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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.

Comparative evaluation of various inflammatory markers favor CRP from the clinical chemistry perspective (Pearson et al., 2003). Although the detection of elevated levels of CRP is not specific to a particular disease, it is a useful indicator of inflammatory processes (Morley and Kushner, 1982). Moreover, systemic low-level inflammation has been related with onset, development, and worsening of many diseases among the elderly (Wilson et al., 2006; Sabatine et al., 2007). Several studies have indicated that elevated levels of CRP are related to the severity of various diseases including CVD (Pearson et al., 2003), late-life disability (Kuo et al., 2006), sleep apnea syndrome (Chung et al., 2007), community-acquired pneumonia (Almirall et al., 2004), and cancer (Elahi et al., 2004). CRP levels could therefore be an independent indicator of medical-care expenditures based on the association between elevated CRP and the severity of certain diseases, deterioration or the need for emergency care in the elderly population. The results of the present study confirm that CRP levels are a useful predictor of medical-care expenditures. In contrast, no significant relationship was found between CRP levels and high outpatient expenditures. All the subjects in this study population were >70 years of age, and 86.8% persons received outpatient services (only 1.5% for inpatient services) during the first month of the survey. Moreover, 94.1% of the subjects received outpatient services (4.9% for inpatient services) during the first 3 months of this survey. These data indicated that almost all subjects received outpatient services at the baseline, suggesting that outpatient expenditures only reflect chronic disease status, and are not indicative of disease progression or a decline in health status associated with total medical-care expenditures.

Considering the results of this study, CRP screening and reduction of CRP by interventions may reduce medical costs in the elderly populations. In fact, a previous study estimated the potential cost-effectiveness of CRP screening in middle-aged patients without overt hyperlipidemia (Blake et al., 2003). The results of this study indicated that a strategy involving CRP screening to target statin therapy for the primary prevention of CVD could be relatively cost-effective. Whether reducing serum CRP levels through targeted therapy will lead to reduced medical-care expenditures in elderly subjects remains an important research question. Preliminary randomized control trials showed a significant effect of antibiotics on CRP (Stone et al., 2002; Wiesli et al., 2002). A treatment-induced reduction of CRP (including the treatment of causative conditions such as high BMI) from ≥3 mg/L to <1 mg/L would result in about 55% reduction in high inpatient medical expenditures according to our study.

The present study included an examination of the relationship between CRP and medical-care expenditures excluding death-related expenses and expenditures of the last month of the follow-up period. Exclusion of death and last-month of follow-up expenditures did not essentially change the relationship between CRP and medical-care expenditures. These results suggest that the significant association between CRP and medical-care expenditures was independent of all-cause mortality.

Excluding CRP levels, use of NSAIDs was independently and significantly related with higher outpatient, inpatient, and total medical expenditures. This finding is consistent with several previous reports showing that patients taking NSAID incur greater gastrointestinal disease costs, which may partly explain our result (Moore et al., 2000; Solomon et al., 2003). Furthermore, consistent with our previous reports, PA was significantly related with higher inpatient, and total medical expenditures, but not outpatient medical expenditures (Yang et al., 2010). This finding shows that PA may have a beneficial effect on serious diseases needing emergency care. Alternatively, the injury during PA is related with increased medical costs, and may partly explain why PA was not significantly related with outpatient medical expenditures. Interestingly, we found that several disease statuses, such as hypertension, diabetes, history of liver disease and cancer were significantly related with higher outpatient medical expenditures, but not inpatient and total medical expenditures. These findings suggest that a daily outpatient service for several disease statuses may be beneficial for cost-effectiveness as it would prevent worsening of the disease.

This study had several limitations. First, because evaluations were carried out in a public facility and participants were sufficiently active and healthy to participate in the survey, it is possible that the current results do not apply to subjects at higher risk. Second, although this prospective study reliably established a temporal relationship between serum CRP levels and medical-care expenditures, a randomized trial should be undertaken to confirm whether reducing inflammatory status by use of a cost-effective drug would reduce medical expenditures in an elderly population. Third, the usefulness of the data was limited by the lack of diagnostic information for each instance of medical-care expenditure. Because elevated baseline CRP levels were only associated with future high inpatient expenditures, but not with outpatient expenditures, CRP may be a powerful predictor of severe diseases requiring hospitalization. Further study is necessary to clarify the details of these diseases.

5. Conclusions

The present study suggests that elevated baseline CRP levels are an independent predictor of prospective medical-care expenditure increases among Japanese community-dwelling elderly. Further study is required to clarify whether reducing CRP in the elderly by use of a drug is a cost-effective measure.

Conflict of interest statement

All the authors have no conflicts of interest exists to disclose.

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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,

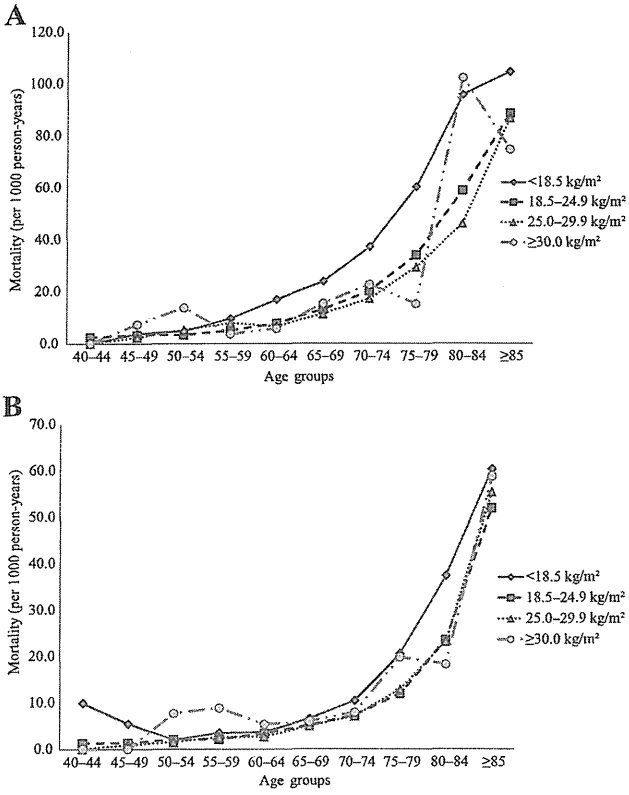

Figure 1 Multiadjusted mortality by BMI categories in each age group in men (A) and women (B).

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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Competing interests None.

Ethics approval The study protocol was approved by the Ethics Committee of Tohoku University School of Medicine. Participants who had returned the self-administered questionnaires and signed them were considered to have consented to participate.

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Preliminary communication

A tomato-rich diet is related to depressive symptoms among an elderly population aged 70 years and over: A population-based, cross-sectional analysis

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ABSTRACT

Background: Enhanced oxidative stress or defective anti-oxidant defenses are related to the pathogenesis of depressive symptoms. Lycopene is the most powerful antioxidant amongst the carotenoids. The aim of this study was to investigate the relationship between different vegetables, including tomatoes/tomato products (a major source of lycopene), and depressive symptoms in a community-based elderly population.

Methods: We analyzed a cross-sectional survey including 986 community-dwelling elderly Japanese individuals aged 70 years and older. Dietary intake was assessed using a valid self-administered diet-history questionnaire, and depressive symptoms were evaluated using the 30-item Geriatric Depression Scale with 2 cut-off points: 11 (mild and severe) and 14 (severe) or use of anti-depressive agents.

Results: The prevalence of mild and severe and severe depressive symptoms was 34.9% and 20.2%, respectively. After adjustments for potentially confounding factors, the odds ratios of having mild and severe depressive symptoms by increasing levels of tomatoes/tomato products were 1.00, 0.54, and 0.48 (p for trend <0.01). Similar relationships were also observed in the case of severe depressive symptoms. In contrast, no relationship was observed between intake of other kinds of vegetables and depressive symptoms.

Limitations: This is a cross-sectional study, and not for making a clinical diagnosis of depressive episodes.

Conclusions: This study demonstrated that a tomato-rich diet is independently related to lower prevalence of depressive symptoms. These results suggest that a tomato-rich diet may have a beneficial effect on the prevention of depressive symptoms. Further studies are needed to confirm these findings.

1. Introduction

For several decades, the health burden of stress-related diseases, including depressive symptoms and anxiety disorders, has been rapidly increasing. The presence of depressive symptoms in later life is recognized as a public health problem. Depressive symptoms contribute a significant independent risk for the onset of coronary disease (Wulsin and Singal, 2003), and disease susceptibility (Zorrilla et al., 2001). Depressive symptoms also worsens the outcomes of many medical disorders, promotes disability and increases mortality (Alexopoulos, 2005).

Several studies have suggested that enhanced oxidative stress or defective antioxidant defenses may be related to affective disorder or the pathogenesis of depressive symptoms (Bilici et al., 2001; Khanzode et al., 2003; Ozcan et al., 2004; Srivastava et al., 2002;

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Tsuboi et al., 2004). A longitudinal study in elderly residents showed preventive effects of vitamin E, a dietetically anti-oxidative compound, on the progression of depressive symptoms in male participants (Shibata et al., 1999). On the other hand, lycopene, a carotenoid antioxidant, is the most powerful antioxidant amongst carotenoids and there is no evidence of toxic effects (Heber and Lu, 2002). In vitro study of singlet oxygen quenching action, lycopene was shown to be 100 times more efficient than vitamin E (Atessahin et al., 2005). Thus, we hypothesized that a tomato-rich diet, a major source of lycopene (tomatoes and tomato-based sauces, juices, and ketchup account for more than 85% of the dietary intake of lycopene for most people (Rao and Rao, 2007)) may have a potentially beneficial effect on the prevention of depressive symptoms. However, to our knowledge, only a few studies have investigated the relationship between tomato/lycopene and depressive symptoms (Tsuboi et al., 2004). Moreover, no studies have fully investigated the relationship between a tomato-rich diet and depressive symptoms in a community-dwelling elderly population.

Because vegetables are good sources of antioxidant phytochemicals that mitigate the damaging effect of oxidative stress, we designed a cross-sectional study to compare the relationship between intake of several vegetables and tomato products with depressive symptoms in community-dwelling elderly participants aged ≥ 70 years.

2. Methods

2.1. Study participants

The Tsurugaya Project included subjects aged 70 years and older who were living in the Tsurugaya area of Sendai, one of the major cities in the Tohoku area of Japan. The data were obtained in 2002 from 1178 individuals giving their informed consent for data analysis. A detailed description of the methods has been published elsewhere (Niu et al., 2005a). The protocol of this study was approved by the Institutional Review Board of the Tohoku University Graduate School of Medicine.

In this study, depressive symptoms were assessed with the aid of the Geriatric Depressive symptoms Scale (GDS) (Brink et al., 1982). Of the 1178 subjects, 1169 completed the GDS. We also excluded those subjects whose did not have any information on diet ($n=94$). Furthermore, those who reported a history of cancer ($n=89$) and cognitive dysfunction (Mini Mental State Examination [MMSE] Score (Folstein et al., 1975) <18) ($n=17$) were also excluded. As a result of these exclusions, the final study population included 986 subjects.

2.2. Assessment of depressive symptoms

Depressive symptoms were assessed according to the Japanese version (Niino et al., 1991) of the 30-item GDS using 2 cut-off points (GDS score, ≥ 11 or 14) or the use of anti-depressive agents, indicating relatively mild to severe depressive symptoms or severe depressive symptoms (Brink et al., 1982).

2.3. Assessment of dietary intake

A brief self-administered diet history questionnaire (BDHQ) included 75 food items with specified serving sizes that were described by natural portions or standard weight and volume measures of the servings commonly consumed in this study population. For each food item, participants indicated their mean frequency of consumption over the past year, in terms of the specified serving size by checking 1 of the 7 frequency categories ranging from "almost never" to "2 or more times/d". The question of tomatoes/tomato products included some commonly eaten tomato foods such as tomato, tomato ketchup, stewed tomato, or tomato stew. According with BDHQ, Other kinds of vegetables were divided into four categories as follow: (1) Green-leaf vegetables, (2) Cabbage and Chinese cabbage, (3) Carrot, onion, burdock, lotus root and pumpkin, (4) Japanese white radish (daikon) and turnips. The mean daily intake of nutrients was calculated using an *ad hoc* computer program developed to analyze the questionnaire. The Japanese food composition tables, 4th edition, and the other sources (Sakai et al., 1995) were used as the nutrient database. The reproducibility and validity of the BDHQs have been described in detail elsewhere (Sasaki, 2005).

2.4. Assessment of other variables

Anthropometrics (height, body weight) were recorded using a standardized protocol. Body mass index (BMI) was calculated as weight (kg)/height^2 (m^2). Blood pressure (BP) was measured at home using 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 15.6 ± 10.5 (mean $\pm$ SD) BP measurements was used as the BP value. Participants who did not measure home BP for at least 3 days were treated as having missing information on hypertension. Hypertension was defined as a home systolic BP ≥ 135 mm Hg or a home diastolic BP ≥ 85 mm Hg or the use of antihypertensive agents (Chobanian et al., 2003).

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 lipids analyses. Blood glucose concentrations were measured using enzymatic methods (Shino-Test, Tokyo, Japan). Diabetes was defined as a casual blood glucose concentration of ≥ 200 mg/dL or the current use of antidiabetic medication.

Sociodemographic variables including gender, age, educational level, and perceived social support (PSS) were also assessed. Educational level attained was assessed by determining age at completion of schooling and was divided into 2 categories: ≤ 12 or >12 years. PSS was evaluated on the basis of responses ("yes" or "no") to the following 5 questions: "Do you have someone to whom you can talk when you are in trouble?" (PSS1); "Do you have someone to whom you can talk when your physical condition is not good?" (PSS2); "Do you have someone who can help you with daily housework" (PSS3); "Do you have someone who can take you to hospital when you do not feel well?" (PSS4); and "Do you have someone who can take care of you when you are ill in bed?" (PSS5). These questions were extracted from a previous study regarding social support and elderly depressive symptoms in a rural community (Muraoka et al., 1996). A single summed score was calculated based on the PSS 1–5. The lack of PSS was defined as PSS score $=0$.

Health-related variables assessed included history of physical illness, pain, cognitive function, instrumental activities of daily living (IADL), and current use of medication. History of physical illness was evaluated on the basis of responses ("yes" or "no") to questions. Pain within the previous 4 weeks was assessed by the question, "Have you had any pain recently? If so, how intensely do you feel such pain?" Possible answers were "no pain," "very mild pain," "mild pain," "moderate pain," and "severe pain." A subject who reported "mild" to "severe" pain was considered to have pain. Cognitive function was assessed on the basis of the MMSE and was classified into 2 categories: 18–23 and ≥ 24. IADLs were assessed using the Rouken–Shiki scale (Koyano et al., 1987) and a cut-off point of 10/11 was used to determine

impairment in IADL. The drug information was confirmed by a well-trained pharmacist.

Information on smoking status and drinking status were obtained from the questionnaire survey. Physical activity (PA) was assessed first by a self-reported single-item question on whether the participant undertook any PA during the past year. If yes, questions were asked about the frequency and duration of walking, brisk walking, and sports. PA was then classified into 3 categories, based on frequency and duration: (1) "High," at least 3–4 times per week for at least 30 min each time; (2) "Low," reporting some activity in the past year, but not enough to meet high levels; and (3) "None," no PA. Furthermore, PA was classified into 6 levels based on the above 3 categories and the type of physical activity, such as walking, brisk walking, and sports: (1) "Level 1," no walking, no brisk walking, no sports; (2) "Level 2," low walking, no brisk walking, no sports; (3) "Level 3," high walking, no brisk walking, no sports; (4) "Level 4," any walking, low brisk walking, no sports; (5) "Level 5," any walking, high brisk walking, no sports; (6) "Level 6," any walking, any brisk walking, low or high sports. Detailed information has been provided in previous reports (Niu et al., 2005b). Finally, subjects were divided into 2 categories: ≤ level 3 or > level 3.

2.5. Statistical analysis

Descriptive data are presented as mean (95% confidence interval [95% CI]) or percentages. Depressive symptoms were used as the dependent variable and the tomato/tomato product and other vegetable intake level as the independent variable. Multiple logistic regression analysis was used to examine the relationship of tomato/tomato product and other vegetable intake with depressive symptoms after adjustment for age, sex, BMI, hypertension, diabetes, history of cardiovascular diseases, smoking and drinking habits, physical activity, cognitive status, impaired IADL, self-reported body pain, educational level, living alone, marital status, lack of PSS, total energy intake, and intake of all kinds of fruits (tertiles), green tea (tertiles) (Niu et al., 2009), and mutual other kinds of vegetables. The odds ratios (ORs) and 95% CIs for depressive symptoms for increasing tomato/tomato product and other vegetable intake levels, with the lowest level as the reference, were also calculated using multiple logistic regression analysis. Interactions between tomato/tomato product and other vegetable intake levels and confounders of depressive symptoms were tested by the addition of cross-product terms to the regression model. 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

Among 986 subjects who were available to be analyzed, 34.9% and 20.2% were classified as having mild and severe and severe depressive symptoms, respectively.

Age- and sex-adjusted participant characteristics according to tomato/tomato product status are presented in Table 1. The proportion of male, current smoker, lower educational level, and widowed or divorced status were significantly lower across the tomatoes/tomato products groups (p for trend ≤ 0.03). The proportion of subjects who were married was significantly higher across the tomatoes and tomato products groups (p for trend = 0.04). Mean total energy intake was significantly higher across the tomatoes/tomato products groups (p for trend < 0.0001). The mean GDS score was significantly lower across the tomatoes/tomato products groups (p for trend < 0.0001). Otherwise, no significant difference

Table 1
Age- and sex-adjusted characteristics according to categories of tomato/tomato product consumption.

	Tomatoes/tomato products consumption			p for trend
	≤ 1 time (wk)	2–6 times (wk)	≥ 1 time (d)	
No.	139	325	522	–
Age (year)	75.5 (74.7–76.3)	75.9 (75.4–76.4)	76.1 (75.7–76.5)	0.45
Sex (male)	49.6	48.3	36.2	< 0.001
BMI (kg/m^2)	23.5 (23.0–24.1)	23.8 (23.5–24.2)	23.9 (23.6–24.2)	0.42
Diabetes	7.9	9.2	9.4	0.70
Hypertension	71.2	68.6	69.0	0.62
History of CVD	14.4	16.0	14.8	0.80
Smoking status	–	–	–	–
Current smoker	25.9	12.9	9.8	< 0.001
Ex-smoker	26.6	35.1	25.9	0.41
Drinking status	–	–	–	–
Current drinker	44.6	44.3	35.8	0.32
Ex-drinker	9.4	12.0	12.3	0.17
PA (> level 3)	38.1	37.9	37.9	0.60
Self-reported total number of physical illness (≥ 2)	63.3	68.6	69.9	0.26
Cognitive ability (18 ≤ MMSE < 24)	5.8	9.9	7.1	0.61
Impaired IADL	12.2	14.2	10.5	0.19
Self-rated health (yes)	79.1	82.5	81.8	0.44
Body pain (yes)	70.5	81.2	77.4	0.23
Lack of PSS (total score=0)	15.1	14.8	13.4	0.34
Educational level (≤ 12 years)	79.1	71.1	67.8	< 0.001
Living alone (yes)	28.1	21.5	25.1	0.13
Marital status married	59.0	63.4	60.5	0.04
Widowed or divorced	37.4	33.2	34.9	0.03
Total energy intake (kcal/d)	1841.7 (1768.4–1915)	1976.7 (1928.8–2024.6)	2084.4 (2045.8–2123)	< 0.0001
GDS	10.9 (10.1–11.8)	9.1 (8.5–9.7)	8.4 (7.9–8.8)	< 0.0001

BMI, body mass index; CVD, cardiovascular diseases; PA, physical activity; PSS, perceived social support; MMSE, Mini Mental State Examination; IADL, Instrumental Activity of Daily Living; GDS, Geriatric Depression Scale.
Variables are presented as mean (95% confidence interval).

Table 2
Adjusted association between consumption of tomatoes/tomato products and other kinds of vegetables and depressive symptoms [a].

Odds ratio (95% confidence interval)	Tomato and tomato product consumption			p for trend[b]
	≤1 time (wk)	2–6 times (wk)	≥1 time (d)	
Tomatoes and tomato products	–	–	–	–
No. of participants	139	325	522	–
No. of mild and severe depressive symptoms, defined as GDS of ≥11 or use of antidepressants	70	111	163	–
Crude	1.00	0.51 (0.34–0.77)	0.45 (0.31–0.66)	<0.001
Age- and sex-adjusted	1.00	0.49 (0.33–0.74)	0.40 (0.27–0.59)	<0.0001
Multiple adjusted [c]	1.00	0.54 (0.35–0.85)	0.48 (0.31–0.75)	<0.01
Green-leaf vegetables	–	–	–	–
No. of participants	188	523	275	–
No. of mild and severe depressive symptoms, defined as GDS of ≥11 or use of antidepressants	80	179	85	–
Crude	1.00	0.70 (0.50–0.99)	0.60 (0.41–0.89)	0.01
Age- and sex-adjusted	1.00	0.69 (0.49–0.97)	0.58 (0.39–0.85)	<0.01
Multiple adjusted [c]	1.00	0.78 (0.51–1.19)	0.72 (0.45–1.15)	0.19
Cabbage and Chinese cabbage	–	–	–	–
No. of participants	200	605	181	–
No. of mild and severe depressive symptoms, defined as GDS of ≥11 or use of antidepressants	78	203	63	–
Crude	1.00	0.79 (0.57–1.10)	0.84 (0.55–1.27)	0.37
Age- and sex-adjusted	1.00	0.78 (0.56–1.09)	0.79 (0.51–1.20)	0.24
Multiple adjusted [c]	1.00	1.07 (0.71–1.64)	1.46 (0.85–2.50)	0.18
Carrot, onion, burdock, lotus root and pumpkin	–	–	–	–
No. of participants	102	556	328	–
No. of mild and severe depressive symptoms, defined as GDS of ≥11 or use of antidepressants	42	199	103	–
Crude	1.00	0.83 (0.60–1.15)	0.61 (0.41–0.92)	0.02
Age- and sex-adjusted	1.00	0.78 (0.56–1.09)	0.56 (0.37–0.85)	<0.01
Multiple adjusted [c]	1.00	1.31 (0.77–2.27)	1.34 (0.74–2.45)	0.44
Japanese white radish (daikon) and turnips	–	–	–	–
No. of participants	265	519	202	–
No. of mild and severe depressive symptoms, defined as GDS of ≥11 or use of antidepressants	105	178	61	–
Crude	1.00	0.80 (0.59–1.08)	0.66 (0.45–0.97)	0.03
Age- and sex-adjusted	1.00	0.78 (0.57–1.06)	0.61 (0.41–0.90)	0.01
Multiple adjusted [c]	1.00	0.94 (0.65–1.37)	0.70 (0.43–1.13)	0.17

[a] GDS, Geriatric Depression Scale.
[b] Obtained by using multiple logistic regression analysis.
[c] Adjusted for age, sex, BMI, hypertension, diabetes, history of cardiovascular disease, smoking and drinking habits, physical activity, cognitive status, impaired instrumental activities of daily living (IADL), self-reported body pain, educational level, living alone, marital status, lack of perceived social support (PSS), total energy intake, all kinds of fruits, green tea, and mutual other kinds of vegetables.

was observed among tomatoes/tomato products groups (p for trend ≥0.13).

Table 2 shows the adjusted relationship between tomatoes/tomato products and other kinds of vegetables and mild and severe depressive symptoms. The ORs for mild and severe depressive symptoms decreased across the levels of tomato/tomato product intake. Age- and sex-adjusted ORs (95% CI) for depressive symptoms across tomato/tomato product intake levels were 1.00, 0.49 (0.33–0.74), and 0.40 (0.27–0.59) (p for trend <0.0001). These results were unchanged when adjusted for multiple confounding factors. Similar relationships were also observed when males and females were analyzed separately (p for interaction=0.08). Of the other covariants, smoking/drinking status and educational level were related with depressive symptoms. The tests for interactions between the categories of tomato/tomato product intake and these potential confounders in the final models were not found to be significant. Furthermore, because depressive status is also related to unhealthy eating habits and appetite (Andreasson et al., 2007; Cassano and Fava, 2002), a sensitivity analysis was added to assess the relationship between tomatoes/tomato products and depressive symptoms, excluding those who had very low (under 2.5%) or high (upper 2.5%) energy intake. However, this exclusion did not change the above results. Similar results were also observed when a cut-off of ≥14 or the use of antidepressants was used to indicate severe depressive symptoms. In the final model, the ORs (95% CI) for severe depressive symptoms across tomato/tomato product intake levels were 1.00, 0.64 (0.39–1.08), and 0.60 (0.37–0.99). In contrast to tomato/tomato product intake, no relationship was observed between intake of other kinds of vegetables and the prevalence of depressive symptoms (Table 2). Similar results were also observed when a cut-off of ≥14 or the use of antidepressants was used to indicate severe depressive symptoms (data not shown).

4. Discussion

This study examined the relationship between the intake of various vegetables, including tomatoes/tomato products, a main source of lycopene, and depressive symptoms among a community-dwelling elderly population aged 70 years and over. These results suggest that a high intake of tomatoes/tomato products was independently related to a lower prevalence of depressive symptoms. In contrast to tomato/tomato product intake, no relationship was observed between intake of other kinds of vegetables and depressive symptoms.

In this study, we have hypothesized that the intake of tomatoes/tomato products may have a potentially beneficial effect on the prevention of depressive symptoms. Although several studies have investigated the relationship between dietary antioxidant nutrients, such as folic acid and vitamin E, and depressive symptoms, few studies have reported the relationship between intake of tomatoes/tomato products and depressive symptoms (Alpert et al., 2000; Maes et al., 2000; Miyake et al., 2006; Shibata et al., 1999; Tsuboi et al., 2004). Only one study has assessed the correlations between serum lycopene and depressive score, in subjects consisting of 66 healthy female volunteers aged 38–70 years (Tsuboi et al., 2004). However, in that study, many confounding factors were not considered and the results have not suggested a significant correlation between lycopene and depressive score. In this larger community-based population study we adjusted for a considerable number of confounding factors. The current results suggest that high tomato/tomato product intake levels are independently related to a lower prevalence of depressive symptoms. Moreover, we also conducted a stratified analysis for sex. Similar relationships were also observed when males and females were analyzed separately.

Lycopene is the red-colored carotenoid predominantly found in tomatoes, but in few other fruits or vegetables (Bramley, 2000). Lycopene has the strongest antioxidant activity of various common carotenoids (Di Mascio et al., 1989). Oxidative stress may accelerate aging and increase the risk of chronic diseases, such as coronary heart disease, cancer, and rheumatoid arthritis; dietary intake of tomatoes/tomato products containing lycopene have been shown to be related to decreased risk of these chronic medical illnesses (De Pablo et al., 2007; Heber and Lu, 2002). Since these chronic medical illnesses are also related to the occurrence of depressive symptoms, particularly in elderly people, the presence or degree of these chronic medical illnesses may be a potential mechanism linking intake of tomatoes and tomato products to depressive symptoms. Furthermore, since enhanced oxidative stress or defective antioxidant defenses may be related to depressive symptoms, lycopene may directly link tomato and tomato product intake to depressive symptoms because of their anti-oxidative effect. Further study is needed to confirm these findings.

In the present study, lycopene concentration from tomatoes/tomato products was not calculated. In fact, food frequency questionnaires generally used in epidemiological studies vary greatly in their usefulness in estimating the true variation in lycopene intake among individuals. A review indicated that dietary intake of tomato/lycopene is difficult to quantify precisely for several reasons: different food habits, inaccurate estimation of dietary intake, the quality of the food database used, and variation of lycopene concentration within a given food (Porrini and Riso, 2005). Moreover, since lycopene is predominantly found in tomato and tomato-based products (at least 85%) (Bramley, 2000), but only in a few other fruits or vegetables (e.g., watermelon, pink grapefruit, guava, and papaya), the frequency of eating tomatoes/tomato products was used to assess the relationship between tomatoes/lycopene and depressive symptoms in this study.

This study had several limitations. First, the GDS has been designed for measuring the intensity of depressive symptoms and not for making a clinical diagnosis of depressive episodes. Therefore, a larger sample population using a standardized comprehensive structured diagnostic interview should be studied to confirm the effect of depressive symptoms on functional decline. Second, because this study was a cross-sectional study, we could not conclude that lower tomato and tomato product intake increased the occurrence of depressive symptoms or that depressive symptoms lead to a decline in tomato/tomato product intake. Therefore, a prospective study or trial should be undertaken to confirm the relationship between tomato/tomato product intake and depressive symptoms. Moreover, although we adjusted for a considerable number of confounding factors, we cannot exclude the possibility that depressive symptoms are affected by other dietary habits correlated with habitual dietary intake of tomatoes/tomato products. Therefore, an intervention study is necessary to establish a causal relationship between tomato/tomato product intake and depressive symptoms.

In conclusion, this study demonstrated that the intake level of tomatoes/tomato products, as measured by a self-administered questionnaire, is independently related to a lower prevalence of depressive symptoms in a community-dwelling older population. These results suggest that a tomato-rich diet may have a beneficial effect on the prevention of depressive symptoms. Further studies are needed to confirm these findings.

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Conflict of interest
All the authors have no conflicts of interest exists to disclose.

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