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SERUM CAROTENOIDS AND PULMONARY FUNCTION IN OLDER COMMUNITY-DWELLING WOMEN

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Abstract

Background and Objectives—Deterioration in pulmonary function is associated with greater disability and mortality in older adults. Dietary antioxidants are implicated in lung health, but the relationship between major dietary antioxidants, such as serum carotenoids, and pulmonary function have not been well characterized. Serum carotenoids are considered the most reliable indicator of fruit and vegetable intake.

Subjects and Methods—We examined the relationship between serum α -carotene, β -carotene, β -cryptoxanthin, lutein/zeaxanthin, and lycopene with pulmonary function (forced expiratory volume in one second [FEV₁] and forced vital capacity [FVC]) in a population-based sample of 631 moderately to severely disabled community-dwelling older women (Women's Health and Aging Study I) in Baltimore, Maryland, USA.

Results—Higher serum α -carotene and β -carotene concentrations were positively associated with both FEV₁ and FVC, respectively (all $P < 0.05$), in separate multivariate linear regression models adjusting for age, race, education, cognition, anemia, inflammation, and chronic diseases. Total serum carotenoids were associated with FEV₁ ($P = 0.08$) and FVC ($P = 0.06$), respectively, in similar models. No association was found between β -cryptoxanthin, lutein/zeaxanthin, and lycopene, and FEV₁ or FVC.

Conclusions—Higher serum α -carotene and β -carotene concentrations, which reflect greater intake of orange and dark green leafy fruits and vegetables, were associated with better pulmonary function among older community-dwelling women.

Keywords

aging; carotenoids; lung function; women

Introduction

Pulmonary function declines slowly through adult life and shows a progressive rate of decline after age 70 years (24). Reduced pulmonary function, assessed by forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC), is prevalent in older adults and is most commonly associated with chronic obstructive pulmonary disease, asthma, or fibrotic lung disease (17). Pulmonary function is an independent predictor of impaired physical performance (25) and higher all-cause and cardiovascular mortality (21,26).

Biological factors that have been implicated in the pathophysiology of the aging lung include inflammation and oxidative stress (11,24) and poor dietary intake of antioxidant-rich foods (20). Reduced FEV₁ was associated with low-grade systemic inflammation in the Third National Health and Nutrition Examination Survey (NHANES III) (17,26). Several studies have shown that self-reported dietary intake of fruit and vegetables is associated with pulmonary function and with chronic obstructive pulmonary disease. The relationship between specific food intake and pulmonary health has not been entirely consistent. Higher self-reported dietary intake of fruit was associated with higher FEV₁ in adults in the Netherlands (29), Scotland (12), and Great Britain (28). Self-reported vegetable intake was not associated with FEV₁ in the studies from the Netherlands (29) and Scotland (12). A case-control study from Japan showed that high vegetable, but not fruit, consumption, was associated with a reduced risk of chronic obstructive pulmonary disease (10). In US women, a diet rich in both fruits and vegetables was associated with a lower risk of chronic obstructive pulmonary disease (31).

Serum carotenoid concentrations are considered the most reliable indicator of fruit and vegetable intake (4). The six major serum carotenoids and the food intake they generally reflect are α - and β -carotene (carrots, orange fruit and vegetables, green leafy vegetables), lutein and zeaxanthin (green leafy vegetables, corn), β -cryptoxanthin (citrus fruits, watermelon), and lycopene (tomatoes) (16,33). In a study of community-dwelling Dutch adults, aged 65-85 years, serum α -carotene, β -carotene, and lycopene were independently associated with pulmonary function (5). In contrast, in a study of healthy adults without respiratory disease, aged 35-79 years, in western New York state, only β -cryptoxanthin, but not other carotenoids, was independently associated with pulmonary function (22). The relationship between serum carotenoids and pulmonary function in older, more disabled adults, has not been well characterized.

We hypothesized that serum carotenoids were associated with reduced pulmonary function in older women. To address this hypothesis, we measured serum carotenoids and assessed pulmonary function in a population-based study of older, moderately to severely disabled women living in the community.

Methods

Subjects

Subjects in this study were women, aged 65 and older, who participated in the Women's Health and Aging Study I (WHAS I), a population-based study designed to evaluate the

causes and course of physical disability in older disabled women living in the community. WHAS I participants were recruited from an age-stratified random sample of women aged 65 years and older selected from Medicare enrollees residing in 12 contiguous zip code areas in Baltimore (9). Women were screened to identify self-reported physical disability that was categorized into four domains. The domains of disability were ascertained in a 20-30 minute home interview that included questions related to (1) mobility and exercise tolerance, i.e., walking for a quarter of a mile, walking up 10 steps without resting, getting in and out of bed or chairs, (2) upper extremity function, i.e., raising your arms up over your head, using your fingers to grasp or handle, lifting or carrying something as heavy as ten pounds, (3) higher functioning tasks (a subset of instrumental activities of daily living, not including heavy housework, i.e., using the telephone, doing light housework, preparing your own meals, shopping for personal items), and (4) basic self-care tasks (a subset of non-mobility dependent activities of daily living, i.e., bathing or showering, dressing, eating, using the toilet). WHAS I enrolled the one-third most disabled women ages 65 and older, those with disability in two or more domains. Of the 1409 women who met study eligibility criteria, 1002 agreed to participate in the study in 1992. There were no major differences in sociodemographic or reported health characteristics between eligible participants and those who declined to participate (9).

Data collection

Standardized questionnaires were administered in the participant's home by trained interviewers. Race was assessed in a questionnaire as black, white, or other, current smoking as yes or no, and education as 0-8, 9-11, 12, or >12 years as the highest level of formal education achieved. Two weeks later, a trained registered full-time study nurse practitioner examined each study participant in her home, using a standardized evaluation of physical performance and physical exam. Approximately 75% of women also consented to phlebotomy performed during a separate visit by a trained phlebotomist who followed a standardized protocol.

The definitions for most of the chronic diseases reported in this study were adjudicated by WHAS co-investigators based on standardized algorithms that combined information from the questionnaire, physical examination, and physician contact (9). The diagnosis of angina was based upon physician diagnosis, positive Rose questionnaire, and use of anti-anginal medications. Myocardial infarction was based upon physician diagnosis, electrocardiogram, and medical record review. Congestive heart failure was diagnosed based upon physician diagnosis that was confirmed by medical record review, use of diuretics and a digitalis preparation or vasodilator. Diagnosis of peripheral arterial disease was based upon arm blood pressure conducted in both legs, exertional leg pain, and physician diagnosis of claudication. Stroke diagnosis was based upon physician diagnosis and review of medical records. Diabetes mellitus was diagnosed based upon physician diagnosis and review of medical records, use of insulin or oral hypoglycemic medications, and hemoglobin A_{1c} >10%. Chronic obstructive pulmonary disease was based upon spirometry, review of spirometry results, medical records, and respiratory medications by a study pulmonologist, and physician diagnosis. The Mini-Mental State Examination (MMSE) (3) was administered

at enrollment. Further details on the methods and sampling design of the WHAS studies are published elsewhere (9).

Pulmonary function was assessed using spirometry as described in detail elsewhere (9). Briefly, a PJ5 spirometer (Burdick Inc., Deerfield, WI) with pneumotachograph was connected to a portable computer using software for spirometry developed by the National Institute for Occupational Safety and Health (NIOSH). Nurses who conducted the examination had received training and certification in a NIOSH-approved course on spirometry. Participants with bronchodilators were told not to use them for 6 hours prior to testing. The predicted values for spirometry testing were published by Knudson and colleagues (9). Readings were reviewed by the NIOSH reading center. Field technicians sought to obtain three acceptable spirograms (FEV₁ and FVC within 5%) using the American Thoracic Society Criteria Guidelines (1). Of the 840 participants who underwent spirometry, 639 participants completed acceptable spirograms. Readings deemed “not acceptable” were usually the result of a participant's inability to sustain force expiration after repeated attempts. There were 631 women with acceptable spirograms who also had serum carotenoid measurements.

Demographic characteristics, self-rated health, and information about appetite and eating were measured in the WHAS questionnaires. The study protocol was adherent to the Declaration of Helsinki. The Johns Hopkins University School of Medicine Institutional Review Board approved the study protocol, and written informed consent was obtained from all participants.

Non-fasting blood samples were obtained by venipuncture between 9 AM and 2 PM. Blood samples were delivered to Quest Diagnostics Laboratories (formerly Ciba-Corning Laboratories, Baltimore, MD) on the day of blood drawing for complete blood count and creatinine measurements. Serum creatinine was measured using the Jaffe method. Processing, aliquoting, and freezing were carried out at the Core Genetics Laboratory of the Johns Hopkins University School of Medicine following a standardized protocol. Blood samples were stored continuously at -70°C until the time of analyses of serum carotenoids. Serum α -carotene, β -carotene, β -cryptoxanthin, lutein/zeaxanthin, and lycopene were measured in the laboratory of one of the co-investigators (R.D.S.) using high performance liquid chromatography (27). Within-run and between-run coefficients of variation were 10.7 and 23.9% for α -carotene, 7.0 and 19.1% for β -carotene, 4.7 and 8.5% for β -cryptoxanthin, 4.1 and 4.6% for lutein/zeaxanthin, 10.0 and 14.0% for lycopene. Total serum carotenoids was the sum of the six carotenoids in $\mu\text{mol/L}$. Serum interleukin-6 (IL-6) was measured using a commercial ELISA (Quantikine Human IL-6, R & D Systems, Minneapolis, MN). The minimum detection limit for the IL-6 ELISA reported by the manufacturer is 0.039 pg/mL. Intra-assay and interassay CVs for IL-6 measurements were 4% and 6%, respectively.

Data analysis

Means (standard deviation) and proportions were used to describe the study population. Variables that were skewed, i.e., serum carotenoids, were log-transformed to achieve a normal distribution. A MMSE score of <24 was defined as cognitive impairment (3).

Chronic kidney disease was defined as estimated glomerular filtration rate of <60 mL/min/ 1.73 m² using the Modification of Diet in Renal Disease equation of Levey and colleagues (14). Anemia was defined as hemoglobin <11 g/dL (32). IL-6 concentration >2.5 pg/mL was used as an indicator of inflammation (2). Univariate and multivariate linear regression models were used to examine the relationship between serum carotenoids and other variables with FEV₁ and FVC, respectively, where FEV₁ and FVC were the dependent variable in the models. Variables that reached statistical significance in univariate models were included in the multivariate linear regression models. All analyses were performed using SAS (v. 9.1.3, SAS Institute, Inc., Cary, NC) with a type I error of 0.05.

Results

Serum carotenoid concentrations, pulmonary function, demographic and other characteristics of the participants are shown in Table 1. The prevalence of chronic diseases was fairly high in this population-based sample of women representing the one-third most disabled women living in the community. Spearman correlations between the individual serum carotenoids are shown in Table 2. A moderate to moderately-high correlation was found between each of the serum carotenoids, with the highest correlations found between α -carotene and β -carotene, and the lowest correlations found between lycopene and the other serum carotenoids.

Separate univariate linear regression models were used to examine the relationship between serum carotenoids, demographic factors, inflammation, and chronic diseases with FEV₁ and FVC, respectively. Age, low education, cognitive impairment, anemia, elevated IL-6, heart failure, peripheral artery disease, stroke, and chronic obstructive pulmonary disease were significantly and negatively associated with both FEV₁ and FVC (Table 3). White race, α -carotene, and lycopene, were significantly and positively associated with both FEV₁ and FVC, respectively. Total carotenoids were positively associated with FEV₁ ($P = 0.06$) and significantly and positively associated with FVC. Current smoking, body mass index, β -carotene, β -cryptoxanthin, lutein/zeaxanthin hypertension, angina, diabetes, depression, cancer, and chronic kidney disease were not significantly associated with either FEV₁ or FVC. Stroke was not significantly associated with FEV₁ but was significantly and negatively associated with FVC.

Separate multivariate linear regression models were used to examine the relationship between individual serum carotenoids and total serum carotenoids with FEV₁ (Table 4). Serum α -carotene and β -carotene were significantly associated with FEV₁ in separate models that adjusted for age, race, education (Model 1), additionally for MMSE, anemia, and IL-6 (Model 2), and finally also adjusted for chronic diseases (congestive heart failure, peripheral artery disease, stroke, and chronic obstructive pulmonary disease, Model 3). In a fully adjusted models, total carotenoids were associated positively related FEV₁ but the association was not statistically significant ($P = 0.08$). β -cryptoxanthin, lutein/zeaxanthin, and lycopene were not associated with FEV₁.

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Serum α -carotene and β -carotene were significantly associated with FEV₁ in separate models that adjusted for age, race, education (Model 1), additionally for MMSE, anemia, and IL-6 (Model 2), and, finally also for chronic diseases (congestive heart failure, peripheral artery disease, stroke, and chronic obstructive pulmonary disease, Model 3). Total carotenoids were associated with FEV₁ in Model 3, a finding which was of marginal significance ($P = 0.08$). β -cryptoxanthin, lutein/zeaxanthin, and lycopene were not associated with FEV₁.

Separate multivariate linear regression models were used to examine the relationship between individual serum carotenoids and total serum carotenoids with FVC (Table 5). Serum α -carotene and β -carotene were significantly associated with FVC in separate models that adjusted for age, race, and education (Model 1), additionally for MMSE, anemia, and IL-6 (Model 2), and for chronic diseases (congestive heart failure, peripheral artery disease, stroke, and chronic obstructive pulmonary disease (Model 3). Total carotenoids were associated with FVC in Model 3, a finding which was of marginal significance ($P = 0.06$). β -cryptoxanthin, lutein/zeaxanthin, and lycopene were not associated with FVC.

Discussion

The present study shows that higher levels of serum α -carotene and β -carotene are independently associated with better pulmonary function in older, moderately to severely disabled community-dwelling women. These findings are consistent with a study of over five hundred non-institutionalized Dutch adults, aged 65 to 85 years, in which higher serum α -carotene and β -carotene were positively associated with lung function (5). In a study of middle-aged adults from France, participants with higher β -carotene concentrations at baseline had slower decline in FEV₁ over eight years of follow-up compared to those with low serum β -carotene concentrations (8). High plasma β -carotene concentrations were associated with higher FVC in a population-based study of Dutch adults, aged 20 to 59 years (7). Higher dietary intake of β -carotene, as assessed using food frequency questionnaires, was also associated with higher FEV₁ and FVC in Dutch adults (6).

In contrast to the above studies, two studies showed that of the major serum carotenoids, only serum β -cryptoxanthin was associated with pulmonary function. One study involved adults aged 35 to 79 years (21), and the other study involved adults 17 years and older in NHANES III (18). Foods that are rich in β -cryptoxanthin include oranges and orange juice, watermelon, kiwi fruit, and red peppers. It is unclear why β -cryptoxanthin and β -carotene do not show a consistent relationship with pulmonary function in the various studies, as many fruit and vegetables are rich in both of these specific carotenoids. Although the individual serum carotenoids in the present study showed moderate correlations ranging from about 0.20 to 0.60, it is notable that each of the individual carotenoids was not consistently associated with pulmonary function.

Pathological and animal studies show that β -carotene plays an important role in lung function. Antioxidants such as β -carotene in the lung are considered the first line of defense against oxygen free radicals (20). A pathological study of β -carotene in human lung tissue showed that serum and lung β -carotene concentrations were highly correlated ($r = 0.72$, P

<0.0001) (19). In the ferret model, low dose β -carotene supplementation has been shown to protect the lung against smoke-induced damage (15) and oxidative stress-related DNA damage (30).

There are other antioxidant nutrients that are thought to be protective of pulmonary function in adults, such as vitamin C, vitamin E, selenium, and flavonoids (20). Many of the same foods that are rich in α -carotene and β -carotene are also rich sources of vitamin C and flavonoids. Vitamin C and flavonoids were not measured in the present study, and thus, we cannot exclude that carotenoids are not directly connected with lung health but rather function as proxy biomarkers for other beneficial compound. A study of nearly three thousand adults with chronic obstructive pulmonary disease suggests that a dietary pattern characterized by higher intake of fruit and vegetables, oily fish, and wholemeal cereals was associated with higher FEV₁ (23).

The strengths of the present study were the population-based sample of women and the careful adjudication of chronic diseases diagnoses in the study participants (9). The study included older, moderately to severely disabled community-dwelling women, a group that is at higher risk of impaired pulmonary function. The limitations of the study are that the participants included only women, and the results cannot necessarily be extrapolated to men. In addition, the findings cannot necessarily be generalized to less disabled community-dwelling women.

In a recent trial, 120 adults with chronic obstructive pulmonary disease were randomized to a diet based upon increased consumption of fruit and vegetables (intervention diet) or an ad libitum diet (control group) for three years (13). The participants who were in the group consuming more fruit and vegetables had higher FEV₁ over time, suggesting that a dietary shift to higher fruit and vegetable intake was associated with improvement in pulmonary function (13).

Further controlled dietary intervention studies are needed to determine whether a higher intake of fruit and vegetables can slow the decline of pulmonary function in older adults. Other controlled intervention studies of increased fruit and vegetable intake or more healthy dietary patterns for other aging-related outcomes should include measures of pulmonary function.

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Table 1

Characteristics of participants in the Women's Health and Aging Study I

Characteristic		Mean (SD) or Percent
Age (years)		77.3 (7.8)
Race (%)	White	73.5
	Black	26.5
Education <12 years (%)		63.1
Current smoker (%)		11.0
Body mass index (kg/m ²)		29.4 (11.7)
FEV ₁ (mL)		1.99 (0.60)
FVC (mL)		1.44 (0.45)
Retinol (μmol/L)		2.61 (0.93)
α-carotene (μmol/L) ¹		0.06
β-carotene (μmol/L) ¹		0.32
β-cryptoxanthin (μmol/L) ¹		0.10
Lutein/zeaxanthin (μmol/L) ¹		0.33
Lycopene (μmol/L) ¹		0.46
Total carotenoids (μmol/L) ¹		1.42
Mini-Mental State Exam score <24 (%)		16.1
Anemia (%)		20.4
Interleukin-6 >2.5 pg/mL (%)		55.6
Hypertension (%)		56.7
Angina (%)		22.3
Heart failure (%)		8.4
Peripheral artery disease (%)		19.2
Stroke (%)		5.6
Diabetes mellitus (%)		15.6
Chronic obstructive pulmonary disease (%)		31.3
Depression (%)		16.1
Cancer (%)		10.4
Chronic kidney disease (%)		53.9

¹ Geometric mean.

Table 2

Spearman correlations of serum carotenoids in participants in the Women's Health and Aging Study I

	β-carotene	β-cryptoxanthin	Lutein/zeaxanthin	Lycopene
α-carotene	0.62 $P < 0.0001$	0.49 $P < 0.0001$	0.39 $P < 0.0001$	0.31 $P < 0.0001$
β-carotene		0.44 $P < 0.0001$	0.39 $P < 0.0001$	0.26 $P < 0.0001$
β-cryptoxanthin			0.48 $P < 0.0001$	0.20 $P < 0.0001$
Lutein/zeaxanthin				0.24 $P < 0.0001$

Table 3

Univariate linear regression models for relationship of serum carotenoids and other participant characteristics with FEV₁ and FVC, respectively, among women in the Women's Health and Aging Study I

Characteristic	FEV ₁		FVC	
	Beta (SE)	P	Beta (SE)	P
Age (years)	-0.020 (0.002)	<0.0001	-0.028 (0.002)	<0.0001
Race, white	0.114 (0.040)	0.005	0.241 (0.053)	<0.0001
Education <12 years	-0.149 (0.037)	<0.0001	-0.234 (0.048)	<0.0001
Current smoking	-0.034 (0.057)	0.55	0.048 (0.076)	0.53
Body mass index (kg/m ²)	0.001 (0.001)	0.49	-0.002 (0.002)	0.21
Log α-carotene (μmol/L)	0.043 (0.019)	0.03	0.082 (0.026)	0.002
Log β-carotene (μmol/L)	0.016 (0.022)	0.47	0.031 (0.030)	0.30
Log β-cryptoxanthin (μmol/L)	0.028 (0.022)	0.21	0.042 (0.029)	0.15
Log lutein/zeaxanthin (μmol/L)	-0.046 (0.035)	0.18	-0.050 (0.046)	0.28
Log lycopene (μmol/L)	0.077 (0.027)	0.004	0.118 (0.036)	0.0009
Log total carotenoids (μmol/L)	0.068 (0.037)	0.06	0.106 (0.049)	0.03
Mini-Mental State Exam score <24	-0.217 (0.048)	<0.0001	-0.363 (0.063)	<0.0001
Anemia	-0.105 (0.046)	0.02	-0.225 (0.060)	0.0002
Interleukin-6 >2.5 pg/mL	0.127 (0.036)	0.0004	0.158 (0.048)	0.001
Hypertension	0.008 (0.036)	0.82	-0.027 (0.048)	0.57
Angina	0.018 (0.043)	0.66	0.015 (0.057)	0.78
Heart failure	-0.176 (0.064)	0.006	-0.200 (0.085)	0.02
Peripheral artery disease	-0.147 (0.045)	0.001	-0.149 (0.060)	0.01
Stroke	-0.030 (0.078)	0.69	-0.236 (0.103)	0.02
Diabetes mellitus	0.027 (0.049)	0.57	-0.062 (0.065)	0.34
Chronic obstructive pulmonary disease	-0.358 (0.036)	<0.0001	-0.142 (0.051)	0.005
Depression	-0.056 (0.048)	0.25	-0.096 (0.064)	0.14
Cancer	0.089 (0.058)	0.13	0.133 (0.078)	0.09
Chronic kidney disease	0.031 (0.037)	0.39	-0.006 (0.048)	0.90

Table 4

Separate multivariate linear regression models for the relationship between individual serum carotenoids and total carotenoids with FEV₁ among women in the Women's Health and Aging Study I

Characteristic	Model 1, adjusted for age, race, education		Model 2, adjusted for age, race, education, MMSE, anemia, IL-6		Model 3, adjusted for age, race, education, MMSE, anemia, IL-6, chronic diseases [/]	
	Beta (SE)	P	Beta (SE)	P	Beta (SE)	P
Log α-carotene (μmol/L)	0.050 (0.019)	0.009	0.043 (0.021)	0.04	0.050 (0.018)	0.005
Log β-carotene (μmol/L)	0.055 (0.021)	0.01	0.045 (0.023)	0.04	0.046 (0.020)	0.02
Log β-cryptoxanthin (μmol/L)	0.032 (0.021)	0.13	0.024 (0.022)	0.28	0.024 (0.019)	0.21
Log lutein/zeaxanthin (μmol/L)	0.015 (0.034)	0.66	-0.013 (0.036)	0.72	-0.004 (0.032)	0.89
Log lycopene (μmol/L)	0.029 (0.025)	0.25	0.009 (0.026)	0.73	0.013 (0.023)	0.58
Log total carotenoids (μmol/L)	0.084 (0.034)	0.02	0.056 (0.037)	0.13	0.057 (0.033)	0.08

[/] Chronic diseases include congestive heart failure, peripheral artery disease, stroke, chronic obstructive pulmonary disease.

Table 5

Separate multivariate linear regression models for the relationship between individual serum carotenoids and total carotenoids with FVC among women in the Women's Health and Aging Study I

Characteristic	Model 1, adjusted for age, race, education		Model 2, adjusted for age, race, education, MMSE, IL-6, anemia		Model 3, adjusted for age, race, education, MMSE, IL-6, anemia, and chronic diseases ¹	
	Beta (SE)	P	Beta (SE)	P	Beta (SE)	P
Log α -carotene ($\mu\text{mol/L}$)	0.086 (0.025)	0.0006	0.076 (0.027)	0.005	0.080 (0.026)	0.002
Log β -carotene ($\mu\text{mol/L}$)	0.091 (0.028)	0.001	0.079 (0.029)	0.007	0.077 (0.029)	0.008
Log β -cryptoxanthin ($\mu\text{mol/L}$)	0.046 (0.027)	0.09	0.035 (0.028)	0.22	0.030 (0.027)	0.27
Log lutein/zeaxanthin ($\mu\text{mol/L}$)	0.057 (0.044)	0.19	0.017 (0.046)	0.71	0.017 (0.045)	0.71
Log lycopene ($\mu\text{mol/L}$)	0.047 (0.032)	0.15	0.028 (0.034)	0.58	0.019 (0.033)	0.55
Log total carotenoids ($\mu\text{mol/L}$)	0.131 (0.045)	0.004	0.093 (0.047)	0.05	0.087 (0.047)	0.06

¹ Chronic diseases include congestive heart failure, peripheral artery disease, stroke, chronic obstructive pulmonary disease.