	23.53	18.00	16.66	18.43	20.65	23.52	27.37
18.50	14.81	16.28	18.12	20.53	23.82	18.50	16.90	18.72	21.00	23.96	27.96
19.00	14.89	16.38	18.27	20.73	24.11	19.00	17.14	19.00	21.35	24.41	28.56
19.50	14.97	16.49	18.41	20.93	24.40	19.50	17.37	19.28	21.69	24.85	29.16
20.00	15.04	16.59	18.54	21.12	24.69	20.00	17.60	19.56	22.03	25.29	29.75

Table 4. Median ± 2 SD values of weight-for-height in Japanese children with Noonan syndrome

Male						Female					
Height (cm)	–2SD (kg)	–1SD (kg)	Median (kg)	+1SD (kg)	+2SD (kg)	Height (cm)	–2SD (kg)	–1SD (kg)	Median (kg)	+1SD (kg)	+2SD (kg)
45	2.01	2.23	2.49	2.79	3.14	45	2.13	2.37	2.65	2.96	3.30
50	2.77	3.06	3.40	3.80	4.27	50	2.74	3.06	3.41	3.80	4.24
55	3.62	3.98	4.41	4.91	5.50	55	3.59	3.99	4.45	4.95	5.52
60	4.53	4.97	5.48	6.08	6.79	60	4.52	5.02	5.58	6.21	6.91
65	5.48	5.99	6.57	7.26	8.08	65	5.34	5.92	6.57	7.30	8.12
70	6.45	7.00	7.66	8.42	9.34	70	6.14	6.78	7.50	8.32	9.24
75	7.44	8.05	8.76	9.60	10.61	75	7.09	7.81	8.61	9.52	10.54
80	8.50	9.16	9.94	10.85	11.95	80	8.25	9.04	9.93	10.92	12.05
85	9.61	10.32	11.16	12.15	13.35	85	9.53	10.38	11.34	12.42	13.64
90	10.70	11.48	12.39	13.47	14.79	90	10.77	11.68	12.71	13.87	15.16
95	11.83	12.67	13.66	14.86	16.34	95	11.94	12.93	14.04	15.28	16.68
100	13.05	13.97	15.08	16.42	18.10	100	13.09	14.17	15.37	16.73	18.27
105	14.33	15.36	16.60	18.14	20.11	105	14.28	15.46	16.80	18.32	20.05
110	15.67	16.82	18.24	20.04	22.42	110	15.55	16.87	18.38	20.11	22.11
115	17.08	18.39	20.02	22.16	25.11	115	16.96	18.47	20.21	22.23	24.58
120	18.62	20.09	21.99	24.54	28.26	120	18.52	20.26	22.29	24.69	27.55
125	20.32	22.00	24.20	27.26	31.99	125	20.25	22.28	24.70	27.62	31.22
130	22.17	24.10	26.70	30.47	36.70	130	22.30	24.71	27.65	31.33	36.04
135	24.16	26.43	29.55	34.27	42.76	135	24.90	27.75	31.34	35.97	42.20
140	26.38	29.06	32.82	38.71	50.04	140	28.14	31.43	35.64	41.25	49.14
145	28.86	32.02	36.50	43.62	57.69	145	32.26	35.93	40.69	47.15	56.51
150	31.64	35.31	40.49	48.58	63.77	150	37.21	41.31	46.70	54.14	65.24
155	34.71	38.91	44.70	53.34	68.07	155	42.66	47.29	53.45	62.17	75.71
160	37.90	42.67	49.04	58.07	71.98	160	48.31	53.49	60.50	70.66	87.24
165	41.05	46.45	53.44	62.83	76.10	165	54.04	59.78	67.67	79.42	99.70

was markedly larger than that in girls with TS. Height SDS declined again because of pubertal delay, but increased gradually with the onset of pubertal period. In contrast, height SDS in girls with TS declined gradually and continuously until the pubertal age of normal children. It then dropped drastically around the pubertal period of normal children, but recovered slightly afterwards. As a result of these differences, girls with NS were taller than those with TS at both 9 and 20 yr of age —by 0.3 SDs and 1.2 SDs, respectively (Fig. 1a). Patterns of weight gain in children with NS were also different from those in children with TS. At all ages, the weight SDSs of children with NS were below those of normal children, while those in girls with TS were above those of normal children (Fig. 1b). The growth pattern of BMI in girls with NS was also different from that in girls with TS. Specifically, in the preschool age group (1–5 yr), the median SDS of the BMI in girls with NS gradually increased, reaching a peak at around 3.5 yr of age. In contrast, the peak SDS of the BMI in girls with TS occurred at around 2 yr of age. In addition, after preschool age, the gradual BMI increase in girls with NS was milder than that in girls with TS (Fig. 1c). However, these different growth patterns may mainly be due to the methodological effect of smoothing, as the BMI growth before preschool age is not a simply increasing curve. Figure 2 compares the WFH median line among children with NS and, those with TS, and normal children by sex. The WFH in children with NS is almost the same as that

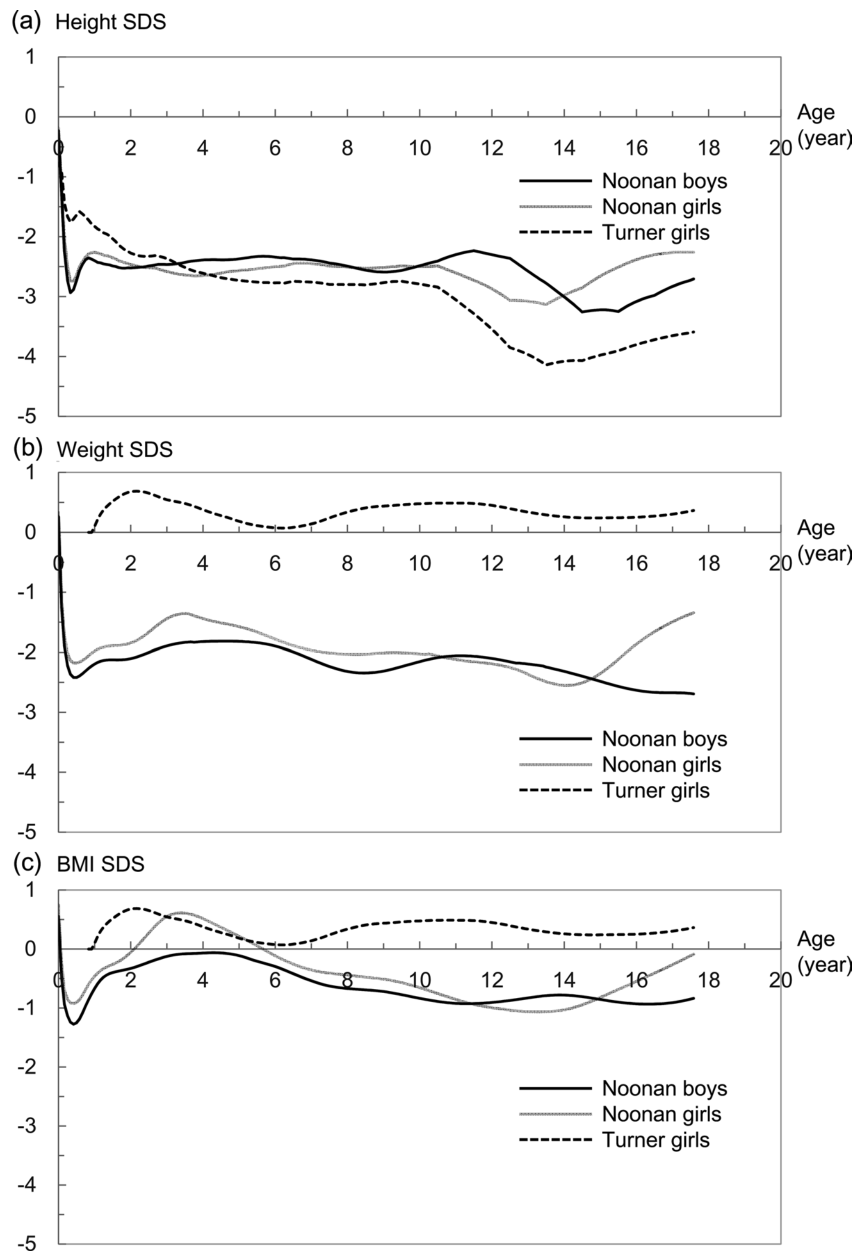

Fig. 1. Median height (a), weight (b), and BMI (c) standard deviation scores in the normal population compared with those in boys with NS, girls with NS, and girls with TS. Black, gray and black dotted lines indicate boys with NS, girls with NS, and girls with TS, respectively.

in the normal population. In contrast, in subjects below 100 cm in height, the WFH in girls with NS is almost the same as that in girls with TS. In subjects above 100 cm in height, girls with NS showed a slower increase in WFH than did girls with TS.

Discussion

In the present study, there were no differences in NS-specific height SDSs between the initial and the later values (mean difference: –0.12, 95% CI: –0.26–0.023, $P = 0.10$). Our validation

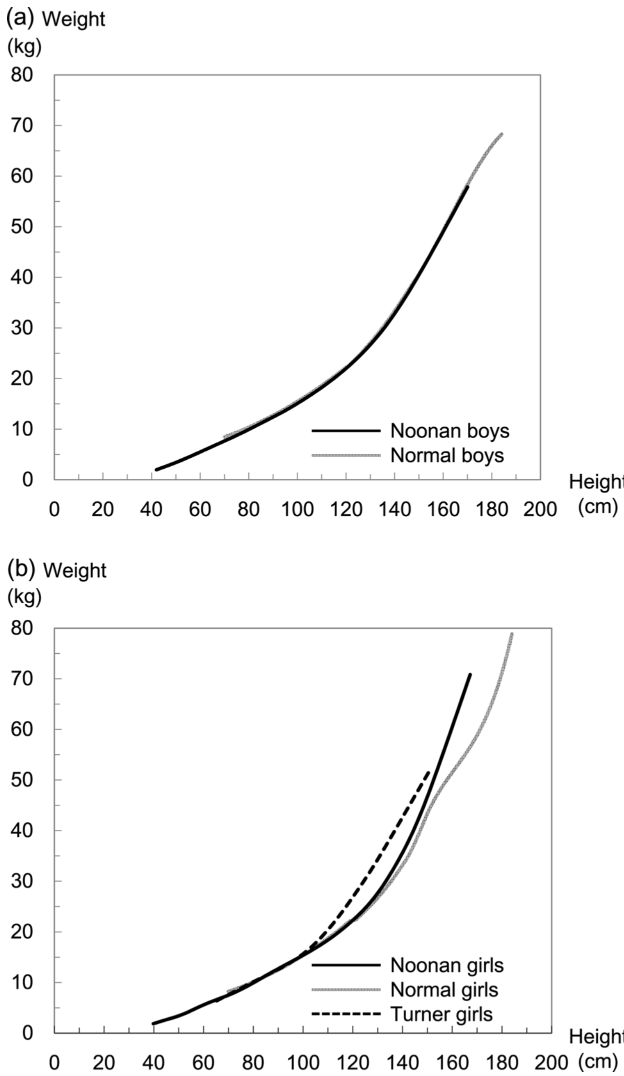

Fig. 2. Comparisons of WFH median lines between individuals with NS, those with TS, and the normal population in boys (a) and girls (b). Black, black dotted and gray lines indicate individuals with NS, those with TS, and the normal population, respectively.

data were derived from the same cohort used to establish NS-specific height references. However, only 11.6% of the available validation data from the younger age group, and 38.3% of the data from the older age group, were used in the charts. Nonetheless, we believe that the mean differences analyzed in the present study could be used to validate the height reference chart. In addition, most normal children grow within a weight range of roughly two centile spaces (4/3 SD), and within a height range of one centile space (2/3 SD) (14). On the basis of the present study, we cannot conclusively state that our recently published NS-specific growth references represent optimal growth charts for children with NS. However, our findings suggest that they can be applied to evaluate longitudinal growth in a clinical setting.

In the present study, we established new NS-specific WFH charts, because our recently published references did not include WFH charts (5), and clinicians in Japan often use WFH to evaluate childhood obesity (15, 16). In addition, we demonstrated that the WFH growth pattern in children with NS was almost the same as that in normal children; to do so, we compared the WFH growth charts between these two groups. It has been reported that clinicians should interpret anthropometric indices cautiously when evaluating obesity in children with an aberrant growth pattern (17). However, our results suggest that obesity can be evaluated in children with NS using the WFH of the normal population.

The height growth patterns of individuals with NS were different from those of children with TS. More specifically, we found three stages of the growth process that differed between them. First, individuals with NS had a more rapid decline in height SDS during the first year of life than girls with TS. The reason for this is not clear, but it may be due to the differences in feeding problems between the syndromes. Second, children with NS retained a similar height SDS throughout childhood, while girls with TS exhibited a gradual decline in height SDS. Third, children with NS had a delayed pubertal spurt, whereas girls with TS did not have any obvious pubertal spurt. To the best of our knowledge, this was the first study to detail the different growth patterns between children with NS and TS. Future studies should consider these different growth patterns when evaluating growth or response to growth-promoting treatment.

Furthermore, the pattern of weight gain differs between the patients of these two syndromes. At all ages, the weight SDSs of children with NS were below those of normal children, while those of girls with TS were above those of normal children. These different growth patterns are in line with the findings of previous reports. For instance, it has been reported that the prevalence of overweightness is low among adult patients with NS (18), and that girls with TS frequently become overweight as they mature (17, 19, 20).

Finally, the BMI growth pattern in girls with NS also differs from that in girls with TS. Notably, the gradual BMI increase that occurs in girls with NS after preschool age is milder than that which occurs in girls with TS. This growth pattern of lower BMI in children with NS has been reported in other countries (21, 22). It has been hypothesized that energy metabolism is modified in children with NS (22), but the mechanism remains unknown. Further investigation is needed to clarify the underlying mechanism behind the relatively thin physical appearance of patients with NS.

In conclusion, we established auxological reference values for clinical practice among Japanese children with NS; we also clarified the differences in growth patterns among children with NS, girls with TS, and individuals in the normal population.

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