Table 2 Clinical characteristics of females according to clustering of metabolic risk factors (MetRFs) and obesity status

Number of MetRFs	Non-obese (BMI < 25 kg/m^2)			Obese (BMI ≥ 25 kg/m^2)		
	0 or 1	2 or 3	*P*	0 or 1	2 or 3	*P*
n	513	127	–	168	83	–
Age (years)	59.7 ± 10.5	64.5 ± 8.4	< 0.001	61.3 ± 10.3	64.0 ± 7.4	0.029
Height (cm)	152.4 ± 6.3	150.7 ± 5.8	0.006	150.7 ± 5.8	150.9 ± 5.2	0.536
Body weight (kg)	49.9 ± 6.0	50.9 ± 5.7	0.091	62.5 ± 6.4	63.1 ± 6.5	0.471
BMI (kg/m^2)	21.5 ± 2.1	22.4 ± 1.8	< 0.001	27.2 ± 2.1	27.7 ± 2.3	0.135
FPG (mg/dL)[a]	87.8 ± 7.8	97.9 ± 13.8	< 0.001	91.1 ± 10.9	99.1 ± 16.8	< 0.001
HbA1c (%)	5.5 ± 0.5	5.8 ± 0.6	< 0.001	5.7 ± 0.5	5.9 ± 0.6	0.004
FSI (μU/mL)[a]	5.1 ± 3.2	7.0 ± 4.9	< 0.001	7.6 ± 5.0	9.6 ± 4.6	0.002
HOMA-R[a]	1.1 ± 0.5	1.6 ± 0.9	< 0.001	1.6 ± 0.8	2.3 ± 1.4	< 0.001
SBP (mmHg)	126 ± 15	139 ± 10.5	< 0.001	134 ± 14	140 ± 10	< 0.001
DBP (mmHg)	74 ± 9	79 ± 8.7	< 0.001	78 ± 10	81 ± 8.4	0.016
TC (mg/dL)	204 ± 29	206 ± 30	0.396	212 ± 30	213 ± 32	0.793
TG (mg/dL)	82 ± 31	122 ± 61	< 0.001	94 ± 34	135 ± 62	< 0.001
HDL-C (mg/dL)	64 ± 13	58 ± 16	< 0.001	60 ± 11	55 ± 13	0.004
Serum uric acid (mg/dL)	4.3 ± 1.0	4.5 ± 0.9	0.188	4.7 ± 1.0	4.8 ± 1.3	0.235
Adiponectin (μg/mL)	12.5 ± 5.8	10.3 ± 5.0	< 0.001	10.3 ± 4.9	9.9 ± 5.6	0.266
Urinary albumin (mg/gCr)	16 ± 44	40 ± 127	< 0.001	28 ± 51	41 ± 87	0.169
Albuminuria, n (%)[b]	41 (8)	24 (19)	< 0.001	40 (24)	19 (23)	0.872
Hypertension, n (%)	172(33)	99(77)	< 0.001	101(60)	64(77)	0.008
Hyperlipidemia, n (%)	90(17)	98(77)	< 0.001	37(22)	67(80)	< 0.001
Diabetes, n (%)	11(2)	22(17)	< 0.001	7(4)	18(21)	< 0.001
Drinking alcohol (n(%))	92(18)	18(14)	0.314	25(15)	8(10)	0.247
Smoking (never / past / current), n	468/30/15	122/4/1	0.172	150/14/4	82/1/0	0.020
Elevated BP, n (%)	255(49)	126(99)	< 0.001	122(72)	82(99)	< 0.001
Elevated TG/reduced HDL-C, n (%)	32(6)	104(81)	< 0.001	8(5)	67(81)	< 0.001
Elevated FPG, n (%)	7(2)	38(30)	< 0.001	3(2)	23(27)	< 0.001

Data are means ± SD or n (%). [a]Subjects with FPG > 140 mg/dL were excluded (non-obese: n = 21 and 10 for 0 or 1 MetRFs and 2 or 3 MetRFs, respectively; obese: n = 10 and 6 for 0 or 1 MetRFs and 2 or 3 MetRFs, respectively). Serum adiponectin and urine albumin levels were log-transformed for statistical analyses. Differences in the continuous and categorical variables were analyzed by ANOVA and χ^2 tests, respectively.

cies of subjects without work were not significantly different between the subjects with or without a clustering of MetRFs in either non-obese (26.3 *vs.* 22.6%, $P = 0.387$) or obese (28.3 *vs.* 24.4%, $P = 0.520$) subjects. Furthermore, in the subjects with work, energy expenditure at work was similarly significantly lower in non-obese (12.3 ± 7.2 *vs.* 14.7 ± 7.9 MET·h/day, $P = 0.010$) and obese (12.6 ± 6.5 *vs.* 15.4 ± 7.8 MET·h/day, $P = 0.007$) men with a clustering of MetRFs. We also examined the effects of physical activity intensity on the association between energy expenditure and clustering of MetRFs in men. However, we found no differences in values between subjects with or without a clustering of MetRFs in either non-obese or obese subjects.

We next determined the association between energy expenditure at work with the clustering of MetRFs in men by multiple logistic regression analysis. This analysis revealed a significant association between these two factors, after adjusting for age, BMI, alcohol intake, and total energy intake. The odds ratios (OR) (per 1 METs) were 0.972 (95% confidence interval [CI]: 0.945–0.999; $P = 0.044$) and 0.961 (95% CI: 0.925–0.998; $P = 0.039$) in non-obese and obese men, respectively (Table 5).

Alcohol intake was significantly higher in non-obese men with a clustering of MetRFs than in those without ($P < 0.001$), but was not significantly different in obese men ($P = 0.411$) (Table 3). Multiple logistic regression analysis showed that, in non-obese subjects, alcohol intake was significantly associated with the clustering of MetRFs after adjusting for age, BMI, total energy intake, and energy expenditure at work with an OR (per 10 g/week) of 1.022 (95% CI: 1.007–1.037; $P = 0.005$). This association was further confirmed in an

Table 3 Lifestyle characteristics according to clustering of metabolic risk factors (MetRFs) in non-obese and obese males

Number of MetRFs	Non-obese (BMI < 25 kg/m^2)			Obese (BMI ≥ 25 kg/m^2)		
	0 or 1	2 or 3	*P*	0 or 1	2 or 3	*P*
Nutritional Intake						
Total energy intake						
(kcal/day)	2462±703	2371±824	0.213	2545±704	2339±671	0.034
/BW (kcal/kg/day)	42.3±12.3	39.6±14.6	0.279	36.1±10.1	32.6±9.8	0.023
Carbohydrate (%)	58.3±7.0	57.3±7.9	0.248	58.1±8.1	57.7±8.0	0.659
Fat (%)	20.8±4.9	20.4±5.6	0.287	20.4±5.3	20.9±5.0	0.453
Protein (%)	12.8±2.6	12.8±2.6	0.812	12.5±2.5	12.8±2.9	0.398
Salt (g/day)	13.2±3.7	13.4±5.3	0.095	13.6±3.7	13.2±4.1	0.120
Alcohol (g/week)	117±134	154±165	< 0.001	111±133	109±134	0.411
Energy expenditure (MET·h/day)						
Total	36.3±6.3	35.0±5.0	0.083	35.9±6.1	34.4±5.3	0.056
According to types						
Sleep	7.6±1.2	7.8±1.4	0.164	7.6±1.3	7.8±1.5	0.341
Sedentary	11.6±4.8	12.0±4.6	0.516	11.5±4.7	12.1±4.6	0.443
Work	11.3±9.3	9.0±8.2	0.025	11.6±9.4	9.0±7.9	0.017
Housework	0.9±1.6	1.2±2.5	0.136	0.7±2.0	0.5±1.0	0.395
Walking or bicycle	3.6±4.7	3.6±3.6	0.891	3.3±4.1	3.6±4.9	0.536
Exercise	0.44±1.2	0.56±1.5	0.568	0.4±1.2	0.4±0.8	0.516
Leisure time	0.6±1.6	0.6±1.1	0.904	0.5±1.1	0.8±2.5	0.182
According to intensity						
Light intensity (<3.0)	27.2±6.5	27.7±5.0	0.475	27.4±6.4	27.4±5.3	0.982
Moderate to Vigorous (≥3.0)	9.1±10.6	7.3±7.3	0.156	8.6±10.1	7.0±8.8	0.268
Vigorous (≥6.0)	0.1±0.7	0.1±0.1	0.162	0.1±0.4	0.1±0.1	0.194

Data are means ± SD. Intakes of macronutrients are expressed by % total energy consumption. Differences between subjects with 0 or 1 and 2 or 3 MetRFs were analyzed by ANOVA adjusted for age and BMI.

Table 4 Lifestyle characteristics according to clustering of metabolic risk factors (MetRFs) in non-obese and obese females

Number of MetRFs	Non-obese (BMI < 25 kg/m^2)			Obese (BMI ≥ 25 kg/m^2)		
	0 or 1	2 or 3	*P*	0 or 1	2 or 3	*P*
Nutritional Intake						
Total energy consumption						
(kcal/day)	2110±583	2065±627	0.396	2187±589	2109±578	0.304
/BW (kcal/kg/day)	42.8±13	41.1±14	0.416	35.4±10.5	33.6±9.8	0.248
Carbohydrate (%)	58.8±6.5	59.2±7.4	0.449	59.2±6.4	59.4±6.8	0.586
Fat (%)	24.7±4.6	24.4±4.8	0.307	24.4±4.5	24.3±5.0	0.592
Protein (%)	14.1±2.6	14.6±3.0	0.390	14.4±2.7	14.7±2.7	0.558
Salt (g/day)	12.4±3.9	12.5±4.1	0.828	13.4±3.8	13.0±3.7	0.684
Alchohol (g/week)	9.1±37	6.6±27	0.581	11±40	3±18	0.290
Energy expenditure (MET·h/day)						
Total	36.3±5.3	35.4±5.0	0.395	36.5±5.6	35.9±6.3	0.791
According to type						
Sleep	7.2±1.2	7.4±1.1	0.655	7.4±1.1	7.1±1.0	0.015
Sedentary	11.1±4.7	12.0±4.6	0.248	10.9±5.3	12.3±4.3	0.111
Work	6.8±7.7	4.6±6.7	0.099	6.6±7.9	4.7±7.6	0.286
Housework	7.3±3.9	6.6±3.7	0.212	7.2±4.5	7.5±4.3	0.386
Walking or bicycle	2.8±3.6	3.5±3.7	0.189	3.0±3.5	2.6±3.5	0.251
Exercise	0.3±0.8	0.4±0.9	0.248	0.2±0.8	0.2±0.6	0.463
Leisure time	0.5±1.5	0.7±1.8	0.728	0.9±2.3	1.2±6.1	0.644
According to intensity						
Light intensity (<3.0)	29.8±4.6	29.2±3.7	0.329	30.6±4.7	29.1±4.5	0.059
Moderate to Vigorous (≥3.0)	6.5±7.1	6.2±6.2	0.992	6.0±6.2	6.8±9.0	0.961
Vigorous (≥6.0)	0.1±0.3	0.1±0.6	0.626	0.1±0.2	0.2±0.9	0.942

Data are means ± SD. Intakes of macronutrients are expressed by % total energy consumption. Differences between subjects with 0 or 1 and 2 or 3 MetRFs were analyzed by ANOVA adjusted for age and BMI.

Table 5 Logistic regression analysis of energy expenditure as a predictor of clustering of metabolic risk factors

	Univariate		Model 1		Model 2	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Men[a]						
Non-obese	0.971 (0.949–0.994)	0.013	0.971 (0.945–0.997)	0.026	0.970 (0.944–0.997)	0.032
Obese	0.966 (0.937–0.997)	0.029	0.957 (0.923–0.992)	0.018	0.962(0.926–0.999)	0.043
Women[b]						
Non-obese	0.956 (0.932–0.981)	< 0.001	0.973 (0.947–1.000)	0.049	0.975 (0.948–1.003)	0.076
Obese	0.979 (0.949–1.010)	0.185	0.991 (0.959–1.025)	0.606	0.992 (0.958–1.028)	0.663

[a]Energy expenditure at work, [b]Energy expenditure at work and for housework
ORs are presented per 1 METs. Model 1: adjusted for age and BMI. Model 2: adjusted for age, BMI, total energy intake, and alcohol intake.

analysis in which the non-obese men were stratified into four categories of alcohol (none; light: 1–139 g/week; heavy: 140–279 g/week; very heavy: ≥ 280 g/week). In these four categories, the prevalence of a clustering of MetRFs was 22.8% (n = 29/98), 26.6% (n = 33/91), 30.0% (n = 36/84), and 38.3% (23/37), respectively (*P* for trend = 0.027 ; none *vs.* very heavy: *P* = 0.027).

In women (Table 4), we found no significant differences in lifestyle factors between those with or without a clustering of MetRFs, in either non-obese or obese women. The frequencies of subjects without work were higher in the subjects with a clustering of MetRFs than those without in non-obese (51.2 *vs.* 41.1%, *P* = 0.041) or obese (53.0 *vs.* 41.7%, *P* = 0.089) subjects. However, in the subjects with work, energy expenditures at work were not significantly different between the subjects with or without a clustering of MetRFs in non-obese (9.5 ± 7.0 *vs.* 11.6 ± 6.8 MET·h/day, *P* = 0.111) and obese (10.2 ± 8.3 vs. 11.4 ± 7.3 MET·h/day, *P* = 0.611) women. Since women expended a greater proportion of energy during housework, we summed energy expenditure for work and housework. The resulting summed energy expenditure was significantly lower in non-obese women with a clustering of MetRFs than in those without (11.2 ± 7.4 *vs.* 14.1 ± 8.7 MET·h/day, *P* = 0.036), but not in the obese women (12.3 ± 8.4 *vs.* 13.9±8.4 MET·h/day, *P* = 0.616). Multiple logistic regression analysis also supported the association between summed energy expenditures and the clustering of MetRFs in non-obese women (OR: 0.956; 95% CI: 0.932–0.981; *P* < 0.001), although the association became marginal following adjustment for age, BMI, total energy intake, and alcohol intake (OR: 0.974; 95% CI: 0.947–1.002; *P* = 0.068) (Table 5).

Discussion

Here, we showed that MetRFs were frequently clustered, even in non-obese subjects (Fig. 1), and that subjects with a clustering of MetRFs were often insulin resistant and had lower serum adiponectin levels compared with subjects without a clustering of MetRFs, even though the former group were not obese (Tables 1 and 2). These results indicate that non-obese subjects with a clustering of MetRFs are at increased risk of CVD, as are obese subjects with a clustering of MetRFs, in other words subjects with MetS. Therefore, identifying lifestyle factors associated with the clustering of MetRFs is important in non-obese subjects as well as in obese subjects, since it may help us to develop potential interventions to prevent CVD in non-obese individuals. Therefore, we examined the associations between lifestyle factors and clustering of MetRFs in non-obese and obese subjects separately.

In men, energy expenditure, particularly at work, was significantly lower in subjects with a clustering of MetRFs than in those without (Table 3). However, total energy intake was significantly lower in men with a clustering of MetRFs than in those without (Table 3). These results appear to be contradictory. Indeed, both lower physical activity and excess energy intake were reported to be associated with the MetS [8-11, 28-31]. MetS is, as described above, essentially obesity in combination with a clustering of other MetRFs. Therefore, greater energy intake and lower physical activity were expected in the subjects with a clustering of MetRFs as compared with subjects without a clustering of MetRFs, in the obese group and potentially in the non-obese group. Unexpectedly, we found that energy intake in

subjects with a clustering of MetRFs was actually lower in both the non-obese and obese groups. Consequently, these results can be explained by the assumption that the lower energy intake was still in excess taking into account the individual's needs based on the low physical activity and clustering of MetRFs. In fact, multiple logistic regression analyses showed that energy expenditure at work was significantly associated with clustering of MetRFs after adjusting for possible confounding factors, including total energy intake, in non-obese and obese subjects (Model 2 in Table 3). An association of the MetS with lower physical activity but not excessive energy intake was also reported in Japanese subjects [29]. Together, it seems that lower physical activity, rather than excessive energy intake, is the predominant risk factor for the clustering of MetRFs in non-obese Japanese males.

Alcohol intake was significantly higher in non-obese males with a clustering of MetRFs than in those without ($P = 0.005$), but was not significantly different in obese males ($P = 0.935$). Similarly, the analysis of non-obese males stratified into the four groups based on alcohol consumption (none, light, heavy, and very heavy) showed a positive linear association between the amount of alcohol intake and the clustering of MetRFs. Both analyses indicate that increasing alcohol intake increases the risk of clustering of MetRFs in non-obese Japanese males. However, earlier studies of MetS have shown a J-shaped relationship between alcohol intake and the risk of MetS [31-33]. Indeed, light alcohol consumption was actually associated with a lower risk of MetS [32-34], while very heavy alcohol consumption was associated with a substantial increase in the risk of MetS [35]. The differences in the relationship between alcohol intake and the risk of clustering of MetRFs might be related to differences in obesity status of the subjects; namely, non-obese versus obese. Differences in types of alcoholic beverages consumed (*e.g.*, beer, wine, and sake) might also affect the results [29, 32]. Further studies are needed to confirm the nature of the relationship between alcohol intake and the risk of clustering of MetRFs in non-obese subjects.

In women, we found a weak association between energy expenditure and clustering of MetRFs in non-obese subjects, but not in obese subjects. Conversely, energy intake was not associated with clustering of MetRFs in either non-obese or obese women. These results suggest that, in non-obese Japanese females, lower physical activity is weakly associated with the clustering of MetRFs, but that no lifestyle factor is markedly associated with the clustering of MetRFs in obese women.

The urine albumin level, a known risk factor for CVD [36, 37], was not significantly higher in none-obese males with a clustering of MetRFs compared with those without. This result does not fully support the concept that subjects with a clustering of MetRFs are at risk for CVD, even though they were not obese. However, because of the relatively small number of subjects included in this analysis and the cross-sectional nature of the study, our results do not reject this concept.

The effects of physical activity and energy intake on MetS have been examined in numerous studies [8-11, 29-32]. However, few studies have examined their effects in non-obese subjects with a clustering of MetRFs. Here, we showed that non-obese men with a clustering of MetRFs may be at increased risk of CVD because of their lower physical activity, but not excessive energy intake, compared with those without. These findings convey an important message that interventions aimed at increasing physical activity rather than focusing on decreasing energy intake is more important to prevent the clustering of MetRFs in non-obese Japanese men. In this context, an about 3% decrease in the risk of a clustering of MetRFs by 1 METs increase in physical activity shown here by the multiple logistic regression analysis seems to have a practical importance. One METs physical activity corresponds to 20 minutes moderate physical activities such as walking, fishing and housecleaning, which seem to be easy to be done. Furthermore, one can increase physical activity more than 1 METs without much effort. Therefore, interventions aimed at increasing physical activity to decrease the risk of a clustering of the MetRFs seem to be effectively performed in the practical settings, although effects of such interventions has to be evaluated in the future.

This study has several strengths and limitations that need to be mentioned. In terms of its strengths, we assessed physical activity and energy intake, both of which were incorporated into statistical models as potential confounding factors. The sample size was also relatively large and consisted of a 'general' population of Japanese individuals. In terms of the limitations, physical activity and energy intake were assessed by questionnaires, although both questionnaires were well validated in prior studies. More pre-

cise, objective assessment of these factors might provide different results, which warrant confirmation in future studies. Furthermore, these questionnaires may harbor problems in multiple comparisons, since they, especially the BDHQ, provide large numbers of variables. In the study, we selected macronutrients, and, salt, and alcohol, which are known to be associated with MetS [31-35, 38, 39], from many such nutritional variables and included 8 variables for physical activities provided by the JALSPAQ. However, although the numbers of variables used were insubstantial, the results reported here could be consequences of chance findings due to multiple comparisons, and, thus, studies specifically targeted to variables of interest seem to be awaited. We also defined obesity according to BMI, whereas waist circumference is normally used as criterion for assessing MetS. Considering that BMI and waist circumference are well correlated, different results may have been obtained had we defined obesity according to waist circumference rather than BMI. Unfortunately, we did not measure waist circumference in many subjects, preventing us from examining this possibility. The participation rate was low (10.1%) and, thus, the subjects might not represent whole population. However, the lack of difference in most of the clinical characteristics observed between the male subjects and the male participants who were not included in the study indicates no obvious selection bias in the study subjects, at least, in men. Enlarging the sample size may validate the results. The final limitation is that this was a cross-sectional study. Therefore, we cannot evaluate the cause–effect relationship for observed associations. Prospective studies that capture these data over a period of time are needed to overcome these limitations.

In conclusion, lower physical activity, but not excessive energy intake, was the predominant lifestyle risk factor for a clustering of MetRFs in Japanese males, independent of their obesity status. Our findings warrant prospective examination to confirm whether the association between lower physical activity and clustering of MetRFs in non-obese subjects is also apparent in other populations/ethnicities.

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分担研究報告

Adiponectin 測定による Metabolic syndrome スクリーニング精度に関する検討

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研究要旨： 健診受診者 6,368 例について Adiponectin 値で Metabolic syndrome の screening が可能か否かを検討した。Adiponectin を 10 分位法で区分し ROC 曲線から WC を必須とした場合と、VFA 100cm^2 以上を必須とした場合で精度を比較した。男性では Adiponectin 4.0 μg/ml を cut off とすると、WC を必須の場合感度 64.7%,特異度 56.0%、女性では 6.1 μg/ml を cut off とすると 69.3%、60.7%であった。VFA の場合は男性では WC と差がないが、女性では 75.3%、60.5%と精度は上昇した。男女とも Adiponectin による screening は可能と言える。

A. 研究目的

Adiponectin 測定は 1 滴の血液で可能であり、これを用いて Metabolic syndrome のスクリーニングが可能であれば、簡単で受診者にとってメリットが大きい。本研究では人間ドック受診者について分析した。

B. 研究方法

対象は 2005 年 11 月から 2013 年 12 月の間に当所の人間ドック健診を受診した 6,368 例（男性 3,461 例、女性 2907 例）で、早朝空腹時の血清脂質、血糖値、IRI、血圧値を測定した。腹囲径（WC）は臍周囲、低線量 CT で内臓脂肪面積（VFA）と皮下脂肪面積を測定した。対象の平均年齢は 45.9±9.4 歳であった。

総 Adiponectin 値はモノクロナル抗体を用いた ELISA 法（積水化学）で測定した。総 Adiponectin を 10 分位法で区分して各群の Metabolic syndrome 診断精度を比較した。なお、危険因子は FPG≧110mg/dl または糖尿病治療中のものを糖代謝異常あり、収縮期血圧 130 以上または拡張期血圧 85 以上、高血圧治療中を血圧異常あり、TG150 以上または HDL コレステロール 40 未満、脂質異常症治療中を脂質異常ありとした。

本研究は Grand Tower Medical Court Life Care Clinic 治験審査委員会で承認を受け、対象例は全て文書による同意を得ている

C. 研究結果

1） Adiponectin の分布

非 Metabolic syndrome の総 adiponectin の平均値は男性 4.70±2.26(n=2424)、女性 7.49±3.29 μg/ml(n=2793)で明らかに女性が高値を示した。一方、Metabolic syndrome ではそれぞれ 3.85±1.94(n=1037)および 5.50±2.96 μg /ml(n=114)で Metabolic syndrome で有意に低値であった。

2) Adiponectin を 10 分位法で区分し腹囲径は必須とし、危険因子を 2 個以上有する者を Metabolic syndrome とした。ROC 曲線から最も精度が高いのは男性では Adiponectin 値の cut off を 4.0 μg/ml 以下で感度は 64.7%、特異度は 56.0%であった。Cut off を 4.5 μg/ml 以下では感度は 74.2%に上昇するが、特異度は 45.4%に低下する。同様に女性についてみると Adiponectin 値の cut off を 6.1 μg/ml 以下では感度 69.3%、特異度 60.7%であった。Cut off を 6.9 μg/ml 以下で感度は 76.3%に上昇するが、特異度は 50.7%に低下した。

3） 内臓脂肪面積 100cm^2 以上を必須とした場合の Adiponectin の screening 精度

Adiponectin を 10 分位法で区分し Metabolic syndrome の screening 精度をみると、男性では Adiponectin 値が 4.0 μg/ml 以下が最も精度が良く、感度 65.4%、特異度 56.9%であった。同様に女性では Adiponectin 値が 6.1 μg/ml 以下の感度は 75.3%、特異度は 60.5%であった。

D.考察

健診を受診した 6,368 例（男性 3,461 例、

女性 2,907 例）において Adiponectin 値によって危険因子を含めて Metabolic syndrome 診断の診断が可能か否かを、症例を増やして検討した。前回までは Adiponectin で VFA の蓄積を予測できるか検討してきた。今回は危険因子を含めて Metabolic syndrome が screening 可能か否かを分析した。

Adiponectin を 10 分位法で区分して WC または VFA を必須として危険因子を 2 個以上有する者の Metabolic syndrome の screening 精度を比較した。今回は症例数も 6368 例と多い事から十分の解析を行うことができた。男性についてみると Adiponectin の cut off を 4.0 μg/ml 以下とするのが精度が最も高く、感度 64.7%、特異度 56.0%であった。VFA からみると、Adiponectin の cut off は同様で、感度は 65.4%、特異度 56.9%も大きな差はない。女性についてみると、精度が最も良いのは Adiponectin の cut off 値が 6.1 μg/ml 以下で WC を必須とした場合は感度 69.3%、特異度 60.7%、VFA を必須とするとそれぞれ 75.3%および 60.5%で、女性では VFA をもとにした方が Metabolic syndrome の screening 精度は上昇するが、男性では腹囲径も VFA も大きな差はない。Adiponectin は VFA が大きくなると低下することから本研究のデータは極めて妥当な結果と思われる。

一方、Metabolic syndrome の基準である臍周囲径の名前は分かり易いが必ずしも VFA と一致するものではなく、臍周囲径と VFA は相関係数 0.65～0.75 の相関を報告している。Metabolic syndrome の頻度は男性の 30.0%に比して女性では 3.9%に過ぎない。

Adiponectin 測定は他の生化学検査のために採血したものを活用して 1 滴の血液で可能であり、Adiponectin が低値の症例に対しては糖尿病、動脈硬化性疾患である心筋梗塞、脳梗塞を予防するための生活習慣への介入も可能である。

このことは Adiponectin で screening した方が効率的と思われる。現在 Adiponectin は単価が高いが、多くの症例に広く用いられれば安価となり、活用可能と思われる。

E. 結論

Adiponectin 測定は 1 滴の血液で測定可能であり、VFA との関連も強い。総 Adiponectin を測定して男性 4 μg/ml、女性 6 μg/ml を cut off とすれば、効率的に Metabolic syndrome を screening 可能と考える。

G. 研究発表

1.論文発表

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2.学会発表

藤川るみ、三玉敦子、伊藤千賀子（2013）アディポネクチン測定はメタボリックシンドロームの診断に有用か男女での検討人間ドック 28:346

藤川るみ、三玉敦子、伊藤千賀子（2014）健診における内臓脂肪面積減少例の臨床的特徴 病態栄養 17:S-175

「特定健診・保健指導におけるメタボリックシンドロームの診断・管理の
エビデンス創出に関する横断・縦断研究」分担報告書

身長・肥満度と脳卒中の発症リスクとの関連

- The Circulatory Risk in Communities Study (CIRCS)-

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研究要旨：身長・BMI と脳卒中の発症との関連を明らかにするため、CIRCS 研究において、40～69 歳の男性 4,822 と女性 7,400 人を対象者に、1985 年から 1994 年までにベースライン調査を行い、2007 年末までに追跡したところ、565 人の脳卒中が発症した。解析において、身長を 4 分位にし、身長低値群を基準にし、脳卒中発症のハザード比(95%信頼区間)を算出した。その結果、身長の低値群（男＜159cm、女＜148cm）に比べ、身長の高値群（男＞166cm、女＞154cm）での脳卒中の多変量調整ハザード比は、男性で 0.70 (0.49-1.00)、女性で 0,44 (0.27-0.70) であった。また、上記の関連を BMI 区分別（中央値 23kg/m²）に解析すると、BMI 低値群（＜23kg/m²）において、BMI 高値群（≧23kg/m²）に比べより強い負の関連を認められた。それぞれの多変量調整ハザードは、男性で 0.47 (0.25-0.87) と 0,91 (0.57-1.46)、相互作用の p 値は 0.047、女性で 0.23 (0.09-0.55) と 0.65 (0.36-1.15)、相互作用の p 値は 0.003 であった。本研究により、小児から青年期の社会環境や身体要素が将来の脳卒中の発症リスクとの関連する可能性を示している。

A．研究目的

先行研究により、小児から青年期の成長の指標としての身長は、脳卒中リスクと負の相関を示すことが報告されている。しかしながら、日本人の成人における身長と脳卒中発症の関連についてのコホート研究は限られている。

B．研究対象と方法

The Circulatory Risk in Communities Study（CIRCS）において、秋田井川町、高知県野市町、茨城県協和地区、大阪府八尾市の 4 地域の住民を対象に、1985～1999 年に循環器健診の受診者でかつ脳卒中または冠動脈疾患既往者を除いた 40-69 歳の男性 4,822 人と女性 7,400 人である。これらの対象者を 2007 年まで脳卒中の発症に関する追跡調査を行った。解析においては身長を 4 分位（男では＜159、159-162、163-166、＞166cm；女では＜148cm、148-150、151-154、＞154cm）に分けて、それぞれの低値群を基準にし、比例ハザード比モデルを用いて、それぞれ群のハザード比(95%信頼区間)を算出した。また、上記の関連をＢＭＩ高値群と低値群(BMI 中央値 23kg/m²)区分別に解析した。交絡因子として、年齢、地域、肥満度（BMI）、脳卒中家族

歴の有無、心拍数、喫煙（非喫煙、過去喫煙、現在喫煙）・飲酒（1合未満、1-2、2-3、3合以上/日）、血清総コレステロール値、血清クリアチニン値、糖尿病の有無、さらに、女性については閉経の有無を調整した。

C．研究結果

本研究により、男女とも身長に低値群に比べ、身長の高値群において脳卒中の発生リスクが有意に低く、上記の負の関連がＢＭＩ低値群でより強く認められた（表１）。身長の低値群（男＜159cm、女＜148cm）に比べ、身長の高値群（男＞166cm、女＞154cm）での脳卒中の多変量調整ハザード比は、男性で 0.70（0.49-1.00）であり、女性で 0,44（0.27-0.70）であった。また、上記の関連を BMI 区分別（中央値 23kg/m²）に見ると、BMI 低値群（＜23kg/m²）と BMI 高値群（≧23kg/m²）のそれぞれの多変量調整ハザードは、男性で 0.47（0.25-0.87）、0,91（0.57-1.46）相互作用の p 値は 0.047、女性で 0.23（0.09-0.55）、0.65（0.36-1.15）相互作用の p 値は 0.003 であった。

D．考察

本研究により、地域一般住民において、男女とも高身長が脳卒中の予防因子である可能性が示された。また、上記の関連が、BMI低値群においてより関連が強いことが明らかになった。

E．結論

本研究により、小児から青年期の成長環境や社会環境が将来の脳卒中の発症予防に働く可能性を示している。

F．データ管理・更新（倫理面への配慮）

対象地区からの転出は町と協力して調査を進めている。氏名や住所など個人を特定できる情報を削除し、解析を行う。この CIRCS コホート研究全体については、大阪大学と大阪がん循環器病予防センター（旧大阪健康科学センター）の倫理審査委員会で倫理審査を受け、承認を得ている。

G.論文発表

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Shimizu Y, Imano H, Ohira T, Kitamura A, Kiyama M, Okada T, Ishikawa Y, Shimamoto T, Yamagishi K, Tanigawa T, **Iso H**	Adult Height and Body Mass Index in Relation to Risk of Total Stroke and its Subtypes: The Circulatory Risk in Communities Study.	J Stroke Cerebrovasc Dis	23	667-674	2014

H. 知的財産権の出願・登録状況

1．特許取得　なし。
2．実用新案登録　なし。
3．その他　なし

表１　身長、ＢＭＩ区分別にみた脳卒中の多変量調整オッズ比*

	身長の4分位、cm			
	低値群	2	3	高値群
男性				
人数	1137	1160	1104	1166
脳卒中	107	82	67	47
ハザード比	1.00	0.85(0.64-1.14)	0.81(0.59-1.11)	0.70(0.49-1.00)
BMI＜23.0 kg/m^2				
人数	612	561	533	546
脳卒中	60	41	29	14
ハザード比	1.00	0.88(0.59-1.31)	0.71(0.45-1.11)	0.47(0.25-0.87)
BMI≥23.0 kg/m^2				
人数	525	599	571	620
脳卒中	47	42	38	33
ハザード比	1.00	0.86(0.57-1.32)	0.91(0.59-1.41)	0.91(0.57-1.46)
女性				
人数	1955	1459	1929	1865
脳卒中	114	66	59	22
ハザード比	1.00	1.01(0.75-1.38)	0.75(0.55-1.04)	0.44(0.27-0.70)
BMI＜23.0 kg/m^2				
人数	831	682	935	1031
脳卒中	51	22	21	6
ハザード比	1.00	0.72(0.43-1.20)	0.56(0.33-0.94)	0.23(0.09-0.55)
BMI≥23.0 kg/m^2				
人数	1124	777	994	834
脳卒中	63	44	38	16
ハザード比	1.00	1.34(0.90-1.97)	0.95(0.63-1.44)	0.65(0.36-1.15)

*身長の４分位（男で＜159、159-162、163-166、＞166cm；、女性で＜148、148-150、151-154、＞154cm）。
多変量調整因：年齢、地域、肥満度（BMI）、喫煙・飲酒、血清総コレステロール、血清クリアチニン、収縮値血圧値、心拍数、高血圧・糖尿病の服薬有無、脳卒中の家族歴、女性の場合は閉経の有無。

Adult Height and Body Mass Index in Relation to Risk of Total Stroke and its Subtypes: The Circulatory Risk in Communities Study

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Background: Several studies have reported that height and risk of stroke are inversely associated based on the hypothesis that height is a marker of childhood physical condition. However, a limited number of studies have taken account of the effect of current physical condition on the relationship between height and risk of stroke. *Methods:* We conducted a prospective cohort study of 12,222 40- to 69-year-old Japanese patients under systematic surveillance for stroke incidence. Because body mass index (BMI) is regarded as a surrogate marker of current physical condition for cardiovascular risk, we performed a stratified analysis of this risk based on BMI. *Results:* During the median 17-year follow-up, there were 565 incident strokes (326 ischemic and 186 hemorrhagic strokes) showing an inverse association between height and risk of stroke independent of classical cardiovascular risk factors. Compared with the lowest height group (<159 cm for men and <148 cm for women) as reference, the multivariable hazard ratios (HRs) and 95% confidence intervals (95% CIs) for the highest height group (>166 cm for men and >154 cm for women) were 0.70 (95% CI 0.49-1.00; $P = .043$) for men and 0.44 (95% CI 0.27-0.70; $P < .001$) for women. When the analysis was restricted to those with BMI <23 kg/m^2, the associations were stronger for both hemorrhagic and ischemic stroke. *Conclusions:* Height was found to be inversely associated with risk of stroke for middle-aged Japanese men and women, especially with lower BMIs. Our findings suggest that childhood social and physical conditions may contribute to the development of stroke in adulthood because height is a surrogate marker of these conditions. **Key Words:** Body mass index—follow-up study—height—risk—stroke.

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Height is an easily measured variable that is thought to be determined during childhood and adolescence by genetic predisposition, nutrition, physical and social environments, and other factors.[1-3] To determine the effect of these factors in early life on adult health, many investigators have examined associations between height and health by positing height as a surrogate marker of childhood social and physical conditions.

Previous studies have reported that height and risk of stroke are inversely associated.[4-6] The Japan Public Health Center-Based Prospective Study (JPHC) found that short stature was associated with an increased risk of total stroke and incidence of either hemorrhagic or ischemic stroke independent of adult socioeconomic status or cardiovascular risk factors.[4] A large prospective study of South Korean men reported a strong inverse association between height and mortality from hemorrhagic stroke.[5] The Asia Pacific Cohort Study Collaboration (APCSC), a large-scale collaborative project, established that height was inversely associated with risk of mortality from both total and hemorrhagic strokes but not from ischemic stroke.[6]

Cardiovascular risk factors can be regarded as determined not only by childhood but also current physical and social conditions. Genetics,[3] insulin-like growth factor (IGF-I),[7,8] renal function,[9] heart rate,[10] aortic pressure,[11] and central aortic pressure[12] have all been investigated as possible intermediate factors in the relationship between height and cardiovascular risk. It can be assumed that such factors, in terms of their influence on risk of cardiovascular disease, must also be strongly affected by current physical condition, which is completely independent from height as a risk factor. However, few studies have taken into account the potential effect of current physical condition on the association between height and risk of stroke. Because body mass index (BMI) is regarded to be a surrogate marker of current physical condition, and because a higher BMI is known to be a classical cardiovascular risk factor, we used long-term follow-up data for middle-aged Japanese patients investigate the association between height and risk of stroke and its subtypes in terms of BMI status.

Methods

Subjects

The Circulatory Risk in Communities Study (CIRCS) is a prospective, community-based study that was launched to prevent cardiovascular disease in Japanese populations.[13] The population surveyed included 4822 men and 7400 women between 40 and 69 years of age. Residents in the northeastern rural community of Ikawa and in the southwestern rural community of Noichi participated in this study between 1985 and 1990; those in the central rural community of Kyowa between 1985 and 1991; and those in the southwestern suburb of Yao between 1985 and 1994. Persons whose heart rate data (2 men and 3 women) and/or serum data (89 men and 103 women) and/or alcohol consumption data (10 men and 16 women) were not available or those with a history of stroke or coronary heart disease (154 men and 70 women) were excluded. The remaining 11,775 persons (4567 men and 7208 women) were followed up until the end of 2004 for residents of Kyowa and Noichi and until the end of 2007 for those of Ikawa and Yao to determine the incidence of stroke. The 671 persons (204 men and 467 women) who moved out of their respective communities during the follow-up and 1451 persons (845 men and 606 women) who died were censored at the date of moving out or date of death. The median follow-up period for this study was 17.1 years.

Baseline Examination

Details of the risk factor survey have been described elsewhere.[13] Briefly, height in stocking feet and weight in light clothing were measured, while BMI was calculated as weight (kg)/height $(m)^2$.

Nonfasting blood samples were obtained, and serum was separated and centrifuged after blood coagulation. Serum samples were also obtained in a siliconized tube. Serum total cholesterol, glucose, and creatinine were determined with the enzyme method, hexokinase method, and noncompensated kinetic Jaffe method, respectively. A Sequential Multiple Analyzer with Computer (Technicon, Tarrytown, NY) was used for all measurements.

Systolic and fifth-phase diastolic blood pressures in the right arm were measured by trained technicians using a standard mercury sphygmomanometer. Trained interviewers obtained information on family history of stroke, smoking status, the use of antihypertensive agents, medical histories, and usual weekly intake of alcohol in units of "*go*" (a traditional Japanese unit of volume corresponding to 23 g of ethanol), which was converted to grams of ethanol per day. One *go* equals 180 mL of sake rice wine and corresponds to 1 bottle (633 mL) of beer, 2 single shots (75 mL) of whiskey, or 2 glasses (180 mL) of wine. Persons who reported consuming ≥0.3 *go* per week were regarded as current drinkers.[13,14] Diabetes mellitus was defined as a fasting glucose level of ≥7.8 mmol/L, a nonfasting glucose level of ≥11.1 mmol/L, and/or the use of a medication for diabetes.

Endpoint Determination

Assessments of medical history, incidence, and death were conducted once a year during the follow-up period. Stroke incidence was ascertained by using 6 complementary sources: (1) national insurance claims, (2) reports by local physicians, (3) ambulance records, (4) death certificates, (5) reports by public health nurses and health volunteers, and (6) cardiovascular risk surveys.[15] Cases with stroke as the underlying cause of death (*International*

Classification of Diseases, 9th revision, codes 430-438) were selected from death certificates. To confirm the diagnosis of stroke, all living patients were visited or asked to complete risk factor surveys. Physicians participating in this study obtained a medical history and a history of neurologic examinations from stroke patients. For death, histories were obtained from the families, and medical records were reviewed.

Stroke was defined as a focal neurologic disorder with rapid onset and persisting for at least 24 hours or until death. This clinical criterion was used to determine the incidence of stroke by a panel of 3 to 4 physicians participating in the study who were blinded to the data from the risk factor survey. The determination of stroke subtype—ischemic stroke, intraparenchymal hemorrhage, or subarachnoid hemorrhage—was conducted primarily by means of computed tomographic (CT)/magnetic resonance imaging (MRI) scans using a standard procedure. Intraparenchymal hemorrhage and subarachnoid hemorrhage were defined as hemorrhagic stroke. CT/MRI scans were available for 93.0% of stroke cases. Stroke cases that were diagnosed clinically but showed no lesion on CT/MRI films were classified according to clinical criteria based on those established by Millikan.[16]

Statistical Analysis

Because a previous Japanese study reported detecting sex differences in the age-adjusted relationship between height and stroke mortality, we conducted a sex-specific analysis.[17] Differences in age- and community-adjusted mean values or the prevalence of possibly confounding factors at baseline by height quartile were calculated by using analysis of variance or logistic regression models. Cox proportional hazard regression models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) of incidence of stroke and its subtypes associated with height levels. We tested proportionality by evaluating the interaction between height and time for stroke incidence and found no violation in the proportional hazard assumption. In addition, subjects were stratified by BMI status because a relatively higher BMI is regarded as one of the most common cardiovascular risk factors.[18] Because the World Health Organization (WHO) has identified a BMI $\geq$23 kg/m^2, which corresponds to the median values of BMI for men and women in our study, as an indicator for enhanced risk of disease for Asian populations,[19] we made 23 kg/m^2 the BMI cutoff point. Adjustments for confounding factors were made in 2 ways. First, we adjusted only for age and community. Second, we included the other possible confounding factors: BMI (kg/m^2), family history of stroke (yes/no), systolic blood pressure (mm Hg), use of antihypertensive agents (yes/no), heart rates (beats per minute), smoking status (never smoker, former smoker, or current smoker), alcohol consumption (never drinker, former drinker, and current drinker [<23 g/week, 23-46 g/week, 46-69 g/week, and >69 g/week]), serum total cholesterol (mg/dL), serum creatinine (mg/dL), diabetes mellitus (yes/no), and for women menopausal status (pre- or postmenopausal).

All statistical analyses were conducted with SAS software (version 9.1; SAS Inc., Cary, NC). All P values for statistical tests were 2-tailed, and values <.05 were considered statistically significant.

Results

Of the 4567 men and 7208 women, 565 suffered incident strokes during the 17-year follow-up period. These were 304 total strokes (192 ischemic strokes, 59 intraparenchymal hemorrhages and 19 subarachnoid hemorrhages, and 34 unclassified strokes) for men, and the corresponding numbers for women were 261, 134, 68, 40, and 19.

Table 1 shows sex-specific baseline characteristics by height quartile. Weight and the ever drinker category were positively associated with height for both men and women. Diastolic blood pressure and serum creatinine were positively associated with height for men, and the current smoker category was inversely associated with height for men. Current smoking and drinking were positively associated, and systolic blood pressure, antihypertensive medication use, BMI, diabetes mellitus, and family history of stroke inversely associated with height for women.

As shown in Table 2, height was inversely associated with the risk of total stroke for both men and women; the multivariable HR of total stroke for the highest versus lowest height quartiles were 0.70 (95% CI 0.49-1.00; P = .043) for men and 0.44 (0.27-0.70; P < .001) for women. When the analyses were restricted to persons with BMI <23 kg/m^2, the inverse associations became stronger. The corresponding HR was 0.47 (0.25-0.87; P = .011) for men and 0.23 (0.09-0.55; P < .001) for women, while no significant associations were observed for persons with BMI $\geq$23 kg/m^2 (P for interaction 0.047 for men and 0.003 for women).

In addition, an inverse association was also observed for either ischemic or hemorrhagic stroke for both men and women with BMI <23 kg/m^2 (Table 3). The multivariable HRs of ischemic and hemorrhagic strokes for the highest versus lowest height quartiles were 0.41 (0.17-0.99; P = .049) and 0.28 (0.09-0.94; P = .035) for men and 0.07 (0.01-0.51; P = .001) and 0.46 (0.16-1.32; P = .054) for women.

Discussion

A major finding of the present study was that height was inversely associated with the risk of total stroke for both Japanese men and women. This association was limited to persons with a relatively lower BMI (<23 kg/m^2) and the association obtained for either ischemic or hemorrhagic stroke.

Table 1. *Sex-specific and age- and community-adjusted mean values and percentages by height quartile*

	Height quartile*				
	Q1 (lowest)	Q2	Q3	Q4 (highest)	*P* value
Men					
Median height (cm)	156	161	164	169	
No. of patients at risk	1137	1160	1104	1166	
Age (y)	57.9	55.6	53.7	50.1	
Family history of stroke†	26	26	25	23	.335
Systolic blood pressure (mm Hg)	133.3	133.4	133.1	132.2	.362
Diastolic blood pressure (mm Hg)	81.1	82.0	82.5	83.0	.002
Antihypertensive medication use (%)	14	14	14	12	.461
Body mass index (kg/m^2)	23.0	23.3	23.2	23.3	.159
Weight (kg)	55.5	60.0	62.8	67.3	<.001
Heart rate (beats/min)	68	67	68	68	.106
Diabetes mellitus (%)	6	6	5	6	.783
Current smoker (%)	60	59	58	54	.019
Ex-smoker (%)	81	82	84	84	.238
Current drinker (%)	76	78	79	81	.069
Ex-drinker (%)	69	73	74	74	.039
Total cholesterol (mg/dL)	191	191	190	190	.637
Serum creatinine (mg/dL)	0.99	1.00	1.01	1.02	<.001
Women					
Median height (cm)	145	149	152	157	
No. of patients at risk	1955	1459	1929	1865	
Age (y)	58.1	54.7	52.7	48.7	
Family history of stroke†	28	29	26	24	.002
Systolic blood pressure (mm Hg)	131.3	130.4	130.3	129.6	.046
Diastolic blood pressure (mm Hg)	78.6	78.5	78.9	78.7	.728
Antihypertensive medication use (%)	15	14	13	11	.033
Body mass index (kg/m^2)	23.8	23.6	23.4	23.0	<.001
Weight (kg)	49	52	54	57	<.001
Heart rate (beats/min)	72	71	71	71	.147
Diabetes mellitus (%)	3	3	2	2	.025
Current smoker (%)	6	5	6	8	.010
Ex-smoker (%)	7	7	7	10	.010
Current drinker (%)	9	10	10	13	.002
Ex-drinker (%)	10	11	11	14	.001
Total cholesterol (mg/dL)	204	203	204	201	.209
Serum creatinine (mg/dL)	0.80	0.80	0.80	0.81	.182
Postmenopausal (%)	62	63	63	62	.934

*Height quartiles were <159 cm, 159-162 cm, 163-166 cm, and >166 cm for men and <148 cm, 148-150 cm, 151-154 cm, and >154 cm for women.

†Family history of stroke: stroke history of parents.

The Japan Public Health Center-Based Prospective Study (JPHC), with an enrollment of 15,564 Japanese men and women between 40 and 59 years of age established inverse associations of height with the incidence of total, ischemic, and hemorrhagic strokes, with multivariable HRs (95% CI) for a height increment of 1SD (6.43 cm for men, 5.79 cm for women) of 0.82 (0.74-0.90), 0.83 (0.73-0.95), and 0.80 (0.70-0.92), respectively.[4] The NIPPON DATA80 study, which followed 3969 and 4955 Japanese men and women for 19 years, reported that height was inversely associated with stroke mortality multivariable HRs (95%CI) for a 5-cm increment of 0.92 (0.79-1.08) for men and 0.77 (0.64-0.91) for women.[17] The Asia Pacific Cohort Study Collaboration (APCSC) reported establishing a significant association between height and risk of total stroke, and especially for hemorrhagic stroke, for both men and women. The multivariable HRs (95%CI) of total, ischemic, and hemorrhagic strokes per 1 standard deviation (6 cm for men and women) increase in height for Asian populations were 0.93 (0.90-0.97), 0.98 (0.92-1.04), and 0.90 (0.84-0.96), respectively, for men and 0.93 (0.88-0.98), 0.98 (0.89-1.07), and 0.86 (0.78-0.95), respectively, for women.[6] We found additional evidence that the significant inverse

Table 2. *Sex-specific hazard ratios and 95% confidence intervals for total stroke in relation to height for total subjects and stratified by body mass index*

	Quartile of height*					
	Q1 (low)	Q2	Q3	Q4 (high)	*P* value for trend	1 Standard deviation increments in height
Men						
Total subjects						
No. of patients at risk	1137	1160	1104	1166		
No. of cases (%)	107 (9.4)	83 (6.1)	67 (7.2)	47 (4.0)		
Age- and community-adjusted HR	1.00	0.87 (0.65-1.15)	0.84 (0.61-1.14)	0.68 (0.47-0.97)	.034	0.91 (0.81-1.03)
Multivariable HR†	1.00	0.85 (0.64-1.14)	0.81 (0.59-1.11)	0.70 (0.49-1.00)	.043	0.91 (0.80-1.03)
BMI <23 kg/m^2						
No. of patients at risk	612	561	533	546		
No. of cases (%)	60 (9.8)	41 (7.3)	29 (5.4)	14 (2.6)		
Age- and community-adjusted HR	1.00	0.85 (0.57-1.27)	0.73 (0.46-1.14)	0.42 (0.23-0.76)	.004	0.82 (0.69-0.98)
Multivariable HR†	1.00	0.88 (0.59-1.31)	0.71 (0.45-1.11)	0.47 (0.25-0.87)	.011	0.85 (0.71-1.01)
BMI ≥23 kg/m^2						
No. of patients at risk	525	599	571	620		
No. of cases (%)	47 (9.0)	42 (7.0)	38 (6.7)	33 (5.3)		
Age- and community-adjusted HR	1.00	0.88 (0.58-1.34)	0.93 (0.60-1.43)	0.92 (0.58-1.46)	.768	0.99 (0.84-1.18)
Multivariable HR†	1.00	0.86 (0.57-1.32)	0.91 (0.59-1.41)	0.91 (0.57-1.46)	.733	0.98 (0.82-1.17)
Women						
Total subjects						
No. of patients at risk	1955	1459	1929	1865		
No. of cases (%)	114 (5.8)	66 (4.5)	59 (3.1)	22 (1.2)		
Age- and community-adjusted HR	1.00	0.97 (0.72-1.32)	0.75 (0.54-1.03)	0.42 (0.26-0.68)	<.001	0.76 (0.67-0.87)
Multivariable HR†	1.00	1.01 (0.75-1.38)	0.75 (0.55-1.04)	0.44 (0.27-0.70)	<.001	0.77 (0.67-0.87)
BMI <23 kg/m^2						
No. of patients at risk	831	682	935	1031		
No. of cases (%)	51 (6.1)	22 (3.2)	21 (2.2)	6 (0.6)		
Age- and community-adjusted HR	1.00	0.69 (0.42-1.14)	0.58 (0.34-0.97)	0.29 (0.10-0.56)	<.001	0.65 (0.53-0.80)
Multivariable HR†	1.00	0.72 (0.43-1.20)	0.56 (0.33-0.94)	0.23 (0.09-0.55)	<.001	0.66 (0.54-0.81)
BMI ≥23 kg/m^2						
No. of patients at risk	1124	777	994	834		
No. of cases (%)	63 (5.6)	44 (5.7)	38 (3.8)	16 (1.9)		
Age- and community-adjusted HR	1.00	1.23 (0.83-1.81)	0.90 (0.60-1.36)	0.62 (0.35-1.10)	.135	0.86 (0.73-1.02)
Multivariable HR†	1.00	1.34 (0.90-1.97)	0.95 (0.63-1.44)	0.65 (0.36-1.15)	.209	0.86 (0.72-1.03)

Abbreviations: BMI, body mass index; HR, hazard ratio.

*Height quartiles were <159 cm, 159-162 cm, 163-166 cm, and >166 cm for men and <148 cm, 148-150 cm, 151-154 cm, and >154 cm for women.

†Adjusted further for age and community, body mass index, smoking, alcohol intake, serum total cholesterol, serum creatinine, systolic blood pressure, heart rates, antihypertensive medication use, diabetes mellitus, family history of stroke, and for women menopausal status.

Table 3. *Sex-specific hazard ratios and 95% confidence intervals for ischemic and hemorrhagic strokes in relation to height for persons with relatively lower body mass index (<23 kg/m^2)*

	Quartile of height*					1 Standard deviation increment in height
	Q1 (low)	Q2	Q3	Q4 (high)	*P* value for trend	
Men						
Ischemic stroke						
No. of cases (%)	38 (6.2)	25 (4.5)	18 (3.4)	6 (1.1)		
Age- and community-adjusted HR	1.00	0.87 (0.52-1.44)	0.78 (0.44-1.38)	0.34 (0.14-0.81)	.020	0.79 (0.63-0.99)
Multivariable HR†	1.00	0.89 (0.53-1.49)	0.76 (0.43-1.34)	0.41 (0.17-0.99)	.049	0.83 (0.66-1.04)
Hemorrhagic stroke‡						
No. of cases (%)	17 (2.8)	12 (2.1)	9 (1.7)	4 (0.7)		
Age- and community-adjusted HR	1.00	0.80 (0.38-1.68)	0.67 (0.29-1.52)	0.29 (0.10-0.90)	.031	0.82 (0.60-1.18)
Multivariable HR†	1.00	0.81 (0.38-1.72)	0.65 (0.28-1.48)	0.28 (0.09-0.94)	.035	0.83 (0.60-1.16)
Intraparenchymal hemorrhage						
No. of cases (%)	13 (2.1)	11 (2.0)	5 (0.9)	4 (0.7)		
Age- and community-adjusted HR	1.00	0.98 (0.44-2.20)	0.52 (0.18-1.47)	0.42 (0.13-1.35)	.080	0.85 (0.59-1.22)
Multivariable HR†	1.00	0.97 (0.43-2.19)	0.50 (0.18-1.42)	0.43 (0.13-1.40)	.084	0.86 (0.60-1.24)
Subarachnoid hemorrhage						
No. of cases (%)	4 (0.7)	1 (0.2)	4 (0.8)	0 (0)		
Age- and community-adjusted HR	1.00	—	—	—		0.71 (0.35-1.42)
Multivariable HR†	1.00	—	—	—		0.57 (0.21-1.52)
Women						
Ischemic stroke						
No. of cases (%)	27 (3.2)	13 (1.9)	12 (1.3)	1 (0.1)		
Age- and community-adjusted HR	1.00	0.75 (0.38-1.46)	0.59 (0.24-1.19)	0.07 (0.01-0.51)	.002	0.65 (0.50-0.86)
Multivariable HR†	1.00	0.77 (0.39-1.45)	0.53 (0.26-1.10)	0.07 (0.01-0.51)	.001	0.65 (0.49-0.86)
Hemorrhagic stroke‡						
No. of cases (%)	20 (2.4)	7 (1.0)	6 (0.6)	5 (0.5)		
Age- and community-adjusted HR	1.00	0.55 (0.23-1.31)	0.41 (0.16-1.03)	0.46 (0.16-1.32)	.049	0.62 (0.45-0.85)
Multivariable HR†	1.00	0.29 (0.25-1.43)	0.42 (0.17-1.08)	0.46 (0.16-1.32)	.054	0.64 (0.46-0.88)
Intraparenchymal hemorrhage						
No. of cases (%)	15 (1.6)	3 (0.4)	3 (0.3)	3 (0.3)		
Age- and community-adjusted HR	1.00	0.32 (0.09-1.13)	0.29 (0.08-1.01)	0.42 (0.11-1.58)	.050	0.51 (0.35-0.73)
Multivariable HR†	1.00	0.34 (0.10-1.21)	0.28 (0.08-1.01)	0.38 (0.10-1.43)	.039	0.50 (0.33-0.74)
Subarachnoid hemorrhage						
No. of cases (%)	5 (0.6)	4 (0.6)	3 (0.3)	2 (0.2)		
Age- and community-adjusted HR	1.00	1.19 (0.32-4.51)	0.75 (0.17-3.23)	0.60 (0.11-3.48)	.507	0.90 (0.51-1.59)
Multivariable HR†	1.00	1.33 (0.35-5.11)	0.85 (0.19-3.74)	0.69 (0.12-3.99)	.123	0.97 (0.55-1.71)

Abbreviation: HR, hazard ratio.

*Height quartiles were <159 cm, 159-162 cm, 163-166 cm, and >166 cm for men and <148 cm, 148-150 cm, 151-154 cm, and >154 cm for women.

†Adjusted further for age and community, body mass index, smoking, alcohol intake, serum total cholesterol, serum creatinine, systolic blood pressure, heart rates, antihypertensive medication use, diabetes mellitus, family history of stroke, and for women menopausal status.

‡Intraparenchymal hemorrhage and subarachnoid hemorrhage.

association between height and risk of stroke were confined to men and women with lower BMI values. In addition, those significant associations were observed for both ischemic and hemorrhagic strokes.

The mechanisms for the associations between height and risk of stroke, especially for nonoverweight persons, warrant discussion. Because height is regarded as a surrogate marker of childhood social and physical conditions while BMI may reflect primarily current physical conditions, a detailed analysis of persons with lower BMI may elucidate a potential effect of childhood conditions.

Throughout the fetal period and childhood, environmental factors, such as nutrition and socioeconomic circumstances, have a profound effect on childhood development.[20]

Adverse socioeconomic conditions early in life have been associated with a risk of stroke mortality,[21] and low intake of animal protein in adulthood with increased blood pressure[22] and the risk of intraparenchymal hemorrhage.[23] Another study of children (>2 years) reported that blood pressure levels either for systolic or diastolic were higher in malnourished children and in those who had recovered from malnutrition after an average follow-up period of 6 years.[24] That finding suggests that malnutrition in childhood may lead to the higher risk of stroke in adulthood.

Genetic factors also may contribute to the effect of short stature. According to a prospective study of 35,000 pairs of twins of Denmark, Finland, and Sweden, twins who died from coronary heart disease were shorter than their monozygotic twin (OR 1.27; 95% CI 1.12-1.44), but such a difference was not found in dizygotic twins (OR 1.07; 95% CI 0.98–1.16).[3] This means that the relationship between height and coronary heart disease mortality could be explained in terms of environmental rather than genetic influences. However, that study did not take stroke as endpoint into account. additional studies are needed to examine if heredity explains the relationship between height and risk of stroke.

As for the mechanism involved, it is plausible that IGF-I mediates the association between height and risk of stroke because IGF-I levels are reportedly positively associated with height in childhood[25] and inversely associated with the risks of ischemic stroke[7] and intraparenchymal hemorrhage.[8]

Birth weight and height correlate strongly with adult height,[26] and low birth weight is known to be associated with altered renal shape, reduced renal volume, and fewer nephrons.[27] Short stature may therefore increase the chance of kidney malfunction and hypertension occurring later in life,[9] which may lead to a higher risk of stroke. In our study, however, the association between height and risk of stroke was observed even after adjustment for serum creatinine levels.

The physical conditions associated with short stature may also explain the association between height and risk of stroke. Persons with shorter stature are likely to have faster heart rates and reduced return time for reflected waves and augmentation of primary systolic pulses, which may then lead to increased central aortic pressure.[12] In addition, while faster heart rates[10] and increased central aortic pressure[11] have been associated with increased risk of cardiovascular disease, adjustment for heart rate did not alter associations in our study.

Our findings should be interpreted with some caution. First, we did not have access to information about childhood physical data, such as blood pressure, or sera data, which tended to limit our estimation of childhood conditions. Second, we did not have access to creatinine clearance data, so no conclusion could be reached about the influence of renal dysfunction on the associations between height and risk of stroke. However, our study showed that these associations remained significant even after adjusting for serum creatinine. We could not conduct a meaningful statistical analysis for subtypes of hemorrhagic stroke because of the limited number of cases among persons with lower BMI. However, similar associations were observed for both intraparenchymal and subarachnoid hemorrhage.

In conclusion, we determined that height was inversely associated with risk of stroke among middle-aged Japanese men and women. That inverse association for either hemorrhagic or ischemic stroke was limited to persons with lower BMI, which suggests that childhood social and physical conditions may contribute to the development of stroke in adulthood.

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