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Impact of blood pressure levels on different types of stroke: the Hisayama study

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Objective **Clinical uncertainty remains whether the blood pressure classification and risk stratifications recommended by the Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2009) are useful in predicting the risks of stroke and its subtypes in the general Japanese population.**

Methods **A total of 1621 stroke-free residents of a Japanese community aged at least 40 years were followed up for 32 years. Outcomes were total and cause-specific stroke (lacunar infarction, atherothrombotic infarction, cardioembolic infarction, cerebral haemorrhage and subarachnoid haemorrhage). Incidence was calculated by the pooling of repeated observations method.**

Results **The age-adjusted incidence of total stroke rose progressively with higher blood pressure levels in both sexes (both *P* for trend <0.0001). A similar pattern was observed for lacunar infarction in both sexes and for cerebral haemorrhage in men: the differences were significant between optimal blood pressure and grades 1–3 hypertension (all $P<0.05$). The age-adjusted incidence of atherothrombotic infarction in either sex and that of cardioembolic infarction and subarachnoid haemorrhage in women significantly increased in grade 3 hypertension (all $P<0.05$). These associations remained substantially unchanged even after adjustment for other risk factors. In regard to risk stratification, the age-adjusted incidence of stroke significantly increased with the level of risk in both sexes.**

Conclusion **Our findings suggest that the blood pressure classification and risk stratifications recommended by the JSH 2009 guidelines are useful in predicting the risk of stroke in a general Japanese population, but the magnitude and patterns of the impact of blood pressure categories are different among stroke subtypes. *J Hypertens* 27:2437–2443 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

Journal of Hypertension 2009, 27:2437–2443

Keywords: blood pressure, stroke, stroke subtype, prospective cohort study, risk factor

Abbreviations: JSH, Japanese Society of Hypertension; LVH, left ventricular hypertrophy; TOD, target organ damage

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Received 24 February 2009 Revised 5 June 2009
Accepted 13 July 2009

Introduction

Recent guidelines for the management of hypertension recommend assessment of total cardiovascular risk using risk factors, target organ damage (TOD) and pre-existing cardiovascular disease, as well as blood pressure levels [1–3]. These classifications have primarily been established based on clinical and epidemiological studies that investigated the risks of coronary heart disease, stroke and other forms of cardiovascular diseases in Western populations. However, there has been shown to be significant heterogeneity in the incidences of stroke and the frequencies of stroke subtypes between Asian and Western populations: the stroke incidence is higher, as is the proportion of stroke due to parenchymatous small arterial lesions, in Asian populations than in Western populations [4–7]. Because of the heterogeneity in the pathogenesis of stroke subtypes, the impact of blood pressure levels should be evaluated separately for each stroke subtype. Despite clear evidence of the associations between blood pressure levels and the incidence of total stroke [1–3,7–10], clinical uncertainty remains about the impact of blood pressure on the risks of different types of stroke, particularly on the risks of cerebral infarction subtypes.

The Hisayama study is a prospective cohort study of cardiovascular disease conducted in the town of Hisayama, Japan [6,11,12]. During the study period, 93% of the first-ever stroke patients underwent morphological examinations by autopsy and/or brain imaging, and more than 80% of the total number of surviving patients participated in five repeated follow-up examinations. This characteristic study design provided us an

A free communication on a portion of this study was presented at the 18th Scientific Meeting of the European Society of Hypertension/the 22nd Scientific Meeting of the International Society of Hypertension held in Berlin in June 2008.

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DOI:10.1097/HJH.0b013e328330e882

opportunity to classify stroke into different types with a high degree of accuracy and to assess the stroke incidence, taking into account the dynamic transition of blood pressure. In the present article, we examined whether the blood pressure classification and risk stratifications recently recommended by the Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2009) [3] are useful in predicting the occurrence of stroke and its subtypes in Japanese.

Methods

Study population and follow-up survey

In 1961, 1621 stroke-free residents of the town of Hisayama, aged 40 years or over (participation rate 88%), were enrolled in the present study [6,11,12]. Members of this cohort have received follow-up evaluations for 32 years from 1 November 1961 through 30 October 1993. Health examinations were repeated in 1967, 1974, 1978, 1983 and 1988, and the participation rates for these examinations were 96, 87, 85, 81 and 98%, respectively.

For patients who did not undergo regular examinations or who moved out of Hisayama, health status was checked yearly by mail or telephone. We also established a daily monitoring system, which connected us with local physicians and the members of the Health and Welfare Office of the town, and used this system to gather information on new events of stroke, inclusive of suspected cases [6,11,12]. When stroke occurred or was suspected, physicians in the study team examined the patients and evaluated their detailed clinical information. The clinical diagnosis of stroke was based on the patient's history, physical and neurological examinations, and ancillary laboratory examinations. During the follow-up period, 1063 patients died, and 861 of these (81%) underwent autopsy to pathologically verify the cause of death and type of stroke. Only two patients were lost to follow-up.

The ethics committee of Kyushu University approved this study, participants provided written informed consent, and the procedures followed were in accordance with national guidelines.

Risk factor assessment

At each examination, blood pressure was measured three times using a standard sphygmomanometer after resting for at least 5 min in a supine position. Korotkoff phase 5 was taken as the diastolic blood pressure unless the sounds persisted at zero, in which case Korotkoff phase 4 was recorded. The mean of three measurements was used in the present analysis. We collected medical history and lifestyle information and conducted physical and neurological examinations. Information on antihypertensive treatment, smoking habits and alcohol intake was obtained using a standard questionnaire, and these factors were classified as being either habitually used or not used. Left ventricular hypertrophy (LVH; Minnesota code 3-1), ST depression (4-1, 2, 3 except for 3-1) and atrial fibrillation (8-3) on electrocardiography (ECG) were separately evaluated. Body weight and height were measured, and body mass index (BMI, kg/m^2) was calculated. Proteinuria was tested by the sulfosalicylic acid method in 1961 and 1967, and by the test paper method in 1974, 1978, 1983 and 1988. Serum cholesterol levels were determined by the Zak-Henly method, including a modification by Yoshikawa, in 1961 and 1967; by the Zurkowski method in 1974; and by the enzymatic method in 1978, 1983, and 1988 [13,14]. Glucose intolerance was determined by an oral glucose tolerance test in patients with glycosuria in 1961 and 1967, casual blood glucose levels in 1974, 1978 and 1983, and a 75-g oral glucose tolerance test in 1988, as well by reference to any medical history of diabetes at each examination [15,16].

Blood pressure classification and risk stratification

The JSH 2009 guidelines propose the following blood pressure categories: optimal blood pressure (systolic blood pressure < 120 mmHg and diastolic blood pressure < 80 mmHg), normal blood pressure (120–129/80–84 mmHg), high normal blood pressure (130–139/85–89 mmHg), grade 1 hypertension (140–159/90–99 mmHg), grade 2 hypertension (160–179/100–109 mmHg) and grade 3 hypertension ($\geq$180/110 mmHg) [3]. The guidelines also recommend a risk stratification system that determines the whole cardiovascular risk using blood pressure categories and the presence or absence of other risk factors and TOD. In this study, risk factors were defined as age ($\geq$65 years), dyslipidemia (total cholesterol >5.7 mmol/l), glucose intolerance and obesity (BMI $\geq 25\ kg/m^2$), and TOD was defined as electrocardiographic LVH (Minnesota code 3-1) and 1+ or more positive proteinuria. On the basis of the risk stratification system of the JSH 2009 guidelines, we classified patients into four risk groups. Specifically, the no additive risk group included patients with optimal and normal blood pressure and those with high-normal blood pressure who did not have risk factors or TOD. The low-risk group included patients with grade 1 hypertension who did not have risk factors or TOD. The moderate-risk group included patients with high-normal blood pressure and grade 1 hypertension who had one to two risk factors and those with grade 2 hypertension who did not have risk factors or TOD. The high-risk group included patients with high-normal blood pressure and grade 1 hypertension who had three or more risk factors, glucose intolerance or TOD, patients with grade 2 hypertension who had 1 or more risk factors, glucose intolerance or TOD and patients with grade 3 hypertension.

Stroke definition

The diagnosis of stroke was based on clinical information and the autopsy findings [6]. In principle, stroke was defined as a sudden onset of nonconvulsive and focal

neurological deficits persisting for more than 24 h, and the stroke was then classified as cerebral infarction, cerebral haemorrhage, subarachnoid haemorrhage or undetermined type of stroke. Cerebral infarction was further divided into four clinical categories: lacunar infarction, atherothrombotic infarction, cardioembolic infarction or undetermined type of cerebral infarction, based on the Classification of Cerebrovascular Disease III proposed by the National Institute of Neurological Disorders and Stroke [17], the criteria for the type of stroke of the TOAST study [18] and the Cerebral Embolism Task Force [19].

During the follow-up period, a total of 410 patients (200 men and 210 women) developed a first-ever stroke, and 381 of these (93%) underwent morphological examinations, including an examination of the cerebrospinal fluid, cerebral angiography, recent brain imaging including computed tomography and magnetic resonance imaging, echocardiography, carotid duplex imaging, and autopsy. Autopsies were performed on 303 stroke cases (74%). Of the 410 stroke cases that developed, 374 (181 men and 193 women) who participated in a follow-up examination within the 7 years previous to the stroke occurrence were eligible for the present study. These stroke cases were divided into 270 cases of cerebral infarction (128 men and 142 women), 68 of cerebral haemorrhage (45 and 23), 32 of subarachnoid haemorrhage (6 and 26) and four of an undetermined type of stroke (2 and 2). The cerebral infarction cases were further subdivided into 153 cases of lacunar infarction (72 and 81), 58 of atherothrombotic infarction (26 and 32), 51 of cardioembolic infarction (28 and 23) and eight of an undetermined type of cerebral infarction (2 and 6).

Statistical analysis

The incidence of stroke and its subtypes was calculated by the pooling of repeated-observations method [12,20,21]. This technique is a generalized person-years approach that incorporates all repeated examinations. It treats each examination interval as a mini follow-up study, in which the nearest risk factor measurements are employed to predict an event in the interval. Observations over multiple intervals are pooled into a single sample to predict the short-term risk of an event. The incidence was compared and the hazard ratios were estimated by the time-dependent Cox's proportional hazards model, in which risk factors other than age and sex were allowed to change in accordance with data from the five follow-up examinations. $P < 0.05$ was considered to indicate statistical significance.

Results

Baseline characteristics

Table 1 shows the mean values or frequencies of risk factors for stroke at each examination by sex. The mean age was 56 years for men and 57 years for women at

Table 1 Means (±SD) or frequencies of risk factors at each examination among men and women

Risk factors	Men						Women					
	1961 ($n=707$)	1967 ($n=559$)	1974 ($n=396$)	1978 ($n=341$)	1983 ($n=278$)	1988 ($n=259$)	1961 ($n=914$)	1967 ($n=768$)	1974 ($n=599$)	1978 ($n=546$)	1983 ($n=436$)	1988 ($n=442$)
Age (years)	56±11	60±10	66±9	68±7.3	72±7	75±6	57±12	61±10	67±9	69±8	72±7	75±6
Systolic blood pressure (mmHg)	135±26	141±28	145±26	139±23	142±24	140±23	135±26	137±27	146±26	145±23	148±24	143±25
Diastolic blood pressure (mmHg)	79±14	82±14	80±12	79±11	80±12	77±12	77±13	79±13	79±12	79±11	79±11	75±11
Blood pressure category (%)												
Optimal (<120/80 mmHg)	30.0	24.5	17.7	20.2	15.5	18.9	32.4	29.0	15.0	13.9	11.2	15.6
Normal (120–129/80–84 mmHg)	18.3	13.8	13.9	14.7	16.2	16.2	16.1	13.9	13.4	13.2	10.8	15.4
High-normal (130–139/85–89 mmHg)	13.3	14.0	13.6	18.8	14.4	15.4	14.3	12.1	14.0	15.0	15.4	14.3
Grade 1 (140–159/90–99 mmHg)	19.4	22.2	27.5	27.0	31.3	30.9	19.4	25.4	30.2	32.1	31.2	30.8
Grade 2 (160–179/100–109 mmHg)	10.6	14.7	15.4	13.2	15.5	11.6	10.9	11.5	16.2	18.9	22.5	16.5
Grade 3 (≥180/110 mmHg)	8.5	10.9	11.9	6.2	7.2	7.0	6.9	8.1	11.2	7.0	8.9	7.5
Antihypertensive agent (%)	2.1	15.4	13.6	19.8	24.1	23.9	2.2	18.1	12.0	17.6	23.6	25.1
Left ventricular hypertrophy (%)[a]	22.0	17.5	19.4	19.1	23.3	18.2	10.3	10.2	10.2	15.0	21.9	14.8
ST depression (%)[b]	2.1	1.1	5.3	2.6	3.0	3.9	3.8	2.6	7.5	5.3	6.0	6.4
Atrial fibrillation (%)[c]	0.7	1.1	3.3	3.2	3.7	4.3	0.7	0.8	1.3	1.3	1.0	2.1
Glucose intolerance (%)	12.2	15.2	20.7	21.4	22.3	25.9	4.8	5.1	9.8	11.7	13.8	25.2
Body mass index (kg/m^2)	21.5±2.4	21.5±2.4	21.2±2.7	21.4±3.0	21.3±3.2	21.5±3.0	21.7±2.9	22.1±3.3	22.2±3.5	22.2±3.4	22.0±3.4	22.1±3.5
Total cholesterol (mmol/l)	3.9±0.9	4.1±0.8	4.6±0.9	4.6±1.0	4.8±1.0	4.6±1.0	4.2±1.0	4.6±1.0	5.1±0.9	5.3±1.0	5.4±1.0	5.4±1.1
Proteinuria (%)	7.1	3.8	16.4	6.3	13.6	8.5	9.4	3.6	13.4	4.8	9.4	7.8
Smoking habits (%)	76.2	70.2	67.0	60.7	52.5	45.2	17.1	14.9	12.2	11.3	8.3	10.9
Alcohol intake (%)	69.3	61.7	61.5	55.1	54.0	52.1	8.3	4.7	5.2	6.4	6.4	6.1

[a]Minnesota code 3-1. [b]Minnesota codes 4-1, 2, 3 except for 3-1. [c]Minnesota code 8-3.

baseline. The mean systolic blood pressure levels and frequency of hypertension (grades 1–3) slightly increased from 1961 to 1988 for both men and women. The frequency of patients taking antihypertensive agents increased from 2.1% in 1961 to 23.9% in 1988 among men and from 2.2 to 25.1% among women. The frequency of glucose intolerance and mean total cholesterol levels also increased from 1961 to 1988 in both sexes.

Incidence and adjusted hazard ratio for stroke and its subtypes

Tables 2 and 3 show the age-adjusted incidence of total stroke and its subtypes according to the blood pressure categories of the JSH 2009 guidelines [3] by sex. The incidence of total stroke and its subtypes, except for that of subarachnoid haemorrhage, was higher in men than in women. In both sexes, the stroke incidence increased steeply with elevation in blood pressure levels (both P for trend <0.0001); the differences between optimal blood pressure and grades 1–3 hypertension were statistically significant (all $P < 0.01$). These associations remained significant even after controlling for age, LVH, ST depression and atrial fibrillation on ECG, glucose intolerance, BMI, total cholesterol, smoking habits and alcohol intake in either sex (both P for trend <0.0001). Similar patterns were observed for cerebral infarction in both sexes and for cerebral haemorrhage in men (all P for trend <0.0001). For women, the incidence of cerebral haemorrhage significantly increased in grade 2 hypertension ($P = 0.02$), as did the incidence of subarachnoid haemorrhage in grade 3 hypertension ($P = 0.01$). For men, subarachnoid haemorrhage did not show a clear relationship with the blood pressure categories, probably due to the small number of events. With regard to subtypes of cerebral infarction, the incidence of lacunar infarction increased with elevation of blood pressure levels in both sexes (both P for trend <0.0001). In contrast, the incidence of atherothrombotic infarction sharply increased in grade 3 hypertension for both sexes (both $P < 0.05$), and the incidence of cardioembolic infarction significantly increased in grade 3 hypertension for women ($P = 0.04$). Comparable associations were observed between blood pressure categories and stroke even after excluding patients taking antihypertensive agents at each examination.

Risk stratification

Figure 1 shows the age-adjusted incidence of stroke by risk groups defined by the risk stratification system proposed by the JSH 2009 guidelines [3] among men and women. The stroke incidence increased steeply with the elevation of risk levels for men and women (both P for trend <0.0001): compared to the no-additive risk group, the stroke incidence was significantly higher in the moderate and high-risk groups for both sexes (all $P < 0.05$) and also in the low-risk group for women ($P = 0.008$).

Table 2 Incidence and adjusted hazard ratio for total stroke and its types by blood pressure categories among men

Type of stroke		Optimal	Normal	High-normal	Hypertension			P trend
					Grade 1	Grade 2	Grade 3	
Total stroke								
	Age-adjusted incidence (per 1000 person-years)	3.1	5.3	5.4	10.0**	20.9**	54.2**	<0.0001
	Multivariate-adjusted hazard ratio (95% CI)	1 (reference)	1.64 (0.76–3.56)	1.52 (0.70–3.31)	3.31 (1.73–6.32)**	4.22 (2.16–8.25)**	5.75 (2.93–11.30)**	<0.0001
Cerebral infarction								
	Age-adjusted incidence (per 1000 person-years)	2.4	2.8	3.8	6.9**	8.9**	19.5**	<0.0001
	Multivariate-adjusted hazard ratio (95% CI)	1 (reference)	1.38 (0.54–3.48)	1.37 (0.55–3.41)	3.10 (1.47–6.55)**	3.29 (1.50–7.21)**	4.88 (2.24–10.65)**	<0.0001
Lacunar								
	Age-adjusted incidence (per 1000 person-years)	1.4	1.1	1.8	4.8**	6.4**	11.2**	<0.0001
	Multivariate-adjusted hazard ratio (95% CI)	1 (reference)	1.11 (0.29–4.15)	1.49 (0.45–4.96)	3.09 (1.13–8.47)*	3.26 (1.14–9.30)*	4.66 (1.63–13.32)**	0.0003
Atherothrombotic								
	Age-adjusted incidence (per 1000 person-years)	0.0	1.0	0.4	1.0	1.1	6.1*	0.0001
	Multivariate-adjusted hazard ratio (95% CI)	–	1 (reference)	0.45 (0.04–4.94)	2.27 (0.48–10.87)	2.48 (0.47–12.97)	5.08 (1.04–24.89)*	0.0004
Cardioembolic								
	Age-adjusted incidence (per 1000 person-years)	1.0	0.7	1.6	1.1	1.2	1.5	0.18
	Multivariate-adjusted hazard ratio (95% CI)	1 (reference)	0.89 (0.19–4.12)	0.81 (0.18–3.79)	1.52 (0.44–5.21)	0.99 (0.24–4.14)	1.39 (0.32–6.06)	0.57
Cerebral haemorrhage								
	Age-adjusted incidence (per 1000 person-years)	0.4	0.9	1.2	3.0*	7.4**	34.3**	<0.0001
	Multivariate-adjusted hazard ratio (95% CI)	1 (reference)	2.22 (0.37–13.34)	2.95 (0.53–16.38)	5.59 (1.21–25.75)*	9.30 (1.98–43.61)**	12.04 (2.47–58.66)**	<0.0001
Subarachnoid haemorrhage								
	Age-adjusted incidence (per 1000 person-years)	0.3	1.6	0.0	0.1	0.5	0.3	0.66
	Multivariate-adjusted hazard ratio (95% CI)	1 (reference)	3.28 (0.28–38.13)	–	1.16 (0.07–19.67)	1.90 (0.09–41.01)	3.41 (0.15–76.27)	0.83

Hazard ratios are adjusted for age, sex, left ventricular hypertrophy, ST depression, atrial fibrillation, glucose intolerance, body mass index, total cholesterol, smoking habits and alcohol intake. * $P < 0.05$. ** $P < 0.01$ vs. normal blood pressure for atherothrombotic infarction and vs. optimal blood pressure for other types of stroke.

Table 3 Incidence and adjusted hazard ratio for total stroke and its types by blood pressure categories among women

Type of stroke	Optimal	Normal	High-normal	Hypertension			P trend
				Grade 1	Grade 2	Grade 3	
Total stroke							
Age-adjusted incidence (per 1000 person-years)	2.0	2.5	3.9	6.3**	11.8**	22.4**	<0.0001
Multivariate-adjusted hazard ratio (95% CI)	1 (reference)	1.53 (0.60–3.89)	2.19 (0.93–5.16)	3.92 (1.84–8.35)**	4.89 (2.24–10.67)**	7.51 (3.39–16.64)**	<0.0001
Cerebral infarction							
Age-adjusted incidence (per 1000 person-years)	1.4	2.1	2.0	4.6**	6.1**	14.3**	<0.0001
Multivariate-adjusted hazard ratio (95% CI)	1 (reference)	1.78 (0.58–5.47)	1.91 (0.65–5.65)	3.91 (1.52–10.06)**	4.38 (1.66–11.57)**	7.14 (2.68–19.05)**	<0.0001
Lacunar							
Age-adjusted incidence (per 1000 person-years)	0.6	1.8	2.0	2.5*	3.3**	6.8**	<0.0001
Multivariate-adjusted hazard ratio (95% CI)	1 (reference)	3.71 (0.76–18.00)	4.68 (1.01–21.62)	4.82 (1.11–20.90)*	6.25 (1.41–27.76)*	8.28 (1.82–37.70)**	0.002
Atherothrombotic							
Age-adjusted incidence (per 1000 person-years)	0.6	0.3	0.0	0.9	1.4	5.3*	0.002
Multivariate-adjusted hazard ratio (95% CI)	1 (reference)	0.50 (0.05–5.59)	–	2.26 (0.48–10.64)	1.92 (0.37–9.87)	3.68 (0.71–19.07)	0.02
Cardioembolic							
Age-adjusted incidence (per 1000 person-years)	0.2	0.0	0.0	1.1	1.1	1.4*	0.001
Multivariate-adjusted hazard ratio (95% CI)	1 (reference)	–	–	4.26 (0.50–36.59)	4.73 (0.49–45.67)	11.09 (1.18–104.43)*	0.0008
Cerebral haemorrhage							
Age-adjusted incidence (per 1000 person-years)	0.2	0.5	0.6	0.5	4.6*	2.4	0.01
Multivariate-adjusted hazard ratio (95% CI)	1 (reference)	3.27 (0.29–36.62)	4.76 (0.48–47.33)	4.33 (0.47–39.71)	13.11 (1.45–18.55)*	7.40 (0.59–92.52)	0.02
Subarachnoid haemorrhage							
Age-adjusted incidence (per 1000 person-years)	0.4	0.0	1.3	1.0	1.0	5.4*	0.001
Multivariate-adjusted hazard ratio (95% CI)	1 (reference)	–	2.22 (0.36–13.67)	3.62 (0.73–17.93)	4.03 (0.71–22.97)	10.50 (1.86–59.20)**	0.0009

Hazard ratios are adjusted for age, sex, left ventricular hypertrophy, ST depression, atrial fibrillation, glucose intolerance, body mass index, total cholesterol, smoking habits and alcohol intake. * $P<0.05$. ** $P<0.01$ vs. optimal blood pressure.

Fig. 1

Age-adjusted incidence of total stroke by risk groups among men and women. *$P<0.05$, †$P<0.01$ vs no additive risk.

Discussion

The present analysis demonstrated strong associations between the blood pressure categories defined by the JSH 2009 guidelines [3] and the incidence of stroke among general Japanese patients. The incidence of total stroke increased with elevation of blood pressure categories and became significantly higher in patients with grades 1–3 hypertension than in those with optimal blood pressure levels. There were also strong associations between the JSH 2009 blood pressure categories and most of the stroke subtypes. These associations did not change even after adjustment for other cardiovascular risk factors. The incidence of stroke also increased with elevation of the risk levels defined by the risk stratification system recommended by the guidelines. A cohort study conducted in Japan has also demonstrated the validity of the risk stratification system of the JSH 2009 guidelines [22]. These findings support the hypothesis that the blood pressure classification and risk stratifications recommended by the JSH 2009 guidelines [3] are useful in predicting the risk of stroke among Japanese.

The incidence of stroke in each blood pressure category in the present analysis was similar to that obtained from other observational studies conducted in Japan [23,24], but was higher than that observed in Western populations [25,26]. These findings are consistent with those of previous epidemiological and clinical studies that demonstrated heterogeneous risks of stroke between Asian and Western populations [5,7,27].

Large-scale cohort studies have clearly demonstrated that blood pressure levels predicted future stroke events in Japan [10,12,23,24,28–32] as well as other countries around the world [7,8]. A number of cohort studies have demonstrated separately significant effects of blood

pressure on the risks of cerebral infarction and cerebral haemorrhage [7,8]. However, few observational studies have examined the association between blood pressure and the risks of cerebral infarction subtypes [6,33]. Our study confirmed the results from previous observational studies and provided more detailed information about the strong association of blood pressure levels with the risks of stroke subtypes in a general population of Japanese. This finding is directly in line with beneficial effects of blood pressure-lowering treatment for most of the stroke subtypes observed in randomized controlled trials [34–37].

In our study, despite the significant associations between blood pressure categories and the incidence of most stroke subtypes, the magnitude and patterns of the impact of blood pressure categories were different among stroke subtypes. The incidence of lacunar infarction in men and women and that of cerebral haemorrhage in men continuously increased with rising blood pressure categories, and the differences were significant between optimal blood pressure and grades 1–3 hypertension, whereas the incidence of atherothrombotic infarction in both sexes and that of cardioembolic infarction and subarachnoid haemorrhage in women significantly increased in grade 3 hypertension. Cerebral haemorrhage and lacunar infarction occur primarily in conjunction with arteriolosclerosis of the cerebral penetrating arteries. These arteries are tiny and mostly arise from larger arteries as unbranching end arteries, and are considered to be directly influenced by blood pressure [38]. In contrast, atherosclerotic diseases of cervical or intracranial large arteries, including atherothrombotic infarction and possibly subarachnoid haemorrhage, generally progress as part of a slow pathoanatomic process that may take a long time to reach a clinical end stage [39], and therefore only severe hypertension may have been able to accelerate the atherosclerotic process in our patients. The weak association between blood pressure and cardioembolic infarction may be due to the fact that hypertension indirectly influences the onset of cardioembolic infarction through the development of embolic sources such as atrial fibrillation and myocardial infarction.

There are several potential limitations to the findings in our study. First, it is possible that our results are biased, because some patients did not return for the follow-up examinations. However, more than 80% of the total number of surviving stroke-free patients participated in each examination, suggesting that such a bias did not invalidate the present findings. Second, we were unable to ascertain all risk factors, TOD and cardiovascular disease for the risk stratification of patients; for example, a family history of premature cardiovascular disease, subclinical atherosclerosis and low estimated glomerular filtration rate were difficult to identify. This limitation was likely to contribute to an underestimation of the stroke risk associated with risk groups, and our estimates for the impact of risk groups on the risk of stroke are probably quite conservative. Finally, cardiovascular risk factors and the risks of stroke and its subtypes have changed in Japan during the long-term follow-up period. However, we used the pooling of repeated-observations method, in which risk factors were allowed to change in accordance with data from the follow-up examinations, and therefore this bias is not likely to invalidate the present findings.

In conclusion, the findings of the present study clearly indicate that the blood pressure classification and risk stratifications recommended by the JSH 2009 guidelines [3] are useful in predicting the risk of stroke among Japanese. Though the magnitude and pattern of the impact of blood pressure were different among stroke subtypes, blood pressure levels were associated with the incidence of most stroke subtypes, suggesting that blood pressure lowering is likely to provide protection against a variety of stroke subtypes.

Acknowledgements

This study was supported in part by Grants-in-Aid for Scientific Research A (No. 18209024) and C (No. 19590633) from the Ministry of Education, Culture, Sports, Science, and Technology of Japan.

There are no conflicts of interest.

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Eur J Appl Physiol (2009) 105:141–152
DOI 10.1007/s00421-008-0883-7

ORIGINAL ARTICLE

Light-intensity activities are important for estimating physical activity energy expenditure using uniaxial and triaxial accelerometers

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Accepted: 23 September 2008 / Published online: 14 October 2008

Abstract This study evaluated the validity of the total energy expenditure (TEE) estimated using uniaxial (ACCuni) and triaxial (ACCtri) accelerometers in the elderly. Thirty-two healthy elderly (64–87 years) participated in this study. TEE was measured using the doubly labeled water (DLW) method (TEE_{DLW}). TEE_{ACCuni} (6.79 ± 1.08 MJ day^{-1}) was significantly lower than TEE_{DLW} (7.85 ± 1.54 MJ day^{-1}) and showed wider limits of agreement (−3.15 to 1.12 MJ day^{-1}) with a smaller correlation coefficient ($r = 0.703$). TEE_{ACCtri} (7.88 ± 1.27 MJ day^{-1}) did not differ from TEE_{DLW} and showed narrower limits of agreement (−1.64 to 1.72 MJ day^{-1}) with a larger correlation coefficient ($r = 0.835$, $P < 0.001$). The estimated intensities of light activities were significantly lower with ACCuni. Greater mediolateral acceleration was observed during 6-min walk tests. The results suggest that ACCtri is a better choice than ACCuni for assessing TEE in the elderly.

Keywords Doubly labeled water · Elderly · Physical activity level · Triaxial accelerometer · Total energy expenditure

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Introduction

The last half century has witnessed a dramatic increase in the world's population aged 60 years and greater (United Nations Department of Economic and Social Affairs-Population Division 2007). The aged, however, are not just older adults, as aging is frequently associated with a diminished ability to maintain a stable energy balance and a decrease in physical activity. These generally lead to fat and weight gain compared to younger adults, but also to muscle atrophy. This tends to progress with aging and can eventually lead to malnutrition, which contributes to further decline of bodily functions and the development of age-associated chronic degenerative diseases (Meydani 2001; Blanc et al. 2004).

Given the negative effects of physical inactivity, assessing the physical activity energy expenditure (PAEE), total energy expenditure (TEE), and physical activity level (PAL) accurately in the elderly is important (Manini et al. 2006). The doubly labeled water (DLW) method is one of the most accurate and valid tools used for evaluating TEE under free-living conditions (Schoeller et al. 1986), and it can also be used to assess PAEE and PAL with a simultaneous measurement of the resting metabolic rate (RMR) (Manini et al. 2006; Ishikawa-Takata et al. 2007).

However, access to the DLW method is limited due to the costs of the isotopes and the methodological effort involved. Moreover, the method does not provide any information about the type, intensity, and duration of each physical activity (Koebnick et al. 2005; Plasqui and Westerterp 2007). Hence, accurate alternative methods, validated using the DLW method, are necessary for epidemiological or interventional studies.

Physical activity monitoring using accelerometers obviates many of the limitations of the DLW method and may be very useful for obtaining objective information for estimating the free-living TEE with few interventions (Wong et al. 1981; Bouten et al. 1996; Davis and Fox 2007; Fox et al. 2007). Recently, several conversion algorithms for accelerometer information have been developed in laboratory settings using indirect calorimetry and validated under free-living conditions using the DLW method (Bouten et al. 1996; Westerterp 1999; Plasqui et al. 2005). However, most of the development and validation were performed in healthy young adults. This is a concern because the elderly differ from the young in terms of the kinetics and kinematics of locomotion (Murray et al. 1969; Judge et al. 1996; Dean et al. 2007). Therefore, this study tested whether the use of accelerometers and calibrations based on studies of young adults are valid in the elderly.

The two major classes of accelerometers described in the literature are the uniaxial accelerometer (ACCuni), which measures vertical acceleration only, and the triaxial accelerometer (ACCtri), which measures accelerations in three-dimensional space. ACCuni and ACCtri have recently been compared in adults or children (Chen and Sun 1997; Kumahara et al. 2004b; Plasqui et al. 2005; Tanaka et al. 2007a, b), but to our knowledge, no study has compared them in elderly participants. This is important because the elderly have less lateral stability and greater variability of lateral movement during walking (Dean et al. 2007), and the lateral instability influences the energy cost of movement (Donelan et al. 2004; Dean et al. 2007). We compared the accelerometers in a free-living environment using DLW as the criterion method, and assessed the accelerations in the anteroposterior, mediolateral, and vertical axes during a 6-min walk in a laboratory environment.

Methods

Participants

Data were obtained from 32 healthy elderly participants (18 women and 14 men, 64–87 years) recruited from participants in an ongoing health study conducted at Kyoto Prefectural University of Medicine during 2005–2006. The participants were invited to attend an information meeting and those interested in participating provided written informed consent. The eligibility criteria for the participants were as follows: not taking prescription medications that could interfere with the study and no history of alcohol abuse. The participants were evaluated by a physician to ensure that they were in good health with no signs or symptoms of metabolic disease or endocrine disorders. The study protocol was approved by the Medical Ethics Committee of Kyoto Prefectural University of Medicine.

Anthropometric measurements were obtained in the morning before the study period. Body weight was measured on an electronic scale to the nearest 0.1 kg. Height was measured to the nearest 0.1 cm. Predicted total body water (pTBW) was measured using a segmental bioelectrical impedance analysis (Muscle-α, Kyoto, Japan) (Miyatani et al. 2001; Ishiguro et al. 2006) to determine the DLW dose for each individual. No significant weight change (-0.1 ± 1.2 kg) was observed during the measurement periods.

The participants recorded a simplified physical activity record (sPAR) during the DLW measurement period, which was validated in an adult population in a study by Koebnick et al. (2005). The sPAR was modified slightly to fit the elderly population; the number of items was reduced for easier recording by the elderly: nine items were deleted and one item (taking a bath unaided) was added.

Resting metabolic rate

The RMR was measured with an indirect calorimeter (AE-300S; Minato Medical Science, Osaka, Japan) for 30 min in the early morning between 05:00 and 07:00 h, after an overnight stay in the facility. Before the study began, each participant was familiarized with the procedures and equipment used in the RMR analysis. RMR was measured under standard conditions with the participant having fasted for over 12 h and lying at complete rest immediately after sleeping (Turley et al. 1993). A $\dot{V}O_2$ variation of less than 25 ml min^{-1} was used to determine whether the collection was acceptable (Turley et al. 1993). Each participant was monitored periodically to ensure that they remained awake. Data collection took place in a thermally regulated environment with minimal light and noise. The calorimeter system was calibrated before the measurement of each participant. The predicted basal metabolic rate (BMR) was also calculated using the equation of the Recommended Dietary Allowances for Japanese (Health Promotion and Nutrition Division-Health Service Bureau Ministry of Health and Welfare 1995), as in previous studies (Rafamantanantsoa et al. 2002; Ishikawa-Takata et al. 2007).

Doubly labeled water

The TEE was measured using the DLW method over a 14-day period. Participants arrived on day 0, and a urine sample was acquired to measure the baseline ^{2}H and ^{18}O enrichment. Between 07:00 and 08:00 h, a premixed dose containing approximately 0.12 g kg^{-1} pTBW of $^{2}H_2O$ (99.8 atom%; Taiyo Nippon Sanso, Tokyo, Japan) and 2.5 g kg^{-1} pTBW of $H_2{}^{18}O$ (10.0 atom%; Taiyo Nippon Sanso) was given to each participant to drink. Urine samples were collected 4 h after dosing, approximately 24 h after dosing, and on the morning of day 15. Aliquots of the urine samples were stored frozen at −15°C for later analysis using isotope ratio mass spectrometry (Europa Scientific ANCA-G and Hydra 20–20 IRMS for ^{18}O; Europa Scientific ANCA-GSL and GEO 20–20 IRMS for ^{2}H; Europa Scientific, Crewe, UK). The gas used for equilibrating the ^{18}O was CO_2 and that used for ^{2}H was H_2. A Pt catalyst was used to equilibrate the ^{2}H. Isotope analyses were carried out at the Iso-Analytical Laboratory (Iso-Analytical Limited, Sandbach, UK). Each sample and the corresponding reference were analyzed in duplicate. The average standard deviations in the analyses were 0.7% for ^{2}H and 0.05% for ^{18}O.

The ^{18}O and ^{2}H dilution spaces (N_O and N_d) were determined by dividing the dose of the tracer administered (as moles of ^{2}H- or ^{18}O-water) by the intercept (^{2}H and ^{18}O enrichment at time zero, respectively) (Coward 1990) due to the influence of delayed isotopic equilibration on the accuracy of the DLW method in the elderly (Blanc et al. 2002, 2004; Manini et al. 2006). In this study, N_d/N_O was 1.038 ± 0.009 (mean ± SD; range 1.017–1.051), which concurred with most previous studies (Racette et al. 1994). Therefore, TBW (mol) was calculated as the mean of N_d (mol) divided by 1.041 for the dilution space estimated using ^{2}H and N_O (mol) divided by 1.007 for the dilution space estimated using ^{18}O (Racette et al. 1994).

The rate of CO_2 production (rCO_2) was determined as 0.4554 × TBW × (1.007 × ^{18}O elimination rate − 1.041 × ^{2}H elimination rate), in which we assumed isotope fractionation applying only to breath water using equation A6 of Schoeller et al. (1986) with the revised dilution space constant of Racette et al. (1994). TEE (kcal day^{-1}) was calculated using a modified Weir's formula (Weir 1949) based on rCO_2 (mol day^{-1}) and the food quotient (FQ), which was calculated from the daily record of the food intake during the 14-day study period using a method described elsewhere (Rafamantanantsoa et al. 2002). This assumes that under conditions of perfect nutrient balance, FQ must equal the respiratory quotient (RQ) (Black et al. 1986). The mean FQ of the participants was 0.86 ± 0.04 (mean ± SD) in this study, which is very similar to the value of 0.87 ± 0.03 for 20- to 59-year-old Japanese healthy adults in a previous study (Ishikawa-Takata et al. 2007).

The PAEE was calculated as (TEE × 0.90) − RMR × (24 − Sleeping time)/24 − 0.95 × RMR × (Sleeping time)/24, thereby removing energy expenditure from the thermal effect of meals and subtracting the energy devoted to basal metabolism, which assumes a 5% difference between RMR and the sleeping metabolic rate. Sleeping time was estimated using sPAR (Mean and SD; 8.3 ± 1.2 h per day). In addition, the PAL was calculated as TEE/BMR (Manini et al. 2006).

Accelerometers

A uniaxial accelerometer (Kenz Activity Monitor Lifecorder EX; Suzuken, Nagoya, Japan) and a triaxial accelerometer (Panasonic Electric Works Co., Ltd, Osaka, Japan) were attached to an elastic belt and worn at the back of the waist for entire 2 weeks, and the data ware trimmed to fit the DLW period. Participants were instructed to wear the accelerometers during waking hours for 2 week, exclusive of time spent bathing or when in water. The daily wearing time and number of days worn were assessed by comparison with the result of the sPAR. If the difference in the non-water activity time of sPAR and the accelerometers data exceeded 3 h in a day, that day was excluded from the analysis.

The uniaxial accelerometer measured 72.5 × 41.5 × 27.5 mm and weighed 60 g, including the battery. The technical and estimation equation details of the uniaxial accelerometer have been described elsewhere (Saito et al. 2004; Kumahara et al. 2004a). It has a linear frequency response with a band pass filter and is drip-proof (not waterproof). It assesses values ranging from zero to two times the acceleration of gravity, and the intensity of physical activity is calculated by calculating the metabolic equivalent (MET) intensity levels of physical activities, which are counted every 4 s using the activity level (1.0–9.0) from the acceleration intensity (Kumahara et al. 2004a). In addition, the energy expenditures due to very small trunk movements and posture effects (e.g., sitting to standing, light desk-work) are calculated by multiplying the BMR by a constant (Kumahara et al. 2004a).

The triaxial accelerometer measures 60 × 35 × 13 mm and weighs 24 g, including the battery. The technical and estimation equation details of the triaxial accelerometer have been described elsewhere (Hara et al. 2006; Matsumura et al. 2008). It has a linear frequency response with a low pass filter and is drip-proof (not waterproof). It samples the acceleration at 20 Hz with a range from zero to two times the acceleration of gravity. It stores the standard deviation of the vector norm of the composite acceleration (K_m) in the three dimensions each minute as follows:

$$K_{\mathrm{m}} = \sqrt{\frac{1}{n-1}\left[\left(\sum_{i=0}^{n} x_i^2 + \sum_{i=0}^{n} y_i^2 + \sum_{i=0}^{n} z_i^2\right) - \frac{1}{n}\left\{\left(\sum_{i=0}^{n} x_i\right)^2 + \left(\sum_{i=0}^{n} y_i\right)^2 + \left(\sum_{i=0}^{n} z_i\right)^2\right\}\right]}$$

where n is number of data for 1 min (n = 1,200), and Σx, Σy, and Σz are the sums of the accelerations for 1 min. It does not round down to store K_{m}. In a study of healthy male young adults (Matsumura et al. 2008), K_{m} was highly correlated (R^2 = 0.86) with the oxygen uptake ($\dot{V}O_2$) while walking or running at seven speeds ranging from 40 to 160 m min^{-1}) and during seven daily activities: performing self-care while standing, changing clothes, cooking, simulating eating supper, washing dishes, doing laundry, and using a vacuum cleaner (Fig. 1). The metabolic equivalent (MET) intensity levels of physical activities are calculated using a simple linear regression of K_{m}. The accelerometers collected minute-by-minute data for the entire 2 weeks, and the data were trimmed to fit the measurement period. The 24-h PAL was calculated for each day as follows:

$$\mathrm{PAL_{ACC}} = \frac{1}{n}\sum_{i=0}^{n} \mathrm{METs}_i$$

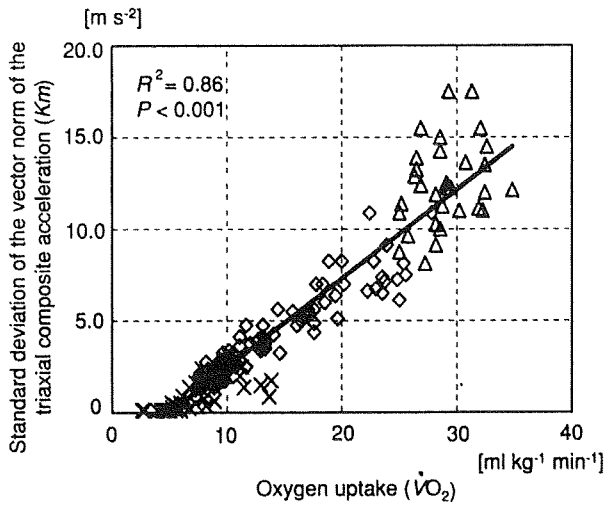

Fig. 1 The relationship between oxygen uptake ($\dot{V}O_2$) and the standard deviation of the vector norm for the triaxial composite acceleration (K_{m}) of the triaxial accelerometer (Panasonic Electric Works Co., Ltd, Osaka, Japan) during walking (*open diamond*), running (*open triangle*), and daily activities (*multi symbol*) in healthy male young adults. Walking and running were performed at seven speeds ranging from 40 to 160 m min^{-1}. The daily activities included self-care while standing, changing clothes, cooking, simulating eating supper, washing dishes, doing laundry, and using a vacuum cleaner. Reproduced from Matsumura et al. (2008, Japanese with English abstract) with permission of the copyright owner

where n is number of data (n = 1,440) during 24 h. TEE was calculated as PAL multiplied by RMR or BMR.

Six-minute walk test

In the laboratory, the participants walked for a total of 6 min under two conditions: they were told to walk faster than their usual walking speed under the fast condition, and slower than their usual walking speed under the slow condition. The order of the speed and direction of walking (clockwise or counterclockwise) were counterbalanced, with a 6-min rest between the two trials. The participants walked continuously around an oval 35-m track. They wore identical shoes that we provided to eliminate the effect of sole type. The triaxial accelerometer was attached to an elastic belt and worn at the back of the waist. We compared the results with those for healthy young individuals 10–32 years old. To assess the magnitude of the acceleration in each axis, the standard deviations of the accelerations in each axis (AP, anteroposterior; ML, mediolateral; V vertical) were calculated from 15 s after starting to 15 s before stopping to exclude the effect of gait initiation and termination. Since the walking speed affected the magnitude of the accelerations (Iwashita et al. 2003), the comparison of acceleration needs standardization of walking speed. All regressions of accelerations in the AP, ML, and V axes on walking speed returned nonsignificant intercepts in the linear regression analysis (P = 0.192–0.667). Therefore, the accelerations divided by the walking speeds were used for the analysis. The ratio of the accelerations of ML to V was also calculated for further analysis.

Statistical analysis

All analyses were performed using SPSS 12.0 for Windows (SPSS Inc., Chicago, IL, USA). The results are given as the means ± SD and range. For all of the analyses, an alpha of 0.05 was used to denote statistical significance. The relationships among $\mathrm{TEE_{DLW}}$, $\mathrm{TEE_{ACCuni}}$, and $\mathrm{TEE_{ACCtri}}$ were examined using linear regression analysis. Pearson correlation coefficients were compared statistically using the methods described by Meng et al. (1992). To eliminate the effects of weight, height, age, percent body fat, and gender on the relationship between $\mathrm{TEE_{DLW}}$ and TEE estimated

using the accelerometers, partial correlation coefficients were calculated adjusted by those variables. Multiple stepwise linear regression analysis was also applied to examine the significance of the accelerometer data in the estimation of TEE. Bland–Altman plot analyses (1995) were performed to compare TEE_{ACCuni}, TEE_{ACCtri}, and TEE_{DLW} in the elderly. The differences between elderly and young individuals were examined using one-way analysis of variance (ANOVA). To appreciate the variability in the relationship between gait speed and the accelerations, linear regression analysis was applied and the standard error of the estimate (SEE) of gait speed from the magnitude of the accelerations was calculated in young adults and elderly, respectively.

Results

The physical characteristics of the participants are shown in Table 1. The measured PAL ranged from 1.34 to 2.20 in individual participants, with a mean of 1.66. PAL was not significantly correlated with age in either men ($r = -0.057$, $P = 0.847$) or women ($r = 0.144$, $P = 0.570$). In the participants, the predicted BMR was highly correlated with the measured RMR ($r = 0.937$, $P < 0.001$), the slope of the regression line did not differ significantly from 1.0 (95% confidence interval (CI): 0.98–1.30), and the intercept did not differ significantly from zero (95% CI: −1.35 to 0.15). Eleven participants reported riding a bicycle at least once in the measurement period and the average time spent riding was 16.0 ± 28.7 min day^{-1} for all participants. Eight participants reported swimming at least once in the measurement period and the average time spent swimming was 5.2 ± 9.9 min day^{-1} for all participants.

The total energy expenditure (TEE) measured using DLW, ACCuni, and ACCtri, both with the measured RMR and predicted BMR, are shown in Table 2. The correlation between the daily average ACCuni and ACCtri output was moderate ($r = 0.691$, $P < 0.001$). Although the correlation between TEE_{ACCuni} and TEE_{ACCtri} was very high ($r = 0.941$, $P < 0.001$), ACCuni significantly underestimated TEE compared to DLW, for both the measured RMR and predicted BMR (−11.7 and −12.5%). In contrast, TEE_{ACCtri} did not differ significantly from TEE_{DLW} with either the measured RMR or predicted BMR (2.5 and 1.6%). All of the correlation coefficients were significant ($P < 0.001$), although the correlation coefficients between TEE_{ACCuni} and TEE_{DLW} ($r = 0.695$ and 0.703) were significantly lower ($P < 0.05$) than the correlation coefficients between TEE_{ACCtri} and TEE_{DLW} ($r = 0.819$ and 0.835). The correlation coefficient between PAL_{ACCuni} and PAL_{DLW} ($r = 0.328$, $P > 0.05$) was not significant, but was significantly lower ($P < 0.05$) than the correlation coefficient between PAL_{ACCtri} and PAL_{DLW} ($r = 0.621$, $P < 0.001$).

We evaluated the influence of body weight and other physical characteristics on the relationship between the results using the DLW and accelerometer methods. The correlation coefficient between TEE_{ACCuni} divided by body weight and TEE_{DLW} divided by body weight ($r = 0.554$, $P < 0.01$) was significantly smaller ($P < 0.05$) than the correlation coefficient between TEE_{ACCtri} divided by body weight and TEE_{DLW} divided by body weight ($r = 0.760$, $P < 0.001$). The partial correlation between TEE_{ACCuni} and TEE_{DLW} adjusted for gender, age, weight, height, and percent body fat was not significant ($r = 0.163$, $P = 0.437$). In contrast, the partial correlation between TEE_{ACCtri} and TEE_{DLW} adjusted for gender, age, weight, height, and percent body fat was still significant ($r = 0.617$, $P < 0.001$). The results of the stepwise regression analysis for TEE are shown in Table 3. The output of ACCuni did not contribute significantly to estimating TEE, while the output of ACCtri contributed significantly to estimating TEE independent of the physical characteristics.

The linear regressions of TEE_{DLW} against TEE measured using the uni- and triaxial accelerometers with the predicted BMR (TEE_{ACCuni} and TEE_{ACCtri}) are shown in Fig. 2a and b. The slopes of the regression did not differ significantly from 1.0 for both the uni- and triaxial accelerometers. The intercept was significantly different from zero for ACCuni, but did not differ significantly from zero for the regressions obtained using ACCtri. The Bland–Altman agreement plots between TEE_{DLW} against TEE_{ACCuni} and TEE_{ACCtri} are shown in Fig. 2c and d. The limit of agreement was −3.15 to 1.12 MJ day^{-1} between TEE_{DLW} and TEE_{ACCuni}, and −1.64 to 1.72 MJ day^{-1} between TEE_{DLW} and TEE_{ACCtri}. The limit of agreement between TEE_{DLW} and TEE_{ACCtri} (3.36 MJ day^{-1}) was

Table 1 Physical characteristics of participants ($n = 32$)

	Mean ± SD (range)
Age	74 ± 6 (64–87)
Weight (kg)	53.5 ± 9.1 (37.1–76.5)
Height (cm)	154.9 ± 8.9 (141.8–175.4)
BMI (kg/m^2)	22.2 ± 2.5 (17.0–27.5)
Percent body fat (%)	31.9 ± 6.9 (14.7–43.5)
Measured RMR (MJ day^{-1})	4.74 ± 0.75 (3.50–6.41)
Estimated BMR (MJ day^{-1})	4.66 ± 0.61 (3.56–5.87)
TEE (MJ day^{-1})	7.85 ± 1.54 (5.25–11.23)
PAEE (MJ day^{-1})	2.41 ± 0.99 (0.94–4.59)
PAL	1.66 ± 0.24 (1.34–2.20)

BMI body mass index, *RMR* resting metabolic rate, *BMR* basal metabolic rate, *TEE* total energy expenditure, *PAEE* physical activity energy expenditure, *PAL* physical activity level

Table 2 Summary of total energy expenditure (TEE) estimated by accelerometers in the elderly

Estimation methods	TEE (MJ day^{-1})[a]	%difference[b]	r[c]
DLW	7.85 ± 1.54 (5.25–11.23)		
ACCuni × mRMR	6.88 ± 1.22 (5.00–9.61)***	−11.7 ± 14.3% (−42.4–12.9%)	0.695
ACCuni × pBMR	6.79 ± 1.08 (5.09–9.39)***	−12.5 ± 14.0% (−40.8–12.4%)	0.703
ACCtri × mRMR	8.02 ± 1.45 (5.70–10.57)	2.5 ± 11.5% (−19.8–23.2%)	0.819
ACCtri × pBMR	7.88 ± 1.27 (5.74–10.33)	1.6 ± 11.1% (−18.3–28.2%)	0.835

DLW doubly labeled water, *ACCuni* uniaxial accelerometer, *ACCtri* triaxial accelerometer, *mRMR* measured resting metabolic rate, *pBMR* predicted basal metabolic rate

[a] Values are means ± SD; range in parentheses

[b] Percent difference from TEE measured by DLW. Values are means ± SD; range in parentheses

[c] Correlation coefficients with TEE measured by DLW

*** Significantly smaller than TEE measured by DLW: $P < 0.001$

Table 3 Multiple stepwise linear regression analysis for predicting total energy expenditure measured by DLW

Predicted variables	Coefficients							
	The uniaxial accelerometer				The triaxial accelerometer			
	Standardized	Unstandardized		P	Standardized	Unstandardized		P
	β	B	SEE		β	B	SEE	
ACC output				0.950	0.508	4:825	0.892	<0.001
Gender				0.524	−0.420	−1.296	0.378	<0.01
Age				0.877				0.718
Weight				0.452	0.467	0.079	0.021	<0.001
Height	0.777	0.133	0.020	<0.001				0.289
BMI				0.997				0.316
Percent body fat				0.783				0.534
(Constant)		−12.740	3.096	<0.001		−3.812	2.085	0.078

BMI body mass index, *ACC output* the average METs of the measurement period obtained by uni-axial and tri-axial accelerometers

Average METs were calculated solely as just a function of acceleration intensity (for details, see the "Methods" section)

Height was excluded and replaced by weight in the final step of the analysis using the triaxial accelerometer

The final models explained 62 and 77% of the TEE in the analysis using the uniaxial and triaxial acceleromters, respectively

smaller than that between TEE_{DLW} and TEE_{ACCuni} (4.27 MJ day^{-1}). The differences among TEE_{ACCuni}, TEE_{ACCtri}, and TEE_{DLW} were not significantly correlated with age, weight, height, BMI, TBW, percent body fat, total muscle mass, or BMR ($r = -0.325$ to 0.211, $P > 0.05$). None of these variables increased the validity of TEE obtained by conventional methods from the linear regression models when added to the model. The Bland–Altman agreement plots between PAEE estimated using DLW ($PAEE_{DLW}$), and those using ACCuni and ACCtri ($PAEE_{ACCuni}$ and $PAEE_{ACCtri}$) had similar results to TEE (Fig. 2e, f).

Figure 3 shows the estimated duration of activities at each intensity using ACCuni and ACCtri. No significant differences were observed in the moderate (3–5.9 METs) and vigorous (>6.0 METs) activities. In contrast, ACCuni showed a significantly shorter duration for 2–2.9 MET activities ($P < 0.001$), and a significantly longer duration for 1.1–1.9 MET activities compared to ACCtri ($P < 0.001$).

Figure 4 shows the magnitude of the acceleration in each axis and the ratio of the magnitude of the mediolateral acceleration to the vertical acceleration during slow and fast walking in the young and elderly individuals. No significant main effects of age and no significant interactions were observed for the magnitude of the acceleration in the vertical (V) and anteroposterior (AP) axes (Fig. 4a, c). Conversely, the magnitude of the acceleration in the mediolateral (ML) axis was greater in the elderly (significant main effect for age group with no significant interactions) (Fig. 4b). Furthermore, the acceleration ratio of ML to V had a significant main effect of age ($P < 0.01$) with no significant interaction ($P = 0.377$) and no significant main effect of gait speed ($P = 0.148$) in the two-way ANOVA (age groups × gait speeds) (Fig. 4d).

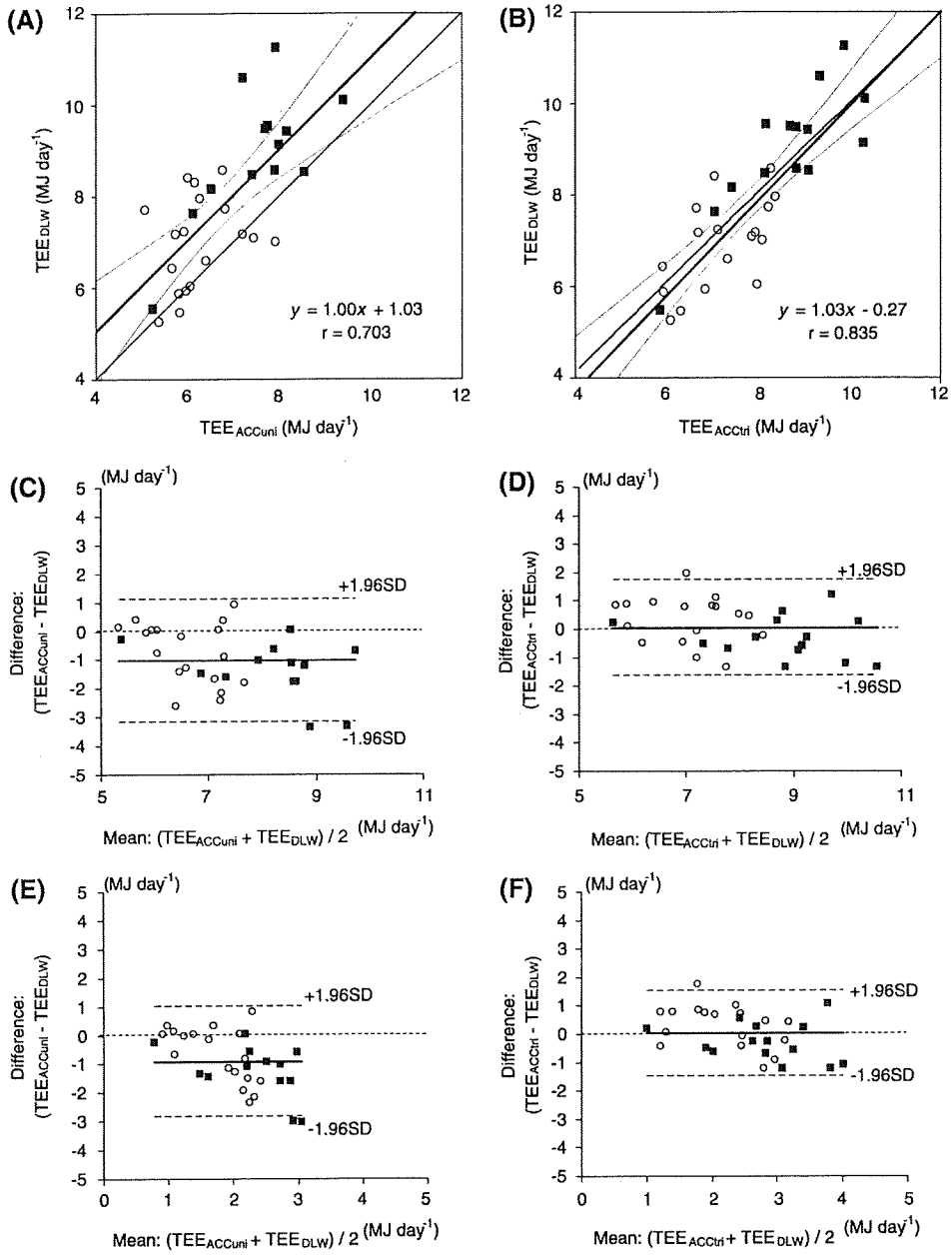

Fig. 2 The linear regressions of the total energy expenditure measured using doubly labeled water (TEE_{DLW}) against the total energy expenditure estimated using the (**a**) uniaxial (TEE_{ACCuni}) and (**b**) triaxial (TEE_{ACCtri}) accelerometers for healthy male (*filled square*) and female (*open circle*) elderly participants (n = 32). Bland–Altman agreement plots showing the difference between the total energy expenditure measured using doubly labeled water (TEE_{DLW}) and estimated using the (**c**) uniaxial (TEE_{ACCuni}) and (**d**) triaxial (TEE_{ACCtri}) accelerometers. A negative sign for the difference indicates an underestimation and a positive sign denotes an overestimation. TEE_{ACCtri} did not differ significantly from TEE_{DLW}, but TEE_{ACCuni} was significantly lower than TEE_{DLW}. Bland–Altman agreement plots indicated that the estimation of physical activity energy expenditure (PAEE) had similar results to those of TEE (**e**, **f**)

In the linear regression analysis, the SEE of gait speed was 0.12 m s^{-1} ($R^2 = 0.692$, $P < 0.001$) with the magnitude of V acceleration as a predictor, 0.15 m s^{-1} ($R^2 = 0.522$, $P < 0.001$) with the magnitude of AP acceleration, 0.17 m s^{-1} ($R^2 = 0.413$, $P < 0.001$) with the magnitude of ML acceleration, and 0.11 m s^{-1} ($R^2 = 0.735$, $P < 0.001$) with the magnitude of the vector norm of the composite acceleration from ACCtri. The correlations of gait speed with the uniaxial accelerations were significantly lower in the elderly ($r = 0.569$–0.755, $P < 0.001$, in each axis) than in the young adults ($r = 0.813$–0.917, $P < 0.001$, in each axis). The correlation of gait speed with the triaxial composite acceleration did not differ from the correlations of gait speed against the V acceleration in young adults ($r = 0.917$ vs. $r = 0.917$), but was slightly higher than the correlation of gait speed with the V acceleration in the elderly ($r = 0.808$ vs. $r = 0.755$).

Discussion

We compared the validity of ACCuni and ACCtri for estimating TEE and PAEE in the elderly population. Compared to the DLW method, ACCtri had more accuracy and precision for estimating TEE and PAEE than ACCuni

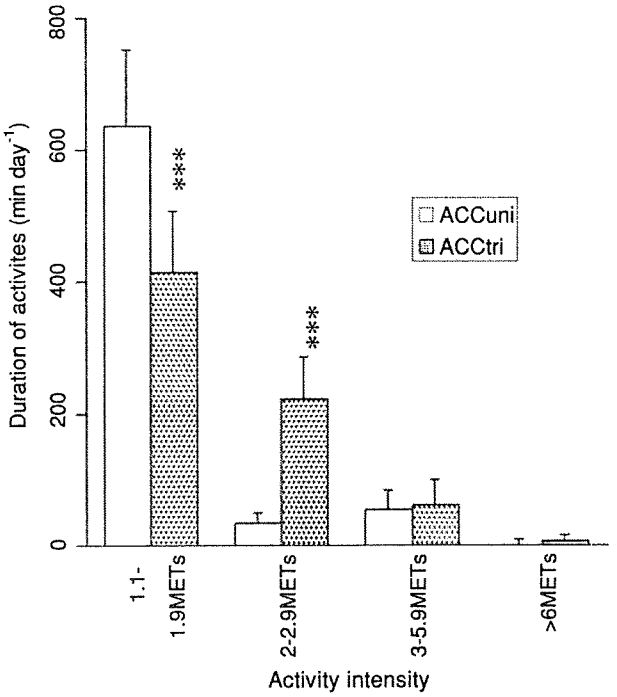

Fig. 3 The estimated duration of activities at each intensity using both ACCuni and ACCtri in the elderly participants. A significant difference between ACCuni and ACCtri was observed for light activities (1.1–2.9 METs)

(Fig. 3). This can be explained by the underestimated intensities of sedentary activities with ACCuni (Fig. 4). Furthermore, the output of ACCtri, but not ACCuni, contributed significantly to estimating TEE independent of gender, age, weight, height, and percent body fat (Table 3).

The number of commercial accelerometers for assessing energy expenditure has increased dramatically. We selected the devices used in this study for the following reasons: ACCuni and ACCtri have same measurement range of acceleration, are similar in size, use simple regression models to convert acceleration into PAL, do not need any individual calibrations, and have been calibrated with Japanese healthy young adults. In this study, the correlation between TEE_{ACCuni} and TEE_{ACCtri} was high ($r = 0.941$, $P < 0.001$), and it was reasonable to compare the two instruments. Although the correlation between the two was high, the accuracy and precision were significantly higher for ACCtri than ACCuni.

Several studies using the DLW method have validated the use of accelerometers for estimating energy expenditure in the elderly. Starling et al. (1999) examined Caltrac, a uniaxial accelerometer, and found that it significantly underestimated PAEE in participants between 45 and 84 years old (−50 to −55%). Meijer et al. (2001) examined Tracmor, a triaxial accelerometer, and found that it agreed with PAEE measured using the DLW method with a high correlation in 55–74-year-old participants. The results in our study agree with those studies, and suggest that ACCtri is a more suitable device than ACCuni in the elderly. Moreover, compared to conventional questionnaire methods in the literature (Morio et al. 1997; Rothenberg et al. 1998; Bonnefoy et al. 2001; Seale et al. 2002;

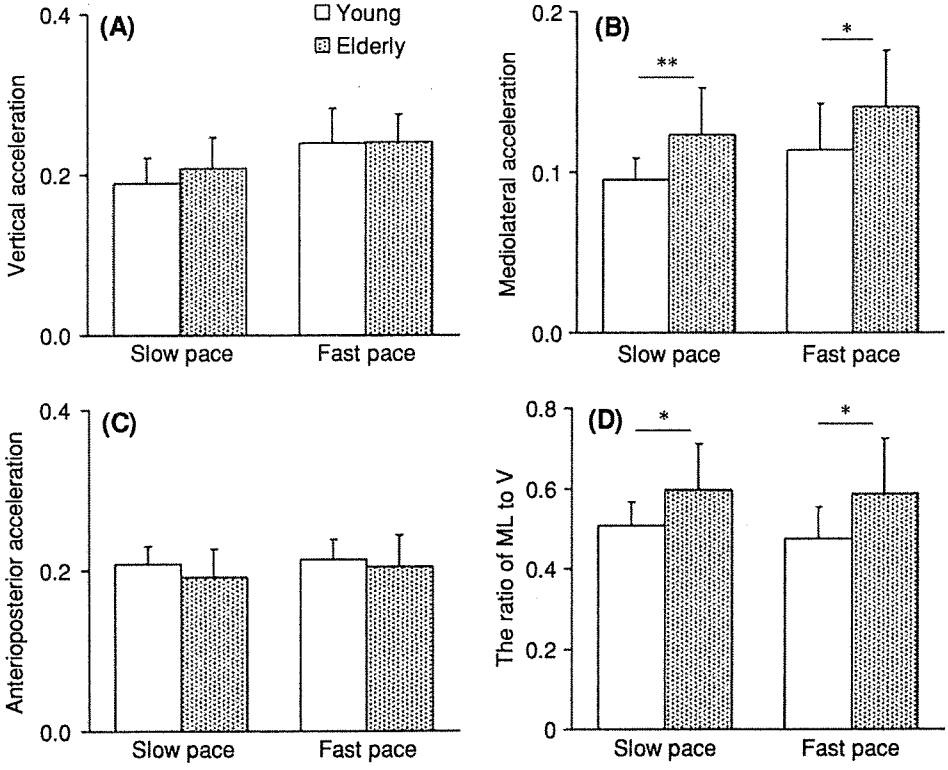

Fig. 4 The accelerations divided by the walking speed during level walking at slow and fast paces (**a**) in the vertical (*V*), **b** mediolateral (*ML*), and **c** anteroposterior axes in young and elderly participants. Only the variability of the ML acceleration had a significant main effect of group. The ratio of the variability of the ML acceleration to the variability of the V acceleration (**d**) also had a significant main effect of group

Table 4 A summary of studies comparing TEE and PAEE measured using the DLW method in which TEE and PAEE were estimated using conventional methods in the elderly or the adults including participants aged 60 year and over

Methods	Mean difference (MJ day^{-1})	Range of limits of agreement (MJ day^{-1})	*N*	Age (year)	References
PAEE					
ACCtri	0.03	3.03	14 M, 18 F	75 ± 6	This study
ACCuni-Lifecorder	−0.91*	3.84	14 M, 18 F	75 ± 6	This study
ACCuni-Caltrac	−2.75*	6.30	32 M	66 ± 11	Starling et al. (1999)
	−2.07*	3.50	35 F	67 ± 9	Starling et al. (1999)
MLPA	−3.15*	8.14	32 M	66 ± 11	Starling et al. (1999)
	−2.04*	5.84	35 F	67 ± 9	Starling et al. (1999)
	−1.31*	7.33	19 M	73.4 ± 4.1	Bonnefoy et al. (2001)
YPAS	−0.44	11.84	32 M	66 ± 11	Starling et al. (1999)
	−0.04	8.14	35 F	67 ± 9	Starling et al. (1999)
	0.38	4.64	19 M	73.4 ± 4.1	Bonnefoy et al. (2001)
College Alumni	−1.00*	7.00	19 M	73.4 ± 4.1	Bonnefoy et al. (2001)
TEE					
ACCtri	0.03	3.36	14 M, 18 F	75 ± 6	This study
ACCuni-Lifecorder	−1.06*	4.27	14 M, 18 F	75 ± 6	This study
	−2.37*	3.58	24 M	48 ± 10	Rafamantanantsoa et al. (2002)
Armband accelerometer	−0.49*	3.73	13 M, 32 F	35.1 ± 14	St-Onge et al. (2007)
Flex HR	0.70	7.23	6 M	68.8 ± 2.5	Morio et al. (1997)
	0.60	3.31	6 F	71.3 ± 2.4	Morio et al. (1997)
	−0.96*	4.66	9 F, 3 M	73 ± 0	Rothenberg et al. (1998)
	0.24	6.71	24 M	48 ± 10	Rafamantanantsoa et al. (2002)
Factorial method	−0.10	5.92	6 M	68.8 ± 2.5	Morio et al. (1997)
	−0.80	4.78	6 F	71.3 ± 2.4	Morio et al. (1997)
Activity record	−0.66	7.37	9 F, 3 M	70 ± 0	Rothenberg et al. (1998)
	−1.40*	3.13	24 M	48 ± 10	Rafamantanantsoa et al. (2002)
7-d activity recall	1.16*	11.30	19 M	73.4 ± 4.1	Bonnefoy et al. (2001)
	1.26	9.70	14 M	74.1 ± 4.1	Seale et al. (2002)
	0.07	10.77	13 F	73.5 ± 4.2	Seale et al. (2002)
QAPSE	−1.50*	9.31	19 M	73.4 ± 4.1	Bonnefoy et al. (2001)
College Alumni	6.65*	18.74	65 F	59.9 ± 7.5	Mahabir et al. (2006)
Five City Project	1.72*	7.03	65 F	59.9 ± 7.5	Mahabir et al. (2006)
$CAPS_{Typical\ Week}$	−3.35*	75.14	65 F	59.9 ± 7.5	Mahabir et al. (2006)
$CAPS_{Four\ Week}$	1.22*	24.77	65 F	59.9 ± 7.5	Mahabir et al. (2006)

* Significantly different from zero ($P < 0.05$)

Note: Any accelerometry prediction of EE (TEE or PAEE) may be highly dependent on the degree to which calibration activities resemble the activities that take place during free-living

Mahabir et al. 2006; St-Onge et al. 2007), ACCtri is generally in better agreement with DLW and less prone to significant systematical bias in the elderly (Table 4).

We examined the reasons for the discrepancy between TEE_{ACCuni} and TEE_{ACCtri} in the elderly. The primary discrepancy was that the intensities of light activities (1.1–2.9 METs) estimated using ACCuni were significantly lower than using ACCtri in the elderly. For ACCuni, the energy expenditures of very small trunk movements and posture effects (e.g., sitting to standing, light desk-work) are calculated by multiplying the BMR by a constant because ACCuni could not measure the energy expenditure during sedentary activities accurately in a laboratory environment, as shown by Bouten et al. (1994). Kumahara et al. (2004a) demonstrated that ACCuni underestimated the 24-h energy expenditure determined using whole-body indirect calorimetry and recalibrated METs from the output of ACCuni during walking. We applied this equation to our data, but

TEE_{ACCuni} was improved only 1–3% and was still lower than TEE_{DLW}.

In contrast, for ACCtri, a prediction equation was developed including sedentary activity as well as walking and running (see the Methods section and Fig. 1). In Fig. 1, sedentary activities were spread around a $\dot{V}O_2$ of 7–10.5 ml kg^{-1} min^{-1} (~2.0–2.9 METs) and around a $\dot{V}O_2$ of 3.5–7 ml kg^{-1} min^{-1} (~1.0–1.9 METs). Elderly adults engage in more sedentary and light-intensity activities than young adults (Meijer et al. 2001; Blanc et al. 2004; Harris et al. 2007); therefore, the underestimated intensities of sedentary activities with ACCuni might lead to underestimating TEE in the elderly under normal conditions. Indeed, if we calculate the average energy expenditure error associated with misclassifying 200 min day^{-1} of 2.1–2.9 MET activity as 1.1–1.9 MET activity, this accounts for about two-thirds of the underestimate.

One reason that ACCuni underestimated intensity could be the differences in the kinetics and kinematics of the locomotion between elderly and young people. In this study, the elderly had significantly higher lateral acceleration than young participants during level walking. Elderly people tend to walk with wider steps, less lateral stability, and greater variability of lateral movement during walking (Murray et al. 1969; Judge et al. 1996; Dean et al. 2007). The lateral instability adds an additional energetic cost (Donelan et al. 2004; Dean et al. 2007), and the elderly tend to have greater energetic costs during walking (Mian et al. 2006; Dean et al. 2007; Harris et al. 2007; Ortega and Farley 2007). These changes may not be reflected by the vertical acceleration. Indeed, the correlation between oxygen uptake and vertical acceleration has been reported to be weaker in the elderly than in young participants during treadmill walking (Nichols et al. 1992). The higher lateral acceleration of the elderly in our study agrees with these previous studies, and the underestimation of TEE_{ACCuni} in the elderly might be attributable to the kinetic and kinematic differences in locomotion between elderly and young participants.

Several studies of young adults and children have compared uniaxial and triaxial accelerometers simultaneously (Bouten et al. 1996; Chen and Sun 1997; Eston et al. 1998; Kumahara et al. 2004b; Plasqui et al. 2005; Tanaka et al. 2007a, b). ACCuni underestimated the energy expenditure during high-speed running, sports, and vigorous activities (Eston et al. 1998; Touno et al. 2003; Trost et al. 2006), which has been given as the primary reason for ACCuni underestimating TEE in children or active adults. In contrast, the duration of the vigorous activities did not differ significantly between ACCuni and ACCtri in our study. The underestimated intensity of vigorous activities with ACCuni might not markedly affect the estimated TEE in this population. However, note that typical accelerometers cannot assess several vigorous activities accurately, such as vigorous bicycling, swimming, and hill climbing.

Accelerometers measure body movement and the estimated energy expenditure. Therefore, RMR must be measured to calculate TEE. However, the measurement of RMR is time-consuming and not suitable for a large-scale survey. We demonstrated that the predicted BMR was highly correlated with the measured RMR and the regression line agreed with the line of identity. The accuracy and precision for estimating TEE did not differ between the measured RMR and predicted BMR, implying that TEE can be assessed using ACCtri with the predicted BMR in this population.

In this study, no significant correlation was observed between age, physical characteristics, or body composition and the residual of TEE_{DLW} and TEE estimated using accelerometers. Plasqui et al. (2005) indicated that the multiple regression analysis with age, physical characteristics, and body compositions was improved by the estimation of TEE by ACCtri (Plasqui et al. 2005). In contrast, Brage et al. (2007) reported that none of the routinely available variables (age, gender, and height) contributed significantly to estimating the physical activity intensity with the accelerometer. This difference between the studies may be due to the study population, i.e., the range of age and fatness, or the calculation equation of the accelerometers.

The range of the limit of agreement between TEE_{DLW} and TEE_{ACCtri} (3.36 MJ day^{-1}) was small in comparison with previous studies (Table 4, TEE). The range of the limit of agreement between $PAEE_{DLW}$ and $PAEE_{ACCtri}$ (3.03 MJ day^{-1}) was also small in comparison with previous studies (Table 4, PAEE). However, it is still too large for an accurate estimation at the individual level. Recently, several researchers developed a complex accelerometer algorithm for estimating the energy expenditure of various activities more accurately (Chen and Sun 1997; Westerterp 1999; Crouter et al. 2006a, b; Rothney et al. 2007; Tanaka et al. 2007a, b). Furthermore, it might be necessary to calibrate an accelerometer individually for more accurate estimations (Chen and Sun 1997; Ekelund et al. 2003). However, this would complicate our data analysis, so we just used the single regression models obtained in previous studies without individual calibration. Further research is needed to improve the estimation of TEE and PAEE at the individual level.

In addition, several differences exist between the two accelerometers. The ACCuni acceleration data were rounded down every 4 s for nine grades, while the ACCtri acceleration data were not rounded down. The properties of their filters for accelerations are different. We could not clarify how these differences affect the results and further research into this is needed.

In conclusion, based on a comparison with the DLW method, ACCtri has more accuracy and precision than ACCuni for estimating the daily TEE and PAEE in the elderly. This study indicated plausible reasons for this finding, including the underestimated intensities of light activities with ACCuni and the difference in the mediolateral acceleration during locomotion between the elderly and young adults. The partial correlation between TEE_{DLW} and TEE_{ACCtri}, but not TEE_{ACCuni}, was still significant after adjusting for gender, age, weight, height, and percent body fat. The output of ACCtri contributed significantly to estimating TEE independent of those physical characteristics. The results suggest that ACCtri is more valid for estimating the energy expenditure in the elderly population.

Acknowledgments The authors thank Prof. Dale A. Schoeller (Nutritional Sciences, University of Wisconsin, Madison) for helpful discussions and editing the entire manuscript. The authors also thank the individuals who participated in this study. This study was supported by a research grant to MK from the Ministry of Education, Culture, Sports, Science and Technology, Japan (18300218) and a research grant to YY as part of a research fellowship of the Japan Society for the Promotion of Science for Young Scientists (19-1440).

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