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Impact of obesity, overweight and underweight on life expectancy and lifetime medical expenditures: the Ohsaki Cohort Study

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ABSTRACT

Objectives: People who are obese have higher demands for medical care than those of the normal weight people. However, in view of their shorter life expectancy, it is unclear whether obese people have higher lifetime medical expenditure. We examined the association between body mass index, life expectancy and lifetime medical expenditure.

Design: Prospective cohort study using individual data from the Ohsaki Cohort Study.

Setting: Miyagi Prefecture, northeastern Japan.

Participants: The 41 965 participants aged 40–79 years.

Primary and secondary outcome measures: The life expectancy and lifetime medical expenditure aged from 40 years.

Results: In spite of their shorter life expectancy, obese participants might require higher medical expenditure than normal weight participants. In men aged 40 years, multiadjusted life expectancy for those who were obese participants was 41.4 years (95% CI 38.28 to 44.70), which was 1.7 years non-significantly shorter than that for normal weight participants (p=0.3184). Multiadjusted lifetime medical expenditure for obese participants was £112 858.9 (94 954.1–131 840.9), being 14.7% non-significantly higher than that for normal weight participants (p=0.1141). In women aged 40 years, multiadjusted life expectancy for those who were obese participants was 49.2 years (46.14–52.59), which was 3.1 years non-significantly shorter than for normal weight participants (p=0.0724), and multiadjusted lifetime medical expenditure was £137 765.9 (123 672.9–152 970.2), being 21.6% significantly higher (p=0.0005).

Conclusions: According to the point estimate, lifetime medical expenditure might appear to be higher for obese participants, despite their short life expectancy. With weight control, more people would enjoy their longevity with lower demands for medical care.

ARTICLE SUMMARY

Article focus

- Obese people have higher needs and demands for medical care.
- Obesity is associated with an increased risk of mortality.
- In view of the decreased life expectancy in obese participants, it is unclear whether lifetime medical expenditure increases or decreases as a result.

Key messages

- In spite of their short life expectancy, obese men and women had approximately 14.7% and 21.6% higher lifetime medical expenditure in comparison with normal weight participants, respectively.
- With better weight control, more people would enjoy their longevity with lower needs and demands for medical care.

Strengths and limitations of this study

- This is the first study to have investigated the association between body mass index, life expectancy and lifetime medical expenditure calculated from individual medical expenditure and mortality data over a long period in a general population.
- There was a limit to the accurate estimation of life expectancy and lifetime medical expenditure for obese participants because the Japanese population has a low prevalence of body mass index≥30.0 kg/m^2.

INTRODUCTION

Obesity is closely associated with an increased risk of cardiovascular disease, cancer, hypertension, diabetes mellitus and other medical problems. Previous studies have reported that obese and overweight people have higher needs and demands for medical care than normal weight people.[1–5] However, it is unclear whether obese people have higher lifetime medical expenditure than those of the normal weight people because the former have a comparatively shorter life

expectancy.[6–10] Additionally, underweight people have a higher risk of mortality and thus also tend to have higher medical expenditure per month or per person, based on a 10-year follow-up.[1 4]

Although four previous studies have examined the association between obesity and lifetime medical expenditure,[10–13] the results were inconsistent. One study showed that obese people had lower lifetime medical expenditure than those of the normal weight people,[11] whereas the others indicated that obese people had higher lifetime medical expenditure.[10 12 13] In addition, two of the four studies estimated lifetime medical expenditure from excess risk of cause-specific mortality and mean medical expenditure for the index disease.[10 11] Only the other two studies calculated lifetime medical expenditure on the basis of individual medical expenditure and mortality.[12 13] However, one of those studies followed up the participants for only 2 years[12] and the other calculated lifetime medical expenditure for elderly participants aged 70 years or over.[13] Therefore, the association between body mass index (BMI) and lifetime medical expenditure remains to be fully clarified.

We therefore conducted a 13-year prospective observation of 41 965 Japanese adults aged 40–79 years living in the community, which accrued 392 860 person-years. We examined the association between BMI and lifetime medical expenditure, based on individual medical expenditure and life table analysis.[1 14–17] We collected data for survival and all medical care utilisation and costs, excluding home care services provided home health aides, nursing home care and preventive health services in participants of this cohort study.

MATERIALS AND METHODS

Study cohort

We used data from the Ohsaki National Health Insurance (NHI) Cohort Study.[1 14 16–18] In brief, we sent a self-administered questionnaire on various lifestyle habits between October and December 1994 to all NHI beneficiaries living in the catchment area of Ohsaki Public Health Center, Miyagi Prefecture, northeastern Japan. A survey was conducted of NHI beneficiaries aged 40–79 years. Among 54 996 eligible individuals, 52 029 (95%) responded.

We excluded 776 participants who had withdrawn from the NHI before 1 January 1995, when we started the prospective collection of NHI claim files. Thus, 51 253 participants formed the study cohort. The study protocol was approved by the Ethics Committee of Tohoku University School of Medicine. The participants who had returned the self-administered questionnaires and had signed them were considered to have consented to participate in this study.

For the current analysis, we also excluded participants who did not provide information about body weight and height (n=3543), were at both extremes of the BMI range: lower than the 0.05th percentile for BMI (below 14.41 for men; below 13.67 for women) or higher than the 99.95th percentile for BMI (above 58.46 for men; above 62.00 for women; n=48), those who died within the first year (n=454) or those who had a history of cancer (n=1533), myocardial infarction (n=1233), stroke (n=831) or kidney disease (n=1646). Thus, a total of 41 965 participants (20 066 men and 21 899 women) participated.

Body mass index

The self-administered questionnaire included questions on weight and height, and BMI was calculated as weight divided by the square of height (kilograms per square metre). We divided the participants into groups according to the following BMI categories: <18.5 (underweight), 18.5–24.9 (normal weight), 25.0–29.9 (overweight) and ≥30.0 kg/m^2 (obesity). These BMI categories correspond to the cut-off points proposed by the WHO: normal BMI range (18.5–24.9 kg/m^2), grade 1 overweight (25.0–29.9 kg/m^2), grade 2 overweight (30.0–39.9 kg/m^2) and grade 3 overweight (≥40.0 kg/m^2).[19]

The validity of self-reported body weight and height has been reported earlier.[1] Briefly, the weight and height of 14 883 participants, who were a subsample of the cohort, were measured during basic health examinations provided by local governments in 1995. The Pearson correlation coefficient (r) and weighted κ (κ) between the self-reported values and measured values were r=0.96 (p<0.01) for weight, r=0.93 (p<0.01) for height and r=0.88 (p<0.01) and κ=0.72 for BMI categories.

Health insurance system in Japan

The details of the NHI system have been described previously.[1 4 14 16 18] Briefly, everyone living in Japan is required to enrol in one health insurance system. The NHI covers 35% of the Japanese population for almost all medical treatment, including diagnostic tests, medication, surgery, supplies and materials, physicians and other personnel costs and most dental treatment. It also covers home care services provided by physicians and nurses but not those by other professionals such as home health aides. The NHI covers inpatient care but not nursing home care. Also, it does not cover preventive health services such as mass screening and health education. Payment to medical providers is made on a fee-for-service basis, where the price of each service is determined by a uniform national fee schedule.

If a participant withdrew from the NHI system because of death, emigration or employment, the withdrawal date and the reason for withdrawal were coded in the NHI withdrawal history files. We recorded any mortality or migration by reviewing the NHI withdrawal history files and collected data on the death of participants by reviewing the death certificates filed at Ohsaki Public Health Center. We then followed up the participants and prospectively collected data on medical care utilisation and its costs for all participants in the cohort from 1 January 1995 through 31 December 2007.

Statistical analysis

We conducted the same analysis as the previous study about the association between walking, life expectancy and lifetime medical expenditure.[16] Briefly, we divided the age groups (×) from 40 years according to the following categories: 40–44, 45–49, 50–54, 55–59, 60,64, 65–69, 70–74, 75–79, 80–84 and ≥85 years. Based on person-years and the number of deaths from 1996 until 2007, the multiadjusted mortality rates for each age category were estimated from a Poisson regression model. The dependent variable was mortality, and independent variables were age groups, categories of BMI and the following covariates: smoking status (current and past smoker or never smoker), alcohol consumption (current drinker consuming 1–499 g/week, current drinker consuming ≥450 g/week or never and past drinker), sports and physical exercise (≥3 h/week or <3 h/week), time spent walking (≥1 h/week or <1 h/week) and education (junior high school, high school or college/university or higher). We did not adjust for hypertension and diabetes mellitus in the multivariate models because these variables are considered to occupy an intermediate position in the etiologic pathway between BMI and mortality.

We separately calculated medical expenditure for participants who survived through the index year and for those who died because previous study showed that medical expenditure increased before death.[20] The multiadjusted medical expenditure per year was estimated using a linear regression model adjusted for the above covariates in survivors and decedents.

The estimates of multiadjusted mortality and medical expenditure were used for estimating life expectancy and lifetime medical expenditure from 40 years of age. To estimate life expectancy and lifetime medical expenditure, we constructed life tables per 100 000 persons using Chiang's analytical method on the basis of the latest published complete life tables of Japan for the year 2000.[21 22] Then, life expectancy (e_x) and lifetime medical expenditure (M_x) for each age groups (x) were estimated using the numbers of survivors (l_x), deaths (d_x), static population (L_x), multiadjusted medical expenditure for survivors (a_y) and multiadjusted medical expenditure for the deceased (b_y) as follows:

$$\sum \text{is sum of} y = x$$

$$e_x = \frac{\sum L_y}{l_x}$$

$$M_x = \frac{\sum (L_y \cdot a_y + d_y \cdot b_y)}{l_x}$$

The 95% CIs were estimated using a Monte Carlo simulation based on a Poisson regression model and linear regression model. We repeated 100 000 times, and all analysis were used the SAS V.9.1 statistical software package (SAS Institute Inc., 2004). All p values <0.05 were accepted as statistically significant.

We used a purchasing power parity rate of UK£ 1.00= JPN¥140.[16]

RESULTS

After 13 years of follow-up, we observed 5159 deaths (3356 men and 1803 women) among the 41 965 participants (20 066 men and 21 899 women).

The mean medical expenditure per year for survivors in men was £2393 in underweight, £2055 in normal weight, £2231 in overweight and £2334 in obesity, respectively. In women, it was £2375 in underweight, £1972 in normal weight, £2317 in overweight and £2733 in obesity, respectively. These differences of mean medical expenditure per year for survivors are statistically significant in men and women (ANOVA; p<0.0001). Also, the mean medical expenditure in the year of death for participants in men was £15 445 in underweight, £16 973 in normal weight, £17 811 in overweight and £17 878 in obesity, respectively. In women, it was £12 833 in underweight, £15 584 in normal weight, £17 059 in overweight and £19 635 in obesity, respectively. These differences of mean medical expenditure in the year of death for participants are statistically significant in only women (men, p=0.2241; women, p=0.0059).

Baseline characteristics by BMI category

The baseline characteristics of the study participants according to the BMI categories are shown for men and women (table 1), among whom 3.3% and 3.9% were underweight, 23.6% and 28.4% were overweight and 2.0% and 3.6% were obese, respectively.

Mean age in men decreased linearly with increasing BMI category. In women, mean age was highest in the underweight category. The proportions of men and women who were current and past smokers decreased with increasing BMI, and this tendency was especially marked in men. The proportions of men who had never and past drinker were highest in the underweight category. The proportions of men who did ≥3 h sports and physical exercise per week decreased with increasing BMI. The proportions of men and women who walked ≥1 h/day were the lowest in underweight men and obese women. Educational background increased linearly in men and decreased linearly in women as the BMI category increased. These characteristics showed statistically significant difference.

Mortality in terms of categories for BMI

Figure 1A for men and figure 1B for women show the mortality (per 1000 person-years) in each of the age groups according to the categories of BMI.

In underweight participants, there was a tendency that the mortality was the highest in each age group.

Table 1 Baseline characteristics by BMI categories in 41 965 participants

	Men					Women				
	BMI (kg/m^2)					BMI (kg/m^2)				
	<18.5	18.5–24.9	25.0–29.9	≥30.0	p Value*	<18.5	18.5–24.9	25.0–29.9	≥30.0	p Value
No. of subjects	666	14 278	4730	392	<0.0001	857	14 031	6226	785	<0.0001
Mean age (years)	64.0	59.1	57.4	56.1		63.7	59.8	60.7	61.2	
SD	10.4	10.5	10.2	10.2		10.9	10.1	9.1	9.5	
Smoking status (%)										
Current and past smoker	87.3	82.5	76.6	74.8	<0.0001	18.6	11.2	10.1	10.6	<0.0001
Never smoker	12.7	17.5	23.4	25.2		81.4	88.8	90.0	89.4	
Alcohol consumption (%)										
Current drinker, 1–449 g/week	49.2	61.0	61.4	50.8	<0.0001	18.2	21.8	21.4	19.3	0.0574
Current drinker, ≥450 g/week	9.6	11.7	12.6	15.0		0.6	0.8	0.5	0.9	
Never and past drinker	41.2	27.3	26.0	34.2		81.2	77.4	78.2	79.8	
Sports and physical exercise (%)										
≥3 h/week	17.5	16.1	13.8	10.1	<0.0001	9.8	11.3	11.0	10.8	0.5993
<3 h/week	82.5	83.9	86.2	89.9		90.2	88.7	89.0	89.2	
Time spent walking (%)										
≥1 h/day	41.7	51.4	45.8	42.7	<0.0001	37.9	45.1	41.0	35.6	<0.0001
<1 h/day	58.3	48.7	54.2	57.3		62.1	54.9	59.0	64.4	
Education (%)										
Junior high school	64.2	62.2	58.9	58.8	0.0013	58.3	54.2	62.7	71.3	<0.0001
High school	27.4	30.5	33.4	33.4		34.0	36.9	31.0	24.6	
College/university or higher	8.4	7.3	7.7	7.8		7.7	8.9	6.3	4.1	

*p Values were calculated by χ^2 test (categorical variables) or ANOVA (continuous variables).
BMI, body mass index.

Overweight participants showed similar mortality with normal weight participants, especially women. Overweight men showed slightly lower mortality than normal weight men. In obese participants, the mortality curve was not described smoothly because of small number of participants.

Table 2 shows the mortality ratio with 95% CIs according to the categories of BMI. In underweight participants, the multiadjusted mortality ratio was significantly higher than that in the normal weight participants (men, 1.62, 95% CI 1.41 to 1.86, p<0.0001; women, 1.46, 1.22 to 1.76, p<0.0001). In overweight participants, the multiadjusted mortality ratio was significantly lower in men and non-significantly lower in women than that in normal weight participants (men, 0.91, 0.83 to 0.99, p=0.0260; women, 0.98, 0.88 to 1.10, p=0.7841). In obese participants, the multiadjusted mortality ratio was non-significantly higher than that in normal weight participants (men, 1.14, 0.88 to 1.49, p=0.3177; women, 1.23, 0.98 to 1.55, p=0.0717).

Life expectancy and lifetime medical expenditure by BMI category

Table 3 shows life expectancy and lifetime medical expenditure with 95% CIs according to the BMI categories.

By multiadjusted analysis, obese men and women had approximately 1.7 and 3.1 years non-significantly shorter life expectancy from the age of 40 years in comparison with men and women of normal weight, respectively (men, p=0.3184; women, p=0.0724). Meanwhile, obese men and women had approximately 14.7% non-significantly higher and 21.6% significantly higher lifetime medical expenditure in comparison with normal weight participants, respectively (men, p=0.1141; women, p=0.0005).

In men, multiadjusted life expectancy was greatest for overweight, that is, 44.34 years (95% CI 43.11 to 45.54, p=0.0264), followed by normal weight (43.03 years, 42.22 to 43.73) and obesity (41.36 years, 38.28 to 44.70, p=0.3184) and was shortest for underweight (37.40 years, 35.80 to 38.87, p<0.0001). The multiadjusted lifetime medical expenditure for overweight was the highest, that is, £114 766.9 (95% CI 107 754.1 to 121 966.6, p<0.0001), followed by obesity (£112 858.9, 94 954.1 to 131 840.9, p=0.1141) and normal weight (£98 355.0, 93 615.3 to 103 010.2) and was the lowest for underweight (£93 208.7, 81 704.9 to 104 706.4, p=0.3916).

In women, multiadjusted life expectancy was greatest for overweight, that is, 52.56 years (50.67 to 54.46, p=0.7797), followed by normal weight (52.31 years,

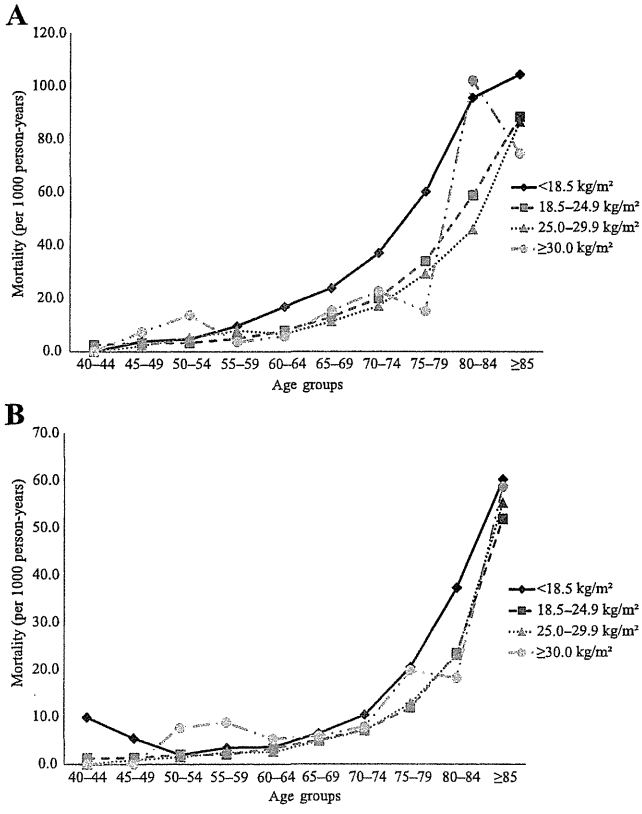

Figure 1 Multiadjusted mortality by BMI categories in each age group in men (A) and women (B).

50.79 to 53.75) and obesity (49.23 years, 46.14 to 52.59, p=0.0724) and was shortest for underweight (46.98 years, 44.63 to 49.29, p<0.0001). The lifetime medical expenditure for obesity was the highest (£137 765.9, 123 672.9 to 152 970.2, p=0.0005), followed by overweight (£129 964.6, 121 845.4 to 138 577.2, p<0.0001) and normal weight (£113 282.9, 106 668.0 to 120 054.6) and was lowest for underweight (£109 382.2, 97 996.6 to 121 008.6, p=0.5174).

DISCUSSION

The present results indicate that (1) obese men and women have 14.7% non-significantly higher and 21.6% significantly higher multiadjusted lifetime medical expenditure than those of the normal weight participants (men, p=0.1141; women, p=0.0005), even though their life expectancy is non-significantly shorter by 1.7 and 3.1 years than those of the normal weight participants, respectively (men, p=0.3184; women, p=0.0724); (2) underweight men and women have 5.2% and 3.4% non-significantly lower lifetime medical expenditure than those of the normal weight participants (men, p=0.5174; women, p=0.3916) because men and women live 5.6 and 5.3 years significantly less than those of the normal weight participants, respectively (men, p<0.0001; women, p<0.0001).

Comparison with other studies

Obese participants had shorter life expectancy than normal weight participants, as has been observed in previous studies.[6–10] Overweight participants had longer life expectancy than normal weight participants. Two of the four previous studies have reported that overweight participants had longer life expectancy than normal weight participants.[7 9] These results support our finding of an association between being overweight and life expectancy. Additionally, an association between BMI and all-cause mortality in the Japanese population has been reported by other data sets.[23–29] All seven previous studies showed that among the BMI categories, the lowest one had the highest mortality risk. These results are consistent with the fact that underweight participants have significantly the shortest life expectancy, as was observed in our study.

Thus, the association between BMI and life expectancy showed same trend with the pooled analyses of the association between BMI and all-cause mortality in Asia and Japan.[30 31]

Our present results support three of the four previous studies of lifetime medical expenditure for obese

Table 2 Mortality ratio for BMI categories in 41 965 participants

	Univariate		Multiadjusted*	
BMI (kg/m²)	Mortality ratio (95% CI)	p Value	Mortality ratio (95% CI)	p Value
Men				
<18.5	1.69 (1.47 to 1.93)	<0.0001	1.62 (1.41 to 1.86)	<0.0001
18.5–24.9	1.00 (Reference)		1.00 (Reference)	
25.0–29.9	0.90 (0.82 to 0.98)	0.0163	0.91 (0.83 to 0.99)	0.0260
≥30.0	1.13 (0.87 to 1.47)	0.3712	1.14 (0.88 to 1.49)	0.3177
Women				
<18.5	1.50 (1.25 to 1.81)	<0.0001	1.46 (1.22 to 1.76)	<0.0001
18.5–24.9	1.00 (Reference)		1.00 (Reference)	
25.0–29.9	1.00 (0.89 to 1.11)	0.9613	0.98 (0.88 to 1.10)	0.7841
≥30.0	1.29 (1.03 to 1.62)	0.0273	1.23 (0.98 to 1.55)	0.0717

*Adjusted for age groups, smoking status, alcohol drinking, sports and physical exercise, time spent walking and education.
BMI, body mass index.

Table 3 Life expectancy and lifetime medical expenditure at age 40 years for BMI categories in 41 965 participants

	Univariate			Multiadjusted*		
BMI (kg/m^2)	Estimate	95% CI	p Value	Estimate	95% CI	p Value
Men						
Life expectancy at age 40 years (years)						
<18.5	36.72	35.10 to 38.17	<0.0001	37.40	35.80 to 38.87	<0.0001
18.5–24.9	42.70	41.91 to 43.37	Reference	43.03	42.22 to 43.73	Reference
25.0–29.9	44.09	42.89 to 45.25	0.0157	44.34	43.11 to 45.54	0.0264
≥30.0	41.23	38.16 to 44.54	0.3733	41.36	38.28 to 44.70	0.3184
Lifetime medical expenditure at age 40 years (£)						
<18.5	94 877.5	83 411.4 to 106 275.7	0.6846	93 208.7	81 704.9 to 104 706.4	0.3916
18.5–24.9	97 244.1	92 662.5 to 101 774.0	Reference	98 355.0	93 165.3 to 103 010.2	Reference
25.0–29.9	114 398.2	107 490.1 to 121 505.3	<0.0001	114 766.9	107 754.1 to 121 966.6	<0.0001
≥30.3	115 362.6	97 361.8 to 134 555.0	0.0501	112 858.9	94 954.1 to 131 840.9	0.01141
Women						
Life expectancy at age 40 years (years)						
<18.5	46.26	43.98 to 48.43	<0.0001	46.98	44.63 to 49.29	<0.0001
18.5–24.9	51.70	50.28 to 53.02	Reference	52.31	50.79 to 53.75	Reference
25.0–29.9	51.74	49.98 to 53.48	0.9582	52.56	50.67 to 54.46	0.7797
≥30.0	48.13	45.23 to 51.22	0.0272	49.23	46.14 to 52.59	0.0724
Lifetime medical expenditure at age 40 years (£)						
<18.5	108 278.3	97 142.8 to 119 593.7	0.5816	109 382.2	97 996.6 to 121 008.6	0.5174
18.5–24.9	111 512.8	105 303.4 to 117 910.4	Reference	113 282.9	106 668.0 to 120 054.6	Reference
25.0–29.9	127 869.3	120 236.3 to 135 932.3	<0.0001	129 964.6	121 845.4 to 138 577.2	<0.0001
≥30.0	134 887.1	121 318.4 to 149 383.6	0.0007	137 765.9	123 672.9 to 152 970.2	0.0005

*Adjusted for age groups, smoking status, alcohol drinking, sports and physical exercise, time spent walking and education.
BMI, body mass index.

participants.[10 12 13] In comparison to previous studies, we calculated lifetime medical expenditure from individual medical expenditure and survival data covering longest follow-up period to date. Meanwhile, one study has shown that obese participants have lower lifetime medical expenditure than normal weight participants.[11] However, that study limited the participants to non-smokers and calculated lifetime medical expenditure from the mortality of a hypothetical cohort and estimated medical expenditure from other cohort. In the present study, overweight participants were found to have higher lifetime medical expenditure than normal weight participants, as had been reported previously.[10 12 13] We consider that this was attributable to the higher medical expenditure per month or per person from the 10-year or 9-year follow-up than for normal weight participants.[1 3 4] On the other hand, with regard to underweight participants, our present findings were inconsistent with those of a previous study that examined the association between being underweight and lifetime medical expenditure.[13] However, that study calculated lifetime medical expenditure for elderly participants aged over 70 years. Elderly underweight participants have high mortality,[32] and medical expenditure increases in the 1 year prior to death.[20] Thus, lifetime medical expenditure from 70 years for underweight participants becomes higher than for participants of normal weight. Our study results are thus inconsistent with those reported previously.

We previously calculated life expectancy and lifetime medical expenditure for smokers and non-smokers from age 40 years by using the same data set as that for the present study.[17] The results indicated that lifetime medical expenditure was non-significantly lower in smokers than in non-smokers, reflecting the 3.5 years shorter life expectancy of smokers. On the other hand, the present study indicated that lifetime medical expenditure was higher for obese participants in spite of their shorter life expectancy. This difference would result from the difference in which obesity and smoking affect one's health and longevity. Previous studies of healthy and disability free life expectancy have agreed that smoking shortens life expectancy without affecting the years of life spent with ill-health or disability, while obesity shortens life expectancy and extends the years of life with ill-health or disability.[33] On the basis of these differences, Reuser *et al* summarised the situation as 'smoking kills and obesity disables'.[7] Extended years with ill-health and/or disability must result in increased lifetime medical expenditure. All these findings suggest that weight control would bring about longer life expectancy and long-term enhancement of the quality of life and a cost saving.

Strengths and limitations

A major strength of our present study is that it is the first in the world to have clarified the association between BMI and lifetime medical expenditure calculated from individual medical expenditure and mortality data over

a long period in a general population from the age of 40 years.[1 14 16–18] The NHI covers almost all medical care utilisation.[1 4 14 16 18] Additionally, in order to reduce bias, we adjusted confounders by including various covariates in our Poisson regression model and linear regression mode.[16] On the other hand, several limitations of our study should also be considered. First, we used self-reported BMI which in a source of error.[34 35] We consider this error to be a non-differential misclassification. This misclassification would lead to attenuation of the true association towards the null. To address this problem, van Dam *et al*[36] studied the association between BMI and mortality using lower BMI cut-off points: 24.5 kg/m^2 to reflect a measured BMI of 25.0 kg/m^2 and 29.0 kg/m^2 to reflect a measured BMI of 30.0 kg/m^2. The association showed similar with original cut-off points. Second, the 95% CI was wide, and there was a limit to the accurate estimation of life expectancy and lifetime medical expenditure for obese participants. Additionally, we did not observe significant association in obese participants without lifetime medical expenditure in women. However, our results are consistent with those of the previous studies.[6–8 10 12 13] In Japan, prevalence of obesity is only 3%.[37] Thus, the reason for non-significant association might be β error because of the lack of statistical power due to small number of obese participants.

Conclusions and policy implication

In summary, even though we observed non-significant association between obesity, life expectancy and lifetime medical expenditure without lifetime medical expenditure in women, lifetime medical expenditure might appear to be higher for obese participants, despite their short life expectancy. With better weight control, more people would enjoy their longevity with lower needs and demands for medical care.

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Contributors All authors contributed to the design of the study. MN, SK, MK, KO-M, TS and IT participated in data collection. MN, SK, AH, MK and SH participated in data analysis. MN, MK, KO-M, TS, AH, MK and SH participated in the writing of the report. SK and IT participated in critical revision of the manuscript. All authors approved the final version of the report for submission.

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Impact of obesity, overweight and underweight on life expectancy and lifetime medical expenditures: the Ohsaki Cohort Study

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Correlation Between High-Sensitivity C-Reactive Protein and Brain Gray Matter Volume in Healthy Elderly Subjects

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Abstract: Although elevated serum high-sensitivity C-reactive protein (hsCRP) is related to atherosclerosis, brain infarction, and cognitive decline, it has not been clarified whether increased hsCRP is associated with the decline in brain gray matter volume. Therefore, the purpose of this study was to determine the relationship between hsCRP levels and brain regional gray matter volume using brain magnetic resonance imaging (MRI) data from 109 community-dwelling healthy elderly subjects. Brain MRIs were processed with voxel-based morphometry using a custom template by applying diffeomorphic anatomical registration using the exponentiated lie algebra (DARTEL) procedure. We found a significant negative correlation between regional gray matter volume of the posterior and lateral aspects of the left temporal cortex and hsCRP level after adjusting for age, gender, and intracranial volume. Our results suggest that subjects who have mild inflammation related to arteriosclerosis have decreased regional gray matter volume in the posterior and lateral aspects of the left

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temporal cortex. Thus, preventing the progression of arteriosclerosis may be important for preventing a decrease in gray matter volume in healthy elderly subjects. *Hum Brain Mapp 00:000–000, 2012.*

Key words: gray matter; high-sensitivity C-reactive protein; magnetic resonance imaging; elderly; voxel-based morphometry; DARTEL

INTRODUCTION

Recent studies have shown that chronic inflammation plays a crucial role in the development of atherosclerosis [Ross, 1999]. High-sensitivity C-reactive protein (hsCRP) is a sensitive marker of systemic low-grade inflammation [Pearson et al., 2003] and is associated with plaque progression and instability in large arteries [Hashimoto et al., 2001; Yamagami et al., 2004]. Additionally, hsCRP is useful to predict several diseases such as stroke and cardiovascular diseases [Pearson et al., 2003; Teunissen et al., 2003; Yaffe et al., 2003]. Increased serum concentrations of hsCRP have been associated with poor memory [Teunissen et al., 2003], poor global cognitive performance [Pearson et al., 2003], and vascular dementia [Ravaglia et al., 2007]. Several higher cognitive functions have been shown to be associated with regional gray matter volume, for example, episodic memory with hippocampus gray matter [Kramer et al., 2007], working memory with dorsolateral prefrontal cortex gray matter [Takeuchi et al., 2010], semantic memory with temporal pole gray matter [Taki et al., 2011], and executive function with lateral prefrontal cortex gray matter [Kramer et al., 2007; Zimmerman et al., 2006]. Therefore, it is plausible that there is a correlation between hsCRP level and regional gray matter volume. Investigating the correlation between hsCRP level and regional gray matter volume is important because a significant correlation would indicate that cognitive decline owing to atherosclerosis is derived from a reduction in gray matter volume, and that medical treatment for atherosclerosis is important not only to prevent the decrease in cognitive function but also to prevent a decrease in gray matter volume.

However, few studies have tested the correlation between hsCRP level and brain structure. A recent study focused on the correlation between hsCRP level and white matter microstructure in healthy adults, and showed that a higher hsCPR level was related with reduced fractional anisotropy of the frontal lobe, the corona radiata, and the corpus callosum [Wersching et al., 2010]. Another study showed that hsCRP level was related with hippocampal volume in patients with type 2 diabetes mellitus [Anan et al., 2011]; nondemented patients with type 2 diabetes mellitus and a higher hsCRP level and showed more hippocampal atrophy compared with those with a normal hsCRP level. Although these findings suggest a significant correlation between hsCRP and regional gray matter volume of the hippocampus, that study focused on patients with type 2 diabetes mellitus, who show atrophy of several gray matter regions including the hippocampus [Korf et al., 2007]. That study also focused only on hippocampal volume, not regional gray matter volume. Therefore, it has not yet been clarified whether there is a significant correlation between hsCRP and regional gray matter volume in healthy subjects using a whole-brain analysis.

The purpose of this study was to investigate the correlation between hsCRP level and regional gray matter volume using brain magnetic resonance imaging (MRI) of 109 community-dwelling healthy elderly subjects within a narrow age window. We applied the brain-image analysis technique of voxel-based morphometry (VBM) [Ashburner and Friston, 2000]. VBM analysis enables a global analysis of brain structures without a priori identification of a region of interest. This approach permits the identification of unsuspected potential brain structural abnormalities. We hypothesized that the gray matter volume of regions fed by the middle cerebral artery would be negatively correlated with hsCRP level because symptomatic atherosclerotic disease is mostly observed in the middle cerebral artery [Kim et al., 2005]; therefore, it was thought that the middle cerebral artery would be more vulnerable to atherosclerosis compared with other intracranial arteries such as the anterior cerebral artery.

METHODS

Study Population

The subjects were selected from participants in the Tsurugaya Project, a comprehensive geriatric assessment (CGA) of the elderly population, which includes assessments of medical status, depressive symptoms, and physical and cognitive functions. Recruitment of subjects was described previously [Taki et al., 2011]. Briefly, the project enrolled 2,730 subjects aged 69 years or older living in Tsurugaya district, Sendai, Japan. The subjects responded to interviews by psychologists and geriatrists based on questionnaires, including the Rome II Modular Questionnaire 8, Geriatric Depression Scale (GDS; http://www.stanford.edu/~yesavage/GDS.html) [Brink et al., 1982; Yesavage et al., 1982], and the Mini-Mental State Examination (MMSE) [Folstein et al., 1975]as part of the CGA. Next, we asked the subjects whether they were willing to undergo an MRI of their brains. We defined healthy subjects as those who showed GDS scores <10 and MMSE scores of 28 or higher. Additionally, we excluded subjects with a history of brain tumors, cerebrovascular diseases,

TABLE I. Subject clinical characteristics

	Men (Range, mean ± SD)	Women (Range, mean ± SD)	*P*
Age (years old)	70–75, 72.4 ± 1.3	69–75, 72.0 ± 1.9	0.187
MMSE[a] (max. 30)	28–30, 29.2 ± 0.8	28–30, 29.0 ± 0.9	0.321
GDS[b] (max. 30)	0–9, 5.2 ± 2.4	1–9, 5.4 ± 2.5	0.632
Duration of education (year)	8–25, 14.4 ± 3.7	8–18, 11.6 ± 2.3	<0.001
Systolic blood pressure (mm Hg)	81–167, 132.6 ± 16.7	105–203, 137.8 ± 20.3	0.163
Diastolic blood pressure (mm Hg)	50–104, 77.1 ± 10.8	63–104, 78.4 ± 10.2	0.544
hsCRP[c] (mg/dL)	0.05–21.7, 1.46 ± 3.1	0.09–34.3, 2.00 ± 4.7	0.491
Total cholesterol (mg/dL)	113–259, 191.8 ± 32.1	146–311, 191.8 ± 32.1	<0.001
Triglyceride (mg/dL)	62–495, 179.8 ± 100.0	58–272, 148.6 ± 59.8	0.050
HDL-C[d] (mg/dL)	32–104, 50.1 ± 13.7	29–113, 59.6 ± 14.8	<0.001

[a]Mini-Mental State Examination.
[b]Geriatric Depression Scale.
[c]High-sensitivity C-reactive protein.
[d]High-density lipoprotein cholesterol.

head trauma, or any neuropsychiatric disease. In total, 79 men and 96 women fulfilled the criteria of "healthy" and gave their consent to undergo brain MRI. From these subjects, we selected healthy male and female subjects separately by random sampling and obtained their brain MRIs. We also obtained hsCRP levels from the blood in each subject. As a result, the study subjects consisted of 55 men and 54 women. The characteristics of the subjects were reported previously [Taki et al., 2011].

Written informed consent was obtained from each subject after a full explanation of the purpose and procedures of the study prior to brain MRI according to the declaration of Helsinki (1991). Approval for these experiments was obtained from the institutional review board of Tohoku University.

Measurement of Serum hsCRP

Blood was extracted from the antecubital vein after an overnight fast. All subjects underwent routine laboratory tests, including assays for serum total cholesterol, serum triglycerides, serum high-density lipoprotein cholesterol, and serum low-density lipoprotein cholesterol. hsCRP concentrations were determined using an immunotechnique on a Behring BN II analyzer (Dade Behring, Tokyo, Japan). The BN II high sensitivity assay utilizes a monoclonal antibody coated on polystyrene particles and fixed-time kinetic nephelometric measurements [Ledue et al., 1998]. The detection limit of this assay is 0.02 mg/L. Clinical characteristics of the subjects are summarized in Table I.

Image Acquisition

Brain MRI was acquired from each subject using two 0.5-T MRI scanners of the same model (Signa Contour, GE-Yokogawa Medical Systems, Tokyo, Japan). The scanner was routinely calibrated using the same standard GE phantom. No major hardware upgrades occurred during the period. All subjects were scanned with identical pulse sequences: 124 contiguous, 1.5-mm-thick axial planes of three-dimensional T1-weighted images (spoiled gradient recalled acquisition in steady state: repetition time, 40 ms; echo time, 7 ms; flip angle, 30; voxel size, 1.02 × 1.02 × 1.5 mm).

Image Analysis

We applied VBM to conduct the image analyses. Specifically, we used the Statistical Parametric Mapping 8 software (SPM8, Wellcome Department of Cognitive Neurology, London, United Kingdom) for the structural segmentation, longitudinal registration, and group statistics, and the "Diffeomorphic Anatomical Registration using Exponentiated Lie algebra (DARTEL)" [Ashburner, 2007] deformation framework for intersubject spatial normalization. As DARTEL produces more accurate registration [Klein et al., 2009], it allows improved sensitivity such as that needed to assess the correlation between regional gray matter volume and hsCRP. Practically, all of the T1-weighted images were first segmented using the New Segmentation algorithm in SPM8 [Ashburner and Friston, 2005] and their resulting gray matter maps were rigidly registered onto their common mean image. Then, the DARTEL toolbox was used to estimate a best set of smooth, pure nonlinear and reversible deformation sets from each subject's tissue map to a common, custom template. To achieve this goal, DARTEL uses an iterative process: by computing constrained warping fields from all subject data to the current average at each step, successive and increasingly sharp average templates are generated, as well as corresponding warping fields for each subject. Finally, our resulting custom template was itself matched to the Montreal Neurological Institute (MNI) space using

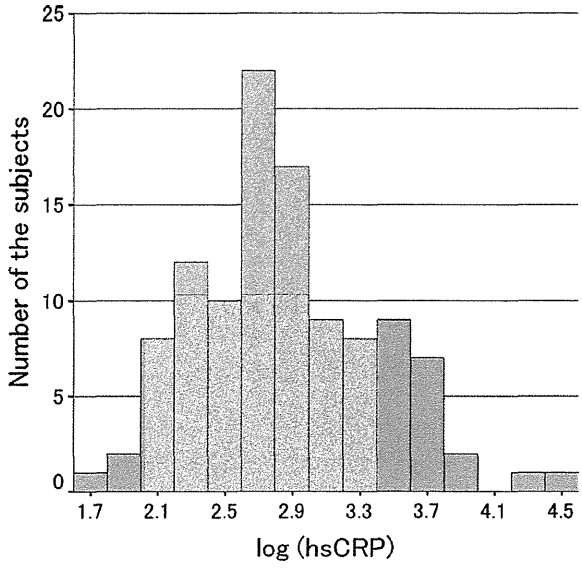

Figure 1.
The distribution of log-transformed hsCRP *P*-levels.

an affine-only registration to map our custom coordinate space to the more standard MNI space [Bergouignan et al., 2009]. We applied modulation, which compensated for the volume change induced by warping [Good et al., 2001], to preserve the amount of gray matter in the process. Finally, the warped gray matter images were smoothened by convolving an 8-mm full-width at half-maximum isotropic Gaussian kernel.

Statistical Analysis

A multiple regression analysis was performed to investigate the correlation between hsCRP level and regional gray matter volume after adjusting for age, gender, and intracranial volume. The intracranial volume was calculated by summing the gray matter volume, white matter volume, and CSF space volume derived in the abovementioned image preprocess step. Intracranial volume adjustment was performed using intracranial volume as an independent variable as described below. As the distribution of hsCRP levels was highly deviated from a normal distribution, the hsCRP data were log transformed to achieve a normal distribution. Age, gender, intracranial volume, and log-transformed hsCRP levels were used as independent variables, and regional gray matter volume was used as the dependent variable. We set the significance level at $P < 0.05$ by controlling false-discovery rate when performing multiple tests of topological features (i.e., clusters of voxels) and with random field theory when performing multiple tests [Chumbley et al., 2010; Morrell et al., 2010].

RESULTS

The distribution of log-transformed hsCRP levels is shown in Figure 1. A significant negative correlation was observed between regional gray matter volume of the posterior and lateral aspects of the left temporal cortex and hsCRP levels after adjusting for age, gender, and intracranial volume ($x, y, z = -60, -33, -2$; $t = 4.46$, $r = -0.345$, $P = 0.014$; Fig. 2). This result indicates that individuals with mild inflammation, which is related with arteriosclerosis, show a decrease in regional gray matter volume in the posterior and lateral aspects of the left temporal cortex. If the statistical threshold was set to a more liberal condition ($P < 0.001$, uncorrected), a correlation between regional gray matter volume and hsCRP level was observed in the bilateral posterior and lateral aspect of the temporal cortex and temporo–parieto–occipital regions after adjusting for age, gender, and intracranial volume. In no region did gray matter show a significant positive correlation with hsCRP level.

DISCUSSION

This is the first study to show a significant negative correlation between regional gray matter volume and hsCRP level in healthy elderly subjects. A significant negative

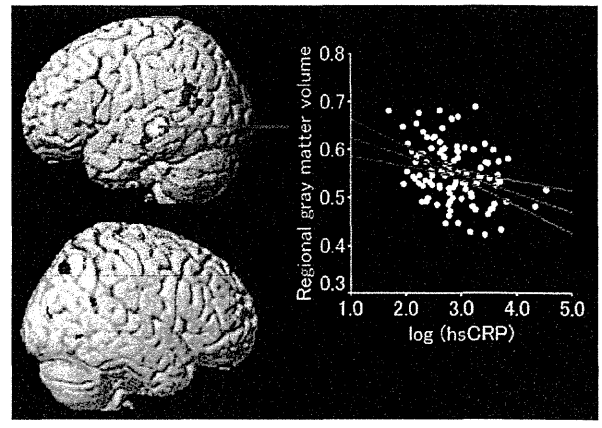

Figure 2.
Gray matter regions that had a significant negative correlation with the log-transformed hsCRP *P*-levels and regional gray matter volume after adjusting for age, gender, and intracranial volume. Upper: Correlation results were superimposed onto right and left lateral-view structural magnetic resonance images. Lower: Relationship between high-sensitivity C-reactive protein *P*-levels and regional gray matter volume (Talairach coordinates, $x = -60$, $y = -33$, $z = -2$). Color scales indicate the *t*-scores. We show the multiple comparisons data ($P < 0.001$, uncorrected) to clarify the extent of the regions. The 95% confidence interval of the regression line is also shown.

correlation was observed in the posterior and lateral aspects of the left temporal cortex. Although the mechanism for the correlation between regional gray matter volume and hsCRP is not well clarified, it is thought that atherosclerosis is associated with gray matter volume loss because hsCRP is a sensitive marker of systemic low-grade inflammation such as that seen in atherosclerosis [Pearson et al., 2003]. Atherosclerosis may be related to a variety of vascular pathologies, including carotid artery wall thickening [De Michele et al., 2002], vascular and coronary endothelial dysfunction [Brook et al., 2001; Sorisky, 2002; Williams et al., 2002], peripheral resistance, and arterial stiffness [Yki-Jarvinen and Westerbacka, 2000]. Therefore, it was thought that atherosclerosis may predispose a patient to a progressive decrease in cerebral blood flow [Nobili et al., 1993; Rodriguez et al., 1987] and alter the supply of oxygen and other nutrients to neurons, leading to chronic ischemia and tissue loss. Additionally, the lower limit of cerebral blood flow autoregulation is shifted to the right on the blood pressure axis to maintain a constant cerebral blood flow in the hypertensive state [Strandgaard, 1976]. This state is vulnerable to minor hypotensive episodes and easily leads to ischemia. From these phenomena, atherosclerosis may result in neuronal loss and gray matter volume decline.

We showed that the volume of the posterior and lateral aspects of the left temporal cortex was significantly and negatively correlated with hsCRP level. As hypothesized, this region is fed by the middle cerebral artery [Martin and Neuroanatomy, 2003]. As symptomatic atherosclerotic disease is mostly observed in the middle cerebral artery [Kim et al., 2005], it is thought that the middle cerebral artery is more vulnerable to atherosclerosis compared with other intracranial arteries such as the anterior cerebral artery. Additonally, the left lateral temporal lobe is significantly and negatively correlated with the rate of brain perfusion and age [Van Laere et al., 2001]; therefore, it may be particularly vulnerable to aging by the atherosclerotic interaction in the left lateral temporal lobe. Furthermore, we showed that the gray matter regions of the rather posterior aspect of the brain showed a tendency toward correlation with regional gray matter volume and hsCRP level in the liberal threshold analysis. Posterior circulation fed by the bilateral vertebral arteries shows vulnerability to atherosclerosis [Baker and Iannone, 1959; Strassburger et al., 1997]. Thus, it is thought that the gray matter regions of the posterior aspect of the brain had a tendency toward correlation with regoinal gray matter volume and hsCRP level.

Although a recent study suggested a significant correlation between hsCRP level and regional gray matter volume of the hippocampus [Anan et al., 2011], we did not find this correlation. This inconsistency may be derived from differences in subject characteristics, as that study focused not on healthy subjects but on patients with type 2 diabetes mellitus, who show atrophy in several gray matter regions such as the hippocampus [Korf et al., 2007]. Therefore, it is possible that diabetes mellitus itself may have affected the results of the correlation between hippocampal volume and hsCRP level. Additionally, although we applied VBM, which enables a global analysis of brain structures without a priori identification of a region of interest, Anan and colleagues focused only on the hippocampus. Thus, the inconsistency in the results was thought to be derived from both the subject characteristics and the methodology applied. In addition, although another study showed that higher hsCPR levels were related to reduced fractional anisotropy of the frontal lobe [Wersching et al., 2010], we did not find a significant correlation between regional gray matter volume in the frontal lobe and hsCRP level. Although there is also a negative correlation between gray matter volume in several regions in the dorsal frontal lobe and hsCRP level if a more liberal threshold such as $P < 0.01$, uncorrected for multiple comparisons is used (data not shown), we cannot deny the possibility that mechanism(s) of the correlation between hsCRP level and gray matter, and white matter structure, may be different. Further studies may help elucidate correlations between brain structure and hsCRP levels.

The present study had several limitations. First, it was a cross-sectional study. Thus, although we have shown a relationship between hsCRP level and gray matter volume, we cannot clarify a causal relationship between hsCRP level and gray matter volume. Longitudinal studies are needed to clarify this issue. Second, we cannot exclude the possibility that our sample may have included subjects with mild cognitive deficits or even early-stage dementia because we used only the MMSE and GDS to screen for what our study defined as "healthy" subjects. To reduce this possibility, we set strict inclusion criteria for healthy elderly subjects by requiring that the MMSE score be 28 or higher. Third, we used two 0.5-T MRI scanners, and although we adjusted the pulse sequences to collect optimized images, the sensitivity of the results may be lower than could be obtained using a 1.5-T MRI scanner, which is more commonly used. Fourth, we did not collect other measures of atherosclerosis, such as plaque thickening or calcification of the internal carotid or middle cerebral artery. Therefore, further studies may be needed to show the correlation between the extent of atherosclerosis and gray matter volume decline.

In summary, we analyzed the correlation between hsCRP level and brain regional gray matter volume in 109 community-dwelling healthy elderly subjects. We found a significant negative correlation between regional gray matter volume of the posterior and lateral aspects of the left temporal cortex and hsCRP level after adjusting for age, gender, and intracranial volume. Our results suggest that individuals with mild inflammation, which is related with arteriosclerosis, show a decrease in regional gray matter volume in the posterior and lateral aspects of the left temporal cortex. Therefore, preventing the progress of arteriosclerosis may help to prevent decreases of gray matter volume in healthy elderly subjects.

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C-reactive protein (CRP) is a predictor of high medical-care expenditures in a community-based elderly population aged 70 years and over: The Tsurugaya project

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ABSTRACT

Because CRP is a strong independent predictor of various diseases, it was hypothesized that CRP may be a useful predictor or treatment target for medical-care expenditures. The aim of this study was to investigate the relationship between CRP and medical-care expenditures in a community-dwelling elderly population. This prospective cohort study was conducted including 925 Japanese subjects aged ≥70 years. A high-sensitivity CRP assay was used by applying the nephelometric method. Hospitalizations, outpatient visits, and expenditures were ascertained through computerized linkage with claims lodged between August 2002 and March 2008 with the Miyagi National Health Insurance (NHI) Association. Since medical-care expenditures were not normally distributed, the category of high medical-care expenditures (>75th percentile of medical-care expenditures: inpatient expenditures >$494/month; outpatient expenditure >$522/month; total expenditures >$1103/month) was used to examine the relation of CRP levels with medical-care expenditures. Multiple logistic regression analysis was used to examine the relationship between CRP cutoff points (low concentrations: <1.0 mg/L; intermediate concentrations: 1.0–3.0 mg/L; or high concentrations: ≥3.0 mg/L) and medical-care expenditures during 6 year-follow up period. After adjustment for potential confounding factors, a positive association of CRP with hospitalization, and total expenditures (p for trend = 0.03 and 0.02, respectively) was found. An elevated baseline CRP level is an independent predictor of increases in prospective medical-care expenditures among community-dwelling elderly. Further study is required to clarify whether reducing CRP by intervention is a cost-effective measure.

1. Introduction

CRP has received substantial attention in recent years as a promising biological predictor of atherosclerotic disease (Pearson et al., 2003). An evolving body of work suggests that even small increases in CRP within the normal range are predictive of future vascular events in apparently healthy, asymptomatic individuals (Ridker et al., 2002). A number of prospective studies have also demonstrated that high baseline levels of CRP are a strong independent predictor of cardiovascular risk (Koenig et al., 1999), recurrent events and/or increased mortality in patients with ischemic stroke (Di Napoli et al., 2001), peripheral vascular disease (Ridker et al., 2001) cancer (Heikkila et al., 2007), and all-cause mortality (Cao et al., 2007). CRP is also correlated with abdominal obesity and metabolic syndrome, and an elevated level increases the risk of developing type 2 diabetes (Barzilay et al., 2001; Pradhan et al., 2001).

Total medical-care expenditures in Japan reached 33 trillion yen (approximately $290 billion) in 2006 (Accessed October 05,

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2007). The ratio of medical-care expenditures to the total national income has increased in recent years, and exceeded 9% in 2006 (Accessed October 05, 2007). In the Japanese census reports of 2006, the proportion of the population aged ≥65 years was 20.7% (Accessed October 04, 2007). A breakdown by age group shows that medical-care expenditures for people aged ≥65 years accounted for 51.0% of the total expenses, with an approximately 4.1-fold difference in per capita medical expenditures between older and younger generations (Accessed October 05, 2007). A reduction in medical-care expenditures for the elderly population through health promotion and disease prevention is therefore a recognized public objective. Because CRP levels are strongly associated with several diseases, CRP status might be a useful predictor of medical-care expenditure in clinical or subclinical practice. However, to our knowledge, no previous studies have assessed the relationship between CRP and medical-care expenditures in a community-dwelling elderly population.

The present report describes the results of a prospective cohort study designed to investigate the relationship between CRP and medical-care expenditures in the Japanese elderly population.

2. Materials and methods

2.1. Study participants

The subjects of the present study were participants of the Tsurugaya project, a population-based longitudinal study designed to clarify the various medical problems associated with geriatric health. The Tsurugaya project is described in detail elsewhere (Niu et al., 2006; Kikuchi et al., 2007). The medical expenditures data were derived from the prospective evaluation of National Health Insurance beneficiaries between August 2002 and March 2008. In 2002, there were 2730 individuals who were ≥70 years of age in the Tsurugaya area, a residential zone within Sendai City, a major city in northern Japan. We invited all of these individuals to participate in a comprehensive geriatric assessment, in which physical, mental, and social functioning were examined to assess for the presence of early deterioration that may result in the need for long-term care and thus to promote healthy aging. Of those invited, 1178 gave written informed consent to be included in the structured survey. Of these 1178, 969 subjects who agreed to have NHI disclose medical care expenditures, coverage of these expenditures under the NHI system, and medical-care utilization from claim history files were initially included. The protocol of this study was approved by the Institutional Review Board of the Tohoku University Graduate School of Medicine.

Subjects whose CRP had not been measured ($n = 18$) were excluded. Patients with a CRP > 10.0 mg/L ($n = 26$) were also excluded because serum CRP concentrations ≥10.0 mg/L are often indicative of acute inflammatory conditions (Pepys and Hirschfield, 2003). As a result of these exclusions, the final study population was comprised of 925 subjects [mean ± standard deviation; age: 76.2 ± 4.7 years; men: 43.1%]. Moreover, no acute inflammatory symptoms were observed in these subjects at baseline.

2.2. Measurement of CRP

CRP concentrations were determined using an immunotechnique on a Behring BN II analyzer (Dade Behring, Tokyo, Japan). The BN II high sensitivity assay utilizes monoclonal antibody-coated polystyrene particles and fixed-time kinetic nephelometric measurements (Ledue et al., 1998).

2.3. Assessment of medical care expenditures and mortality data

We prospectively collected data on medical care use, expenditures, and mortality for all individuals in the cohort study. NHI claims history files were obtained from the Miyagi NHI Association. The files included the number of outpatient visits, the number of days of inpatient care, and charges for outpatient and inpatient care. Incidentally, NHI covers almost all medical care, including diagnostic tests, medication, and surgery, in Japan. When a beneficiary was withdrawn from the NHI, the date and reason were coded on an NHI withdrawal history file. This file identified the survival and emigration status for each subject. Both the NHI claims and withdrawal history files were linked with our baseline survey data file, based on the beneficiary's ID number as the key code.

Monthly medical expenditures for each subject were calculated by dividing the total medical expenditures throughout the observation period by the number of months observed. We used monthly values rather than cumulative values to avoid underestimating medical expenditures for subjects who died or emigrated during the follow-up period. To compare outcomes to those of other countries, the expenditures were converted to US dollars by using a multiplication factor of 80.

2.4. Assessment of other variables

Anthropometrics (height, body weight) were recorded by a standardized protocol. Body mass index (BMI) was calculated as weight (kg)/height^2 (m^2). Blood pressure (BP) was measured at home with an HEM747IC device (Omron Life Science Co. Ltd., Tokyo, Japan), which uses the cuff-oscillometric method to generate a digital display of systolic and diastolic pressures. The mean of 15.0 ± 10.7 (mean ± SD) BP measurements were used as the BP values. Participants who did not measure their home BP on at least 3 days were treated as having missing information on BP.

Blood samples were drawn from the antecubital vein of the seated subject with minimal tourniquet use. Specimens were collected in siliconized vacuum glass tubes containing sodium fluoride for blood glucose, and no additives for albumin, lipids, or CRP analyses.

Total cholesterol (T-C), high-density lipoprotein cholesterol (HDL-C) concentrations, and blood glucose concentrations were measured by enzymatic methods (T-C, Denka Seiken, Tokyo, Japan; HDL-C, Daiichi Pure Chemicals, Tokyo, Japan; blood glucose, Shino-Test, Tokyo, Japan). Information on smoking status, drinking status, use of medication and histories of prior cardiovascular disease (CVD, including ischemic heart disease and stroke), cancer, renal disease, liver disease, and arthritis were obtained from the questionnaire survey. All individuals were told to bring their regular medications to the trial setting, and these were checked and recorded by a well-trained pharmacist. The 30-item Geriatric Depression Scale (GDS) (Niino et al., 1991), was used to assess depressive symptoms. Cognitive functioning was measured with the Mini-Mental State Examination (MMSE) (Folstein et al., 1975). Furthermore, socioeconomic status (SES) is one of the most powerful predictors of health. In this paper, educational attainment was assessed as an indicator of SES by determining the age at completion of schooling and was divided into 3 categories: ≤9 y, 9–12, or >12 y (Fujino et al., 2005).

2.5. Definitions of variables

We categorized the study participants on the basis of the recently proposed cutoff points for CRP as having low concentrations (<1.0 mg/L), intermediate concentrations (1.0–3.0 mg/L), or high concentrations (≥3.0 mg/L) (Pearson et al., 2003).

Hypertension was defined as a home systolic BP of ≥135 mm Hg and/or a home diastolic BP of ≥85 mm Hg or the use of antihypertensive agents (Chobanian et al., 2003). Diabetes was defined as a casual blood glucose concentration of ≥200 mg/dL or current use of antidiabetic medication. Hypercholesterolemia was defined as a concentration of T-C of ≥220 mg/dL or current use of non-statin lipid-lowering agents. We treated statin agents as independent confounding factors because they have been reported to lower CRP concentrations (Ridker, 2001).

Physical activity (PA) was classified into 6 levels based on a self-reported single-item question on whether the participant carried out any PA in the past year. PA was then classified into three categories (high, levels 5 and 6; moderate, levels 3 and 4; low, levels 1 and 2), based on frequency and duration in the participant. Detailed information was provided in previous reports (Niu et al., 2005; Yang et al., 2010). A GDS score of ≥14 or the use of an antidepressant was used to indicate depressive symptoms (Burke et al., 1992). A MMSE score of <24 was used to indicate cognitive impairment (Folstein et al., 1975).

2.6. Statistical analysis

Descriptive data are presented as means (95% confidence interval [CI]) or percentages. The values of the medical-care expenditures, number of days of hospital stay or visits were used as the dependent variable and the CRP levels as the independent variable. The differences between the variables among the CRP levels were examined by analysis of covariance (ANCOVA) for continuous variables or by the multiple logistic regression analysis for variables of proportion after adjustment for age and sex. Since medical-care expenditures were not normally distributed, the category of high medical-care expenditures (>75th percentile of medical-care expenditures: inpatient expenditures >$494/month; outpatient expenditure >$522/month; total expenditures >$1103/month) was used to examine the relationship of CRP levels with medical-care expenditures. Multiple logistic regression analysis was used to examine the relation of CRP levels with high medical-care expenditures after adjustment for age, sex, BMI, smoking and drinking habits/history, PA, use of statin drugs, use of aspirin and use of non-steroidal anti-inflammatory drugs (NSAIDs, not including aspirin), hypertension, diabetes, depressive symptoms, educational attainment, impaired cognitive function, history of CVD, renal disease, liver disease, cancer, and arthritis. Moreover, because the medical-care expenditures of individuals in their last months of life are higher than those in non-dying persons (Felder et al., 2000), we also examined the relationship between CRP and medical-care expenditures by excluding expenditures related to death and those during the last month of the follow-up period. ANCOVA was used to examine the relationship between CRP and the number of days of hospital stay or visits after adjustment for the above confounding factors. All p values for linear trends across the CRP categories were calculated using the median of each CRP category. The interactions were assessed by testing the interaction term added to the adjusted model as a covariate. A significant difference was defined as $p < 0.05$. All statistical analyses were performed using a Statistical Analysis System 9.1 edition for Windows (SAS Institute Inc., Cary, NC, USA).

3. Results

Age- and sex-adjusted baseline characteristics according to the levels of CRP are presented in Table 1. Mean BMI was significantly higher in correlation with higher CRP levels (p for trend <0.0001). Although not statistically significant, the mean HDL-C value was highest in the lowest CRP category (p for trend = 0.06). The prevalence of hypertension, diabetes, ex-smoker status, current

Table 1
Age- and sex-adjusted baseline characteristics according to CRP categories (n = 925).

	Cutoff of CRP (mg/L)			p for trend
	<1	1–3	>3	
No. of participants	645	193	87	
Age (y)	76.2(75.9–76.6)	75.7(75.1–76.4)	76.5(75.5–77.5)	0.58
Sex (male, %)	42.6	46.6	39.1	0.72
BMI (kg/m^2)	23.3(23.1–23.6)	24.7(24.3–25.2)	25.5(24.8–26.2)	<0.0001
Hypertension (%)	64.5	71.5	85.1	<0.0001
Hypercholesterolemia (%)	45.9	52.3	50.6	0.28
HDL-C (mg/dL)	55.9(54.8–56.9)	51.9(50.0–53.8)	52.9(50.1–55.8)	0.06
Diabetes (%)	7.9	10.9	18.4	<0.01
Smoker				
Current smoker (%)	10.5	18.7	10.3	0.41
Ex-smoker (%)	29.0	29.5	36.8	0.049
Drinker				
Current drinker (%)	11.6	11.9	19.5	0.04
Ex-drinker (%)	46.2	42.5	41.4	0.19
Self-reported illness				
Renal (%)	6.1	8.3	10.3	0.10
CVD (%)	14.1	18.1	20.7	0.07
Liver (%)	6.2	11.4	4.6	0.96
Cancer (%)	6.5	7.3	8.1	0.55
Arthritis (%)	17.2	16.5	21.8	0.38
Use of NSAIDs (%)	15.5	16.6	13.8	0.72
Use of statin drugs (%)	17.8	14.5	18.4	0.86
Use of aspirin drugs (%)	9.2	11.9	16.1	0.04
Moderate PA (levels 3 and 4) (%)*	29.9	24.9	33.3	0.73
High PA (levels 5 and 6) (%)*	31.5	28.0	23.0	0.09
Cognitive impaired (MMSE < 24) (%)	11.2	13.0	11.5	0.88
Depressive symptoms (GDS ≥ 14 or use of antidepressant) (%)	20.5	24.9	16.1	0.53
Educational attainment				
≤9 y	24.2	21.2	26.4	0.83
9–12 y	43.6	43.0	47.1	0.61

Note: Variables are presented as adjusted least squares mean (95% CI) or %. p values for trend are based on median values in each category.
* Detailed information was provided in previous reports (see reference, Niu et al., 2005; Yang et al., 2010).

Table 2
Adjusted high medical costs in relation to CRP categories ($n = 925$).

	Cutoff of CRP (mg/L)			p for trend
	<1	1–3	≥3	
No. of participants	645	193	87	–
No. of high-inpatient medical expenditures (>$494/month)	89	31	20	
Odds ratio (95% CI)				
Model 1*	1	1.20(0.76–1.85)	1.87(1.06–3.18)	0.02
Model 2**	1	1.19(0.75–1.85)	1.92(1.07–3.32)	0.02
Model 3***	1	1.03(0.63–1.67)	2.05(1.08–3.80)	0.03
No. of hospital stay (days/month)***,†	1.64(1.12–2.15)	1.76(1.22–2.29)	1.95(1.36–2.54)	0.11
No. of high-outpatient medical expenditures (>$522/month)	164	44	21	–
Odds ratio (95% CI)				
Model 1*	1	0.87(0.59–1.26)	0.93(0.54–1.55)	0.68
Model 2**	1	0.87(0.59–1.27)	0.93(0.54–1.54)	0.87
Model 3***	1	0.72(0.47–1.09)	0.68(0.38–1.20)	0.13
No. of hospital visits (days/month)***,†	7.93(6.56–9.29)	7.39(5.97–8.81)	7.75(6.19–9.3)	0.72
No. of high-total medical expenditures (>$1103/month)	91	28	22	–
Odds ratio (95% CI)				
Model 1*	1	1.03(0.64–1.61)	2.06(1.19–3.46)	0.01
Model 2**	1	1.01(0.63–1.59)	2.14(1.23–3.64)	<0.01
Model 3***	1	0.87(0.53–1.41)	2.23(1.21–4.04)	0.02

p values for trend are based on median values in each category.
* Crude model.
** Adjusted for age, sex.
*** Adjusted for model 2 + BMI, smoking and drinking habits/history, PA, use of statin drugs, use of aspirin and use of NSAIDs (not including aspirin), hypertension, diabetes, depressive symptoms, impaired cognitive function, educational attainment, history of CVD, renal disease, liver disease, cancer, or arthritis.
† Variables are presented as least squares mean (95% CI).

drinking, and use of aspirin was significantly higher in the higher CRP level groups (p for trend ≤0.049). Although not statistically significant, the proportion of patients with a history of renal disease and CVD appeared to be the highest in the high CRP category (p for trend = 0.10 and 0.07, respectively), and high PA showed a higher proportion in the lowest CRP categories (p for trend = 0.09). Otherwise, no significant differences were observed among CRP categories (p for trend ≥0.19).

Because all subjects were >70 years of age and there was no baseline data that could be used for medical-care expenditures, the accumulated total medical-care expenditures for the initial 6 months in relation to CRP levels were compared. After adjustment for potential confounding factors (see Table 2, model 3), no significant relationship between CRP levels and high medical-care expenditures was observed for any type of expenditures, including inpatient, outpatient, and total expenditures (p for trend >0.45).

Table 2 shows the adjusted results of the relationship between CRP levels and high medical-care expenditures. In final models, increasing CRP levels showed a significant positive relationship with high total medical expenditures (p for trend = 0.02). Similar results were obtained with regard to high inpatient medical expenditures (p for trend = 0.03). In contrast, a relationship between the levels of CRP and high outpatient medical expenditures was not found in any model (p for trend ≥0.13). The results of the tests for interaction between the CRP categories and other confounders in the final models were also not statistically significant. Although not statistically significant, increasing CRP levels tended to relate positively to average number of days of hospital stay in multiple models (p for trend = 0.11). No relationship was found between the levels of CRP and average number of hospital visits in the final model (p for trend = 0.72). Excluding CRP levels, several variables were also significantly related with medical expenditures in the final model. Females or individuals with a high or moderate level of PA were less likely to be included in the high total medical expenditures (Odds rate [ORs] = 0.35, 95% CI: 0.19–0.64, in female; ORs = 0.55, 95% CI: 0.34–0.87, in high PA; ORs = 0.46, 95% CI: 0.28–0.74, in moderate PA) or high inpatient medical expenditures category (ORs = 0.32, 95% CI: 0.17–0.58, in female; ORs = 0.47, 95% CI: 0.29–0.77, in high PA; ORs = 0.59, 95% CI: 0.36–0.93, in moderate PA), compared to males or those with a low level of PA. In contrast, the ORs for the high total medical expenditures category were significantly higher among individuals with a history of arthritis (ORs = 2.07, 95% CI: 1.04–3.94) or use of NSAIDs (ORs = 2.08, 95% CI: 1.26–3.40), compared to those without these conditions. For the high inpatient medical expenditures, the ORs were significantly higher among individuals with a history of CVD (ORs = 1.77, 95% CI: 1.06–2.9) or use of NSAIDs (ORs = 2.09, 95% CI: 1.26–3.43), compared to those without these conditions. The ORs for the high outpatient medical expenditures were significantly higher among individuals with several disease statuses or use of medication: hypertension, 1.48 (95% CI: 1.02–2.17); diabetes, 2.76 (95% CI: 1.68–4.51); history of cancer, 2.26 (95% CI: 1.44–3.54); history of liver disease, 2.50 (95% CI: 1.40–4.42); use of statin drugs, 1.76 (95% CI: 1.17–2.64); use of aspirin drugs, 1.97 (95% CI: 1.18–3.25); use of NSAIDs, 2.07 (95% CI: 1.36–3.14), compared to those without these conditions. No significant relationships were observed between other covariates and medical expenditures.

Furthermore, exclusion of deaths ($n = 75$) and last-month expenditures during the follow up period did not essentially change the adjusted high inpatient, outpatient, and total medical expenditures (p for trend 0.04, 0.16, and 0.07, respectively) (data not shown).

4. Discussion

In this longitudinal study, we examined the relationship between serum CRP levels and medical-care expenditures during 6 year-follow up period among the community-dwelling elderly population. The relationship between CRP and medical-care expenditures was also examined by excluding death-related costs and expenditures of the last month of the follow-up period. Higher CRP level was associated with higher medical care expenditures characterized by higher inpatient medical expenditures. The results of the present analysis suggested that elevated baseline CRP levels are an independent predictor of prospective hospitalizations, total medical expenditure, and an increase in the number of days spent in the hospital among community-dwelling elderly.