するが，長期的には胃瘻造設も考慮する．

尿失禁は脱抑制性膀胱によるもので，通常，切迫性尿失禁の様式をとる．まず尿意の有無，排尿回数や尿失禁の頻度，残尿量（ベッドサイドで簡便に測定できる超音波診断装置を使用）を正しく評価する．尿意がないか残尿があれば膀胱カテーテルを用いて膀胱訓練から行い，切迫性尿失禁であれば，①薬物療法（表1），②失禁パッド装着を行う．かさばるおむつの使用はリハビリテーションの妨げになる．

なお，脳血管性痴呆に対するコリンエステラーゼ阻害薬（塩酸ドネペジル）の保険適用はないが，欧米の大規模臨床試験でその有用性が示されている[8]．アルツハイマー病との合併では，認知機能の改善を目的として塩酸ドネペジルを試みる．

次いで，リハビリテーションは生活機能の回復と廃用性変化の防止を目的として行われるが，その目的を達成するためには患者の回復意欲が必須である．脳血管障害ではしばしば自発性低下，うつがみられるため，これらに対して薬物療法（表1）が行われる．また，早期離床をめざしたリハビリテーションが積極的かつ安全に行えるような療養環境の整備も必要である．特に転倒は大腿骨頸部骨折の原因となり，寝たきりは廃用性変化を助長する．めまいに対しては表1に示す薬物が投与される．

第3番目の再発予防については次項で述べる．

Ⅲ．脳血管性痴呆の予防

脳血管性痴呆の予防は脳血管障害の発症予防に尽きる．すなわち，脳血管障害の既知の危険因子（I. 6. 項に既述），特に生活習慣病を是正・治療することが重要で（表1），再発予防にも不可欠である[9]．

脳卒中や脳血管性痴呆が発症した場合，その進展を阻止する目的で再発予防薬を用いる．基本的には同じ臨床病型で再発することが多い点から，その臨床病型に対して確立された再発予防が開始される（表1）．

一方，ビンスワンガー病はその成因（図3）からさまざまな予防法が考案されるが（血圧の管理，抗血小板薬など），確立したものはない．

おわりに

脳血管性痴呆は脳血管障害と共に生活習慣病ととらえられ，予防が可能である．高齢者にみられる白質病変は，無症候であっても脳卒中や痴呆の予知因子と考えられ，予防医学的に重要な所見として認識すべきであろう．

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Effect of smoking habit on age-related changes in serum lipids: A cross-sectional and longitudinal analysis in a large Japanese cohort

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Abstract

To observe the effect of smoking habit on age-related serum lipid levels, we examined a large cohort of Japanese cross-sectionally and longitudinally. The participants included 103,648 Japanese men and women 17–94 years of age, who had received annual health examinations from 1989 to 2003. In cross-sectional analysis, total and LDL cholesterol levels of smokers were lower than those of nonsmokers up to an elderly age in men and up to middle age in women. Smoking was associated with decreased HDL cholesterol levels up to the 65–74 years age group in men and 55–64 years in women. The triglyceride levels were higher in smokers in both genders than those of nonsmokers below 55–64 years. In the longitudinal analysis, although smoking was associated with lower total and LDL cholesterol up to 60 years of age in women, beyond the sixties an inverted association was observed. The associations of smoking with lower LDL cholesterol levels in men and lower HDL cholesterol in both genders were fairly consistent at any given age. The increase of triglyceride levels in female smokers remained rather constant between 25 and 75 years, whereas the increase in triglyceride levels in male smokers was greater with older ages up to middle age. These results suggest that the effect of smoking on the serum lipid levels is dependent on age and gender.

Keywords: Smoking; Total cholesterol; Triglyceride; HDL cholesterol; LDL cholesterol; Longitudinal study; Ageing

Although smoking is well recognized as a risk factor for coronary artery disease and stroke [1,2], the underlying mechanisms and factors responsible for this association are complex and only partially understood [3]. One possible mechanism for the effect of smoking on cardiovascular disease risk is the atherogenic impact of tobacco smoke on serum lipids and lipoproteins. Previous observations suggest that smokers exhibit elevations of triglycerides, total and low-density lipoprotein (LDL) cholesterol, as well as decreases of high-density lipoprotein (HDL) cholesterol as compared with nonsmokers [4–6]. Most conclusions regarding these associations with smoking habit have been drawn from selected groups, including clinical trials or cross-sectional studies targeting adolescents, young adults, and adults. To our knowledge, no study has been done targeting the elderly.

We and other authors have demonstrated that serum lipid levels vary during the ageing process based on the longitudinal observations [7,8]. However, the effect of smoking habit on the age-related changes in serum lipid levels remains unknown, and to our knowledge, no study has examined the longitudinal changes in the smoking effect on serum lipid levels in individual across a broad age range over time.

In the present study, we examined the cross-sectional and longitudinal changes in serum lipid levels in a single cohort of individuals with or without smoking habit to observe the effect of the natural aging process on the effect of smoking on the age-related serum lipid levels.

1. Materials and methods

1.1. Study population

The study population was office workers and their families residing in Aichi Prefecture in the central region of Japan. The

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subjects included 103,648 Japanese (65,789 men and 37,859 women) with an average age of 44.7 years in men and 43.3 years in women, who had received annual examinations at a health examination center in Japan between 1989 and 2003 (Table 1). A total of 2030 subjects who were receiving medication for hyperlipidemia had already been excluded. Our cohort included more males than females, since the number of male workers is greater than the number of female workers in Japan. About 57% of the cohort attended at least one follow-up examination. Average visits for the follow-up examinations were 3.1 times for men and 2.7 times for women.

1.2. Procedures and laboratory methods

The examinations included a questionnaire, a physical examination, an anthropometric measurement, and laboratory analysis of blood samples, all taken on the same day. The anthropometric measurements included height and body weight, which were measured while the subject was wearing light clothing without shoes. The body mass index (BMI) was calculated as weight/height^2 (kg/m^2). Information on smoking status (current cigarette smokers or not) was also recorded using a self-administered questionnaire.

All serum samples were obtained following a 12–14 h fast. Serum was separated promptly, and all lipid analyses were conducted at the clinical laboratory in the health examination center. Serum total cholesterol and triglycerides were measured by using enzymatic methods. HDL cholesterol was measured after dextran sulfate–magnesium precipitation. No differences were seen in the sample collection, laboratory apparatus, or techniques used between 1989 and 2003. LDL cholesterol was estimated by using the method of Friedewald et al. [9].

1.3. Data analysis

The data were analyzed with the Statistical Analysis System (SAS), release 8.2. Smoking status and age-related change of the serum lipids were quite different between men and women. Thus, the data were analyzed separately by gender. We previously demonstrated that there is a birth cohort effect on serum lipid levels based on a 10-year longitudinal analysis of the same cohort, which suggested that higher estimated total and LDL cholesterol levels were observed in younger birth cohorts than in older cohorts [7]. Average of total and LDL cholesterol levels increased with the year of the observation. Therefore, the cross-sectional data were adjusted for the year of the initial examination of each subject and BMI, and lipid levels were estimated for the examination in 1996 and at BMI = 22 (Table 3). The difference in serum lipid levels between smokers and nonsmokers was examined using Student's *t*-test in six age groups divided by decades ranging from less than 25–75 years and older.

Cross-sectional age-related changes in the lipid levels may represent cohort, period, and/or survivor ship effects rather than a true aging effect. Longitudinal data analysis is necessary to examine the effect of smoking habit on true age-related changes of serum lipid levels. Longitudinal changes in serum lipid levels were analyzed by a mixed effect model [10,11], which is a type of statistical analysis commonly used for repeated measurements. It is applied using the SAS procedure PROC MIXED, typically using the PEPEATED statement. Age-related changes of serum lipids were estimated by quadratic curve of age controlling for the observation year and BMI. Fixed effects for the observation year, BMI, age, age square, smoking status, smoking–age interaction, and smoking–age square interaction were included in the model, and random effect of subjects were also included in the model. Responses from points close in time are usually more highly correlated with each other than responses from points far apart in time. Therefore, special methods of analysis are usually needed to accommodate the correlation structure of the repeated measurements. This autoregression was controlled using the autoregressive covariance–structure in the mixed effect model. The least square means for serum lipid values at every age were determined in smokers and nonsmokers. The differences of the lipid levels between smokers and nonsmok-

Table 1
Characteristics of participants

	Men	Women
Number of subjects	65,789	37,859
Total no. of measurements for 14 years	204,064	103,244
No. of measurements per subject for 14 years, mean (S.D.)	3.1 (2.9)	2.7 (2.5)
Age (year), mean (S.D.)	44.7 (9.3)	43.3 (9.4)
Age range (year)	14–94	17–85
Height (cm) at initial measurement, mean (S.D.)	168.5 (6.0)	156.0 (5.4)
Body weight (kg) at initial measurement, mean (S.D.)	65.6 (9.3)	52.4 (7.3)
BMI (kg/m^2) at initial measurement, mean (S.D.)	23.1 (2.8)	21.6 (2.9)
Smoker (%) at initial examination	53.4	11.8
Serum lipid levels at initial measurement		
Total cholesterol (mM), mean (S.D.)	5.15 (0.90)	5.14 (0.94)
LDL cholesterol (mM), mean (S.D.)	3.02 (0.81)	2.94 (0.85)
HDL cholesterol (mM), mean (S.D.)	1.42 (0.34)	1.75 (0.37)
Triglyceride (mM), mean (S.D.)	1.60 (1.16)	0.98 (0.56)

Table 2
Characteristics of participants for longitudinal analysis

	Men	Women
Number of subjects	61,150	37,024
Total no. of measurements for 14 years	204,064	103,244
No. of measurements per subject for 14 years, mean (S.D.)	2.9 (2.8)	2.7 (2.5)
Age (year), mean (S.D.)	44.7 (9.3)	43.4 (9.4)
Age range (year)	14–94	17–85
Follow-up periods (year), mean (S.D.)	2.9 (3.9)	2.8 (3.8)
Height (cm) at initial measurement, mean (S.D.)	168.5 (6.0)	156.0 (5.4)
Body weight (kg) at initial measurement, mean (S.D.)	65.6 (9.3)	52.4 (7.3)
BMI (kg/m^2) at initial measurement, mean (S.D.)	23.1 (2.9)	21.6 (2.9)
Smoker (%) at initial examination	51.5	10.6
Serum lipid levels at initial measurement		
Total cholesterol (mM), mean (S.D.)	5.15 (0.90)	5.14 (0.94)
LDL cholesterol (mM), mean (S.D.)	3.03 (0.81)	2.95 (0.85)
HDL cholesterol (mM), mean (S.D.)	1.42 (0.34)	1.75 (0.37)
Triglyceride (mM), mean (S.D.)	1.60 (1.17)	0.98 (0.56)

ers at each age were obtained by the differences of estimated lipid levels based on the longitudinal analysis using a mixed effect model between smokers and nonsmokers at each age. In the longitudinal analysis, subjects who reported a nonsmoking status at least once during the repeated examinations over a 14-year period were excluded from the smoker group. In addition, subjects who reported current smoking status during at least one point of the repeated examinations were excluded from the nonsmoker group. As a result, all subjects who changed smoking habit as noted during the repeated measurements (4639 males and 835 females) were excluded from the longitudinal analysis. The characteristics of participants for the longitudinal analysis are summarized in Table 2.

2. Results

2.1. Cross-sectional analysis

Fig. 1 shows the smoking rate of the participants between 1989 and 2003. At the initial examination, the rate of smoking in men and women was 53.4 and 11.8%, respectively, which is similar to rates shown in a national survey. The rate of smoking decreased during the periods examined which is consistent with the observation of others [12].

Fig. 2 shows the age-specific means and 3-year moving average of serum lipid levels at initial measurement of each subject of men and women with or without smoking habit from 1989 through 2003 before including the effect of BMI and the time of examination. The age-related changes of serum lipid levels of both male and female smokers were similar to those of nonsmokers. In men, serum total cholesterol level gradually increased from 20–29 years up to 50–59 years, and no further increase was observed after 50–59 years. In women, serum total cholesterol level dramatically increased from 20–29 years up to 60–69 years and then subsequently decreased. These age-related changes were similar in LDL cholesterol levels in men and women. HDL cholesterol levels were rather constant up to 70–79 years in men. In women, HDL cholesterol levels were lower with increasing age. Serum triglyceride levels increased up to 40–49 years, followed by a decline above 50–59 years in men, whereas triglyceride levels in women increased up to 60–69 years and then decreased at 70–79 years.

Total and LDL cholesterol levels of smokers were somewhat lower than those of nonsmokers above middle age in men, but no obvious differences were observed between smokers and nonsmokers in women (Fig. 2). In HDL cholesterol and triglyceride, much lower and higher levels were observed, respectively, in smokers compared with those of nonsmokers at all ages of men and women (Fig. 2).

We previously demonstrated that there was a birth cohort effect on serum lipid levels in this large Japanese cohort [7]. BMI is also known to influence the serum lipid levels [13,14]. Therefore, the cross-sectional data of serum lipid levels at

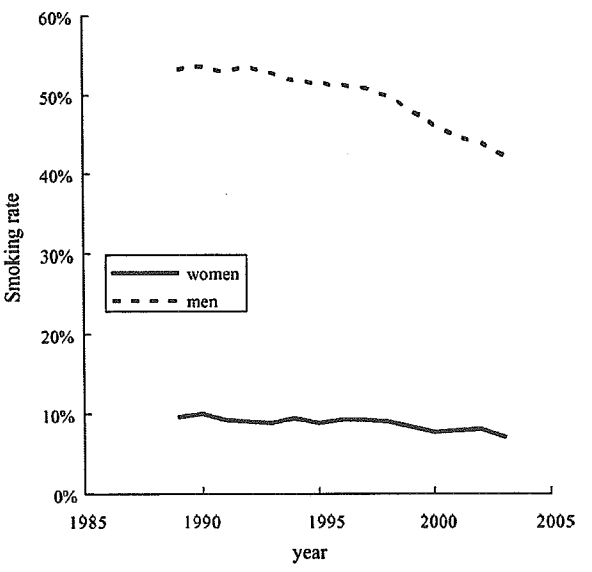

Fig. 1. Trends in smoking rate.

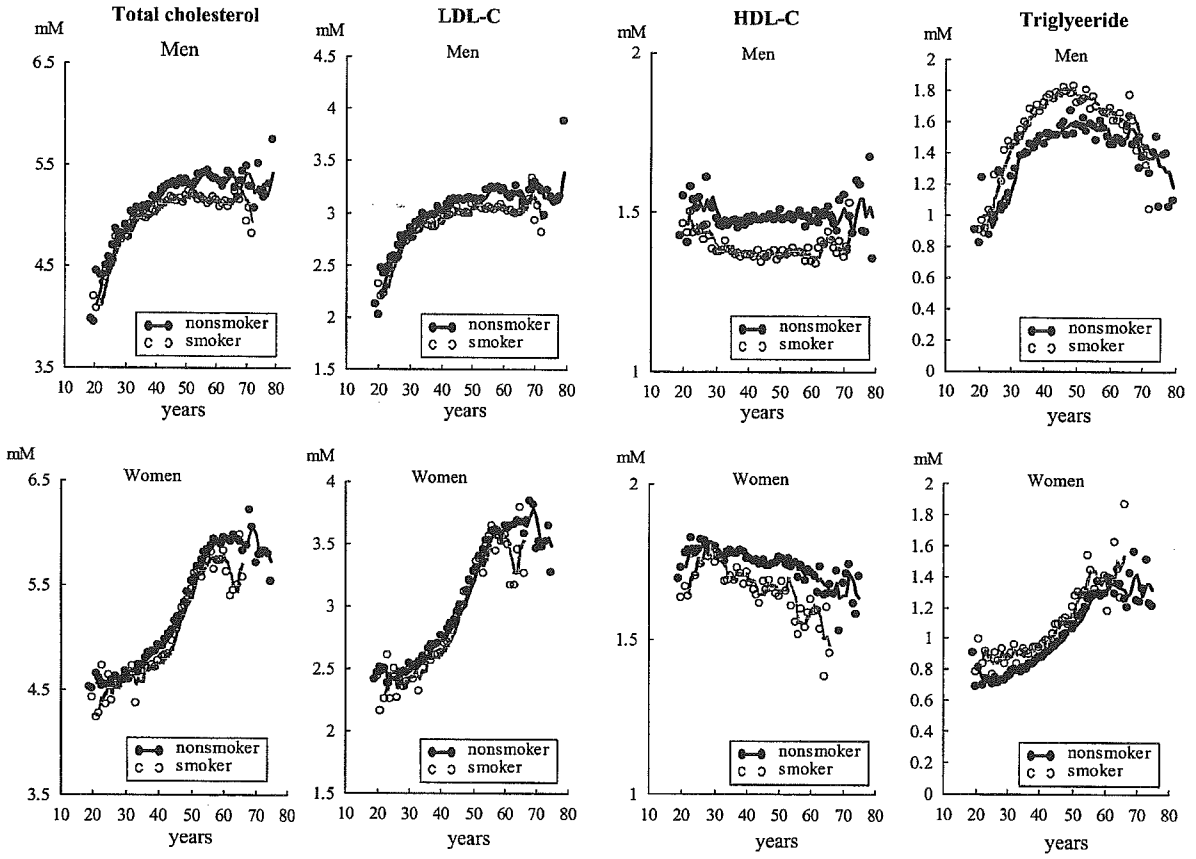

Fig. 2. Effect of aging on serum lipid levels in cross-sectional analysis. The age-specific means of serum lipid levels and a 3-year moving average of serum lipid levels are shown in smokers and nonsmokers at the initial examination.

initial examination of each subject from 1989 through 2003 were adjusted for the year of the individual examination and BMI. Mean values of serum lipid estimates for the examination in 1996 and at BMI = 22 are shown by age group and gender with or without smoking habit in Table 3. Significant differences existed in lipid levels between smokers and nonsmokers. Total and LDL cholesterol in male smokers were lower than those of nonsmokers from 25 to 34 years up to elderly age, while in women the effect of smoking on the total and LDL cholesterol lowering was observed from 35–44 years through 55–64 years and from 25–34 through 35–44 years, respectively. Smoking was associated with decreased HDL cholesterol levels between 25–34 years and 65–74 years in men, and from young adulthood up to 55–64 years in women. The triglyceride levels were higher in male and female smokers than those of nonsmokers below 55–64 years. However, after 65 years no difference in triglyceride levels was observed between male and female smokers and nonsmokers.

2.2. *Longitudinal analysis*

The serum lipid levels of smokers and nonsmokers from age 30 through age 70 at 10-year intervals were estimated for each age using the least square means method in the mixed effects model. These values were adjusted for the examination year in 1996 and BMI = 22. As shown in Table 4, male smokers exhibited lower total and LDL cholesterol levels than those of nonsmoker controls from age 30 through age 70. In women, a similar tendency toward lower total and LDL cholesterol levels in smokers was estimated at 40, 50, and 60 years, and 40 and 50 years, respectively. Both male and female smokers had lower HDL cholesterol levels at any of the 10-year intervals examined. In contrast, higher levels of triglyceride were estimated in smokers of both genders from age 30 to 70 years compared with those of nonsmokers.

Fig. 3 demonstrated the difference of estimated lipid levels (the lipid levels of smokers–those of nonsmokers) between current smokers and nonsmokers at individual age from 25 through 75 years based on the longitudinal analysis. The estimates show that the effect of smoking on the decrease in total cholesterol levels is apparent from 30 up to 65 years in females, with a peak at 45 years old. However, beyond the sixth decades of life the effect of smoking on total cholesterol levels was inverted, showing higher cholesterol concentrations in female smokers than those of nonsmokers. In contrast, the smoking effect on male total cholesterol levels is rather consistent at any given age, although the decrement of

Table 3
The cross-sectional data of serum lipid levels at initial examination of each subject from 1989 through 2003

Age groups (years)	<25		25–34		35–44		45–54		55–64		65–74		75≤	
	Nonsmoker	Smoker	Nonsmoker	Smoker	Nonsmoker	Smoker	Nonsmoker	Smoker	Nonsmoker	Smoker	Nonsmoker	Smoker	Nonsmoker	Smoker
Male														
Number of subjects	154	229	3212	4119	11684	15293	9630	10704	5177	4363	739	366	94	24
Age (year)	21.9 (2.2)	22.5 (1.6)	31.4 (2.4)	31.4 (2.5)	39.4 (2.9)	39.4 (2.9)	49.3 (2.9)	49.0 (2.9)	58.4 (2.6)	58.1 (2.5)	67.7 (2.6)	67.4 (2.4)	78.1 (3.6)	77.8 (3.0)
Total cholesterol (mM)	4.38 (0.81)	4.29 (0.71)	4.95 (0.87)*	4.87 (0.89)*	5.16 (0.89)†	5.05 (0.90)†	5.32 (0.88)†	5.17 (0.90)†	5.38 (0.89)†	5.15 (0.88)†	5.33 (0.82)*	5.13 (0.87)*	5.57 (0.91)*	4.65 (1.04)*
LDL-cholesterol (mM)	2.44 (0.73)	2.39 (0.66)	2.88 (0.77)*	2.82 (0.79)*	3.03 (0.79)†	2.94 (0.81)†	3.14 (0.78)†	3.04 (0.83)†	3.22 (0.80)†	3.05 (0.81)†	3.18 (0.74)	3.06 (0.85)	3.19 (0.89)*	2.63 (0.77)*
HDL-cholesterol (mM)	1.51 (0.29)	1.45 (0.30)	1.48 (0.32)†	1.39 (0.32)†	1.47 (0.34)†	1.37 (0.32)†	1.49 (0.35)†	1.37 (0.33)†	1.48 (0.36)†	1.37 (0.35)†	1.49 (0.37)†	1.41 (0.39)†	1.50 (0.36)	1.43 (0.35)
Triglyceride (mM)	0.97 (0.51)	0.99 (0.49)	1.31 (0.97)†	1.49 (1.11)†	1.48 (1.03)†	1.71 (1.27)†	1.58 (1.13)†	1.78 (1.29)†	1.52 (1.01)†	1.67 (1.14)†	1.49 (0.98)	1.52 (0.95)	1.26 (0.60)	1.29 (0.60)
Female														
Number of subjects	499	131	4579	750	13803	1916	10172	1206	3802	403	501	45	49	4
Age (year)	22.5 (1.5)	22.2 (1.5)	30.9 (2.5)	30.6 (2.7)	39.3 (2.9)	39.3 (2.9)	49.1 (2.9)	48.8 (2.8)	58.0 (2.6)	58.0 (2.6)	67.9 (2.7)	67.7 (2.6)	77.9 (2.8)	76.5 (2.4)
Total cholesterol (mM)	4.57 (0.75)	4.43 (0.83)	4.66 (0.77)	4.59 (0.78)	4.90 (0.80)	4.77 (0.79)†	5.44 (0.92)	5.37 (0.93)*	5.90 (0.93)	5.72 (0.90)*	5.91 (0.94)	5.95 (1.05)	5.71 (0.89)	5.91 (1.60)
LDL-cholesterol (mM)	2.44 (0.66)	2.34 (0.77)	2.53 (0.67)	2.45 (0.70)*	2.73 (0.72)	2.66 (0.74)*	3.21 (0.84)	3.17 (0.87)	3.60 (0.85)	3.53 (0.87)	3.65 (0.85)	3.73 (0.92)	3.39 (0.73)	3.79 (1.59)
HDL-cholesterol (mM)	1.78 (0.32)	1.70 (0.32)*	1.78 (0.35)	1.74 (0.37)*	1.77 (0.36)	1.68 (0.37)†	1.75 (0.39)	1.67 (0.38)†	1.71 (0.41)	1.56 (0.38)†	1.66 (0.40)	1.54 (0.29)	1.75 (0.41)	1.33 (0.25)
Triglyceride (mM)	0.74 (0.34)	0.90 (0.65)*	0.77 (0.40)	0.89 (0.48)†	0.87 (0.43)	0.95 (0.49)†	1.07 (0.60)	1.17 (0.65)†	1.30 (0.73)	1.42 (0.75)*	1.33 (0.67)	1.49 (0.65)	1.25 (0.71)	1.74 (0.62)

Data were adjusted for BMI, and year of initial examination, and expressed at BMI = 22; values are mean (S.D.).
* $p < 0.05$ (nonsmoker vs. smoker).
† $p < 0.0001$ (nonsmoker vs. smoker).

the estimated total cholesterol for smokers is larger with age. The pattern of the difference of the estimated LDL cholesterol between smokers and nonsmokers was similar to the pattern for total cholesterol. The HDL cholesterol value declines constantly in smokers at all ages in both genders. The increase of the estimated triglyceride levels in female smokers is constant between 25 and 75 years, although there is a U shape with the bottom between 40 and 50 years. In males, the effect of smoking on the increase in triglyceride level was stronger with age up to middle age, with the peak between 45 and 50 years. Subsequently the effect decreased with age, and no difference of triglyceride levels was illustrated beyond 70 years.

3. Discussion

There has been debate as to whether the difference in serum lipid levels between smokers and nonsmokers is due to smoking itself or whether other confounding lifestyle factors, e.g., body weight, alcohol consumption, and diet, have a dominant influence. There is now evidence to suggest a causal relationship between smoking and serum lipid concentrations.

The meta-analysis of 54 published studies by Craig et al. shows an increase in plasma concentrations of total cholesterol (3%), triglyceride (9.1%), and LDL cholesterol (1.7%) and a reduction in the concentrations of HDL cholesterol (5.7%) in smokers as compared with nonsmokers [4]. However, as the authors described in the paper, in most of the previous studies lipid levels were not adjusted for age or BMI. Additionally, most studies have had only adolescent, young adult, or middle-aged subjects. To our knowledge no data were available to see the effect of smoking habit on the serum lipid levels in the elderly as well as age-related changes in various lipid levels in a large cohort.

In the present study, we demonstrated that the influence of smoking habit on serum lipid levels is dependent on the subject age based on the cross-sectional as well as longitudinal observation. Based on cross-sectional observation, we showed that there were no significant differences in serum lipid levels between smokers and nonsmokers in young adults (<25 years) in men and women except for HDL cholesterol and triglyceride in women. In addition, we observed that the effect of smoking on the total and LDL cholesterol lowering and the enhancing influence of smoking on triglyceride levels were not detected in the female elderly, although in male smokers, the total and LDL cholesterol levels were higher even at 75 years and older than those of nonsmokers. The result suggests that the effect of smoking on serum lipid levels is dependent on age.

We showed that the total and LDL cholesterol levels in female and male smokers are lower than those of nonsmokers at least in middle age, which is inconsistent with the most of the earlier observations that serum cholesterol concentrations were higher in smokers [4] In the meta-analysis

Table 4
The estimated serum lipid levels of smokers and nonsmokers from age of 30 years through 70 years at 10 years intervals

Age groups (years)	30		40		50		60		70	
	Nonsmokers	Smokers	Nonsmokers	Smokers	Nonsmokers	Smokers	Nonsmokers	Smokers	Nonsmokers	Smokers
Male										
Total cholesterol (mM)										
Mean	4.83	4.76	5.10	5.02	5.25	5.14	5.28	5.14	5.19	5.00
95%CI	4.80–4.85	4.74–4.78†	5.09–5.11	5.01–5.03†	5.24–5.26	5.13–5.15†	5.26–5.29	5.12–5.15†	5.16–5.22	4.96–5.04†
LDL-cholesterol (mM)										
Mean	2.78	2.73	2.98	2.91	3.10	3.02	3.14	3.04	3.10	2.99
95%CI	2.76–2.80	2.71–2.75*	2.97–2.99	2.90–2.92†	3.09–3.11	3.01–3.03†	3.13–3.15	3.02–3.06†	3.07–3.13	2.95–3.03†
HDL-cholesterol (mM)										
Mean	1.51	1.43	1.53	1.41	1.54	1.40	1.54	1.40	1.52	1.40
95%CI	1.50–1.52	1.42–1.44†	1.53–1.54	1.41–1.42†	1.54–1.54	1.40–1.41†	1.53–1.54	1.39–1.41†	1.51–1.53	1.39–1.42†
Triglyceride (mM)										
Mean	1.19	1.35	1.32	1.60	1.38	1.68	1.36	1.60	1.26	1.34
95%CI	1.16–1.22	1.32–1.38†	1.31–1.34	1.59–1.62†	1.36–1.39	1.67–1.70†	1.34–1.38	1.58–1.62†	1.22–1.30	1.29–1.40*
Female										
Total cholesterol (mM)										
Mean	4.63	4.60	5.06	4.96	5.47	5.35	5.86	5.79	6.23	6.28
95%CI	4.61–4.65	4.56–4.65	5.05–5.07	4.93–4.98†	5.46–5.48	5.32–5.38†	5.85–5.88	5.74–5.85*	6.20–6.27	6.15–6.40
LDL-cholesterol (mM)										
Mean	2.53	2.51	2.88	2.82	3.23	3.16	3.56	3.54	3.88	3.96
95%CI	2.51–2.54	2.47–2.55	2.88–2.89	2.79–2.84†	3.22–3.24	3.13–3.19†	3.55–3.58	3.49–3.59	3.85–3.92	3.85–4.08
HDL-cholesterol (mM)										
Mean	1.72	1.66	1.75	1.67	1.76	1.65	1.75	1.61	1.71	1.55
95%CI	1.71–1.73	1.64–1.68†	1.75–1.76	1.65–1.68†	1.76–1.77	1.64–1.67†	1.74–1.75	1.59–1.64†	1.69–1.72	1.50–1.61†
Triglyceride (mM)										
Mean	0.83	0.97	0.93	1.04	1.06	1.19	1.22	1.41	1.42	1.70
95%CI	0.82–0.84	0.94–1.00†	0.92–0.93	1.03–1.06†	1.05–1.06	1.17–1.21†	1.21–1.23	1.37–1.44†	1.40–1.44	1.62–1.78†

The values were estimated for each age using the least square means methods in the mixed effects model, and were adjusted for the examination year in 1996 and BMI = 22.

* $p < 0.05$ (nonsmoker vs. smoker).

† $p < 0.0001$ (nonsmoker vs. smoker).

from Craig et al. [4], serum cholesterol concentrations were higher in smokers in all (22 studies) but one study. In addition, LDL cholesterol levels were higher in the smoking group by 1.7% from six studies compared with nonsmokers. Although the reason for this discrepancy of the effect of smoking in total and LDL cholesterol is not clear, some ethnic differences including dietary habits, physical activities, or life style as well as differences in public health awareness may have contributed to the inconsistency in observations between us and others. In fact, Halfon et al. found smoking to be associated positively with LDL cholesterol in males of European, but not of African descent [15]. Freedman et al. also reported in their longitudinal observation of early adulthood that although white male and female smokers had a larger increase in LDL cholesterol compared with nonsmokers, in black females smoking was inversely associated with LDL cholesterol [6].

We demonstrated in cross-sectional observation that HDL cholesterol levels were lower and triglyceride levels were higher in female as well as male smokers than in nonsmokers at most of the age groups examined, which was in agreement with other published results [4].

In longitudinal study, we observed apparent differences of smoking effect on serum lipid levels with age, except for HDL cholesterol levels, in which the effect of smoking is rather constant with age. The effect of smoking on the estimated total and LDL cholesterol in both genders is similar to the cross-sectional observation that total and LDL cholesterol decreased in male and female smoker up to elderly age and up to middle age, respectively. However, as shown in Fig. 3, the differences of the estimates of total and LDL cholesterol levels between smokers and nonsmokers based on the longitudinal observation suggest that there is an age effect on the influence of smoking on serum cholesterol concentrations. In addition, this analysis illustrated a gender difference with regard to this effect. In men, smoking is associated with lower total and LDL cholesterol at any given age, although there is an age effect in that the difference becomes larger with age. In women, the effect of smoking is not constant; an inverted influence on total and LDL cholesterol is detected, as in women younger than 60 years, the smoking is associated with lower cholesterol, but after 65 years smoking is associated with higher cholesterol levels. The reason for this remains unknown, although the life style changes or hor-

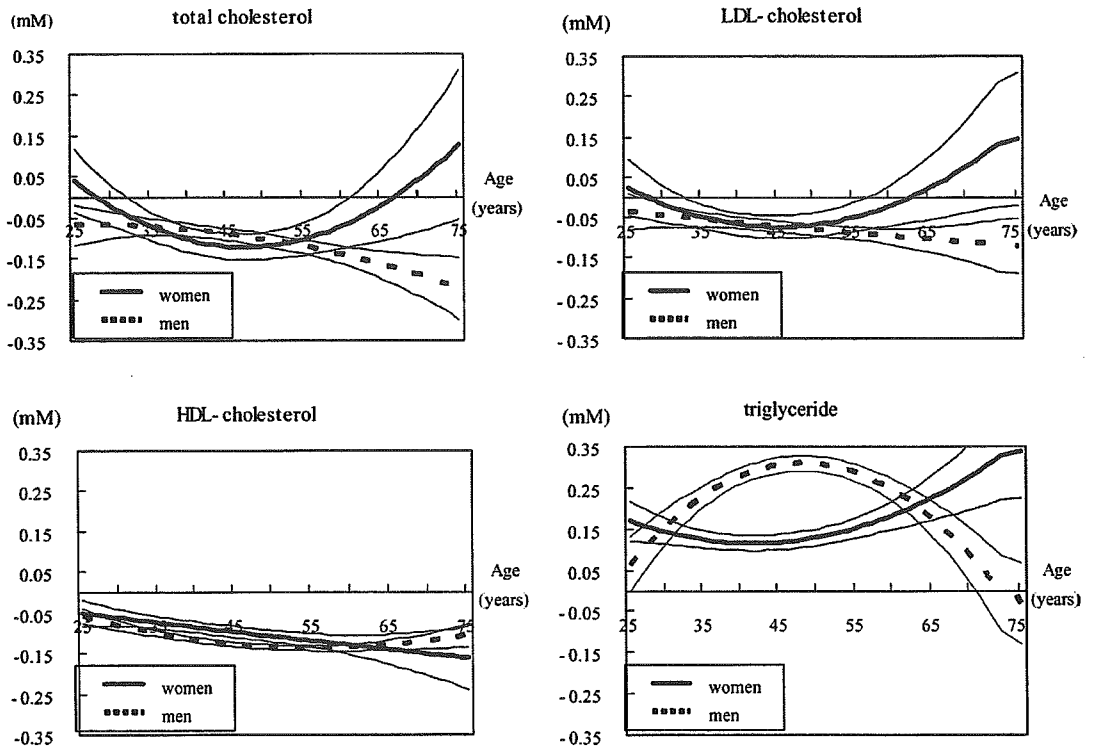

Fig. 3. The difference of estimated lipid levels (the lipid levels of smoker–those of nonsmokers) between current smokers and nonsmokers at individual age from 25 years through 75 years based on the longitudinal analysis. The curves show the average of the difference of estimated lipid levels based on the longitudinal analysis of mixed effect model between smokers and nonsmokers at each age. Thin curves indicate 95% CI.

monal changes in females after menopause might be involved in this inverted effect of smoking.

The effect of smoking on triglyceride levels also exhibits dynamic changes with age and gender difference. Based on longitudinal observation, smoking is associated with higher triglyceride levels at any age examined in both genders. In men, the strongest difference in triglyceride levels between smokers and nonsmokers is seen in middle age, and in women the stronger difference is seen after middle age. The reason for this gender difference and age-dependent effect of smoking on triglyceride levels remains unknown.

It seems that plasma enzymes involved in the metabolism of triglycerides and HDL cholesterol are potentially affected by smoking. However, there are conflicting observations. Some laboratories demonstrated that hepatic lipase is increased in smokers [16], and others demonstrated no difference between smokers and nonsmokers [17], or decreased hepatic lipase in smokers [18]. The hepatic lipase has been shown to be activated in smokers, and lectin:cholesterol acyl transferase activity has been shown to be unchanged [19] or decreased [17] compared with nonsmokers. Plasma cholesterol ester transfer protein activity has been shown to be marginally decreased in smokers in one study [17] and increased in another [19]. Plasma post-heparin lipoprotein lipase activity has been shown not to differ between smokers and nonsmokers in some studies [18,20] and to be increased in smokers in another study [17]. The reasons for these conflicting results on the effect of smoking on plasma enzymes regulating serum lipids and lipoproteins levels are not clear, but it is possible that the effect of smoking on these enzymes is dependent on the gender, age, genetic background, or ethnicity of the subjects.

It should be noted that some selection bias such as healthy worker bias may exist in our study, since most of the subjects were healthy office workers. In addition, the subjects may be aware of their lipid levels, since they had received annual examinations at a health examination center. There is another limitation of this study. Previous observations suggest that the effect of smoking on serum lipid levels is dose-dependent [4,6]. In this study, the data of smoking level in individuals were not available. In addition, alcohol consumption has an effect on serum lipid levels [21]. However, in the present study, the serum lipid levels were not adjusted to account for variations of alcohol consumption.

In the present study, we observed that the effect of smoking on serum lipid levels is age-dependent and that there is a gender difference based on the cross-sectional as well as longitudinal analysis. In men, smoking is associated with lower total and LDL cholesterol at any given age between 25 and 75 years. In women younger than 60 years, smoking is associated with lower cholesterol, but after 60–65 years smoking is associated with higher cholesterol levels. HDL cholesterol levels were lower in male and female smokers than in nonsmokers at most of the age groups examined. Smoking is

associated with higher triglyceride levels in any age examined in both genders except in males above 70 years. In men, the greatest difference in triglyceride levels between smokers and nonsmokers is seen in middle age, and in women, the greatest difference is seen after middle age.

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ORIGINAL ARTICLE

Preproghrelin Leu72Met variant contributes to overweight in middle-aged men of a Japanese large cohort

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Objective: To investigate whether Leu72Met polymorphism of the preproghrelin gene is associated with overweight/obesity in middle-aged and older Japanese.
Design: Cross-sectional analysis.
Subjects: A total of 2238 community-dwelling middle-aged and older Japanese people (age: 40–79 years) who participated in the first wave of examinations in the National Institute for Longevity Sciences – Longitudinal Study of Aging from April 1998 to March 2000.
Measurements: The Leu72Met polymorphism of prepoghrelin gene, anthropometric variables including body weight, body mass index (BMI), waist circumference, waist-to-hip ratio and whole-fat mass and biochemical variables including serum lipid levels, fasting plasma glucose, insulin and homeostasis model assessment for insulin resistance.
Results: The frequencies of the Leu72Leu, Leu72Met and Met72Met alleles were 63.4, 32.7 and 4.0%, respectively. No differences in the genotype distributions of the Leu72Met polymorphism were found between genders or age groups, and no significant associations were observed between polymorphism and anthropometric variables in women and older men. However, middle-aged men who were 72Met allele carriers showed a higher body weight change from body weight at 18 years of age, as well as a higher waist circumference and a tendency to a higher waist-hip-ratio than noncarriers. Although there were no significant differences in the genotype distribution according to BMI in women and older men, a significantly higher frequency of the 72Met allele was found in the higher BMI group (BMI$\geq$25 kg/m^2) of middle-aged men than in the normal-weight group. No significant associations were observed between polymorphism and serum lipid, glucose or insulin levels.
Conclusions: These results suggest that the 72Met allele of the preproghrelin gene is a contributing factor for midlife weight change in men.
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Keywords: ghrelin; polymorphism; preproghrelin; lipid metabolism; glucose metabolism

Introduction

Ghrelin has been shown to be the natural ligand of the previously identified 'orphan' growth hormone secretagogue receptor.[1] Although widely expressed in many tissues, ghrelin is most abundantly produced by the stomach.[1] Ghrelin is much more than a mere natural growth hormone secretagogue, however: it has been found to have profound growth hormone-independent weight- and appetite-increasing effects.[2] Ghrelin stimulates food intake in both rodents and humans,[2,3] and is strongly involved in the regulation of energy homeostasis.[4] This suggests that derangement in the ghrelin system could play a role in obesity. In addition, ghrelin may affect carbohydrate and lipid metabolisms.[5,6]

Recently, three major polymorphisms in the human ghrelin gene were described.[7] One of these nucleotide changes, a single-base substitution C214A with Met replacing Leu at codon 72 in the preproghrelin amino-acid sequence, seems to be associated with an earlier onset of obesity,[7–9] but it has also been proposed that 72Met could provide protection against the accumulation of fat.[10] Thus, previous studies on preproghrelin genetic variants have arrived at contradictory findings as to their role in obesity. Additionally, most studies have had only child and adoles-

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cent subjects, whereas few studies have targeted the middle aged or elderly, or randomly sampled community-dwelling individuals.

The aim of the present study was to test whether genetic variants in the preproghrelin gene (Leu72Met) could play a role in predisposing carriers to overweight/obesity or be associated with anthropometric data, serum lipid levels and values related with glucose metabolisms in a middle-aged to elderly Japanese population.

Materials and methods

Subjects

The present study consisted of a cross-sectional analysis of 1110 women and 1128 men who participated in the first wave of examinations in the National Institute for Longevity Sciences – Longitudinal Study of Aging (NILS-LSA) from April 1998 to March 2000. The subjects of the NILS-LSA were male and female residents 40–79 years old. The population of Obu city and Higashiura town in the Aichi prefecture in central Japan was stratified by both age and gender, and randomly selected from resident registrations in cooperation with the local governments. The number of male and female participants was to be the same to test gender difference. Age at the base line is to be 40–79 years and the number of participants in each decade (1940s, 1950s, 1960s, 1970s) is to be the same. The examinations include various areas of gerontology and geriatrics such as medical examinations, anthropometry, body composition, physical functions, physical activities, psychological assessments, nutritional analysis and molecular epidemiology. The subjects will be followed up every 2 years. The details of the NILS-LSA have been described elsewhere.[11] Randomly selected men and women were invited by mail to attend an explanatory meeting. At that meeting, the procedures for each examination and the follow-up schedule were fully explained. Written, informed consent to the entire procedure was obtained from each participant. The study was approved by the Ethics Committee of the National Institute for Longevity Sciences.

Anthropometric variables

Body weight was measured to the nearest 0.01 kg using a digital scale, height was measured to the nearest 0.1 cm using a wall-mounted stadiometer and body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Waist circumference and waist-to-hip ratio (WHR) were used as the indices for body fat distribution in this study. Waist-to-hip ratio was calculated as the ratio of waist circumference measured at the mid-point between the anterior superior iliac crest and the lowest rib-to-hip circumference. Whole-body fat mass, assessed by dual-energy X-ray absorptiometry (QDR-4500; Hologic, Madison, OH, USA), was used as an index for determining body composition. The subjects' weight at 18 years of age was obtained by questionnaire. Weight change was defined as the current weight minus the weight at 18 years of age.

Biochemical assays of blood

An antecubital blood sample was drawn from each subject after an overnight fast. Serum total cholesterol, triglycerides and low-density lipoprotein cholesterol were determined enzymatically, serum high-density lipoprotein cholesterol was measured by the heparin–manganese precipitation method and fasting plasma glucose was assayed by the glucose oxidase method. Lipoprotein (a) was measured in plasma using a commercially available ELISA. Plasma insulin was measured by radioimmunoassay. The homeostasis model assessment for insulin resistance (HOMA-IR) was calculated as fasting serum insulin (μU/ml) × fasting plasma glucose (mmol/l)/22.5.[12]

Determination of preproghrelin genotypes

Genotypes were determined using a fluorescence-based allele-specific DNA primer assay system (Toyobo Tsuruga Gene Analysis, Tsuruga, Japan). The polymorphic regions (Leu72Met (C214A)) of preproghrelin were amplified by polymerase chain reaction with allele-specific sense primers labeled at the 5′-end with either fluorescein isothiocyanate (5′-CCG ACC CGG ACT TCC XTT-3′) or Texas red (5′-GTA CCG ACC CGG ACT TCC XG-3′) and with an antisense primer labeled at the 5′-end with biotin (5′-GGC TCC GCC CGG AAG ATG-3′). The reaction mixtures (25 μl) contained 20 ng of DNA, 5 pmol of each primer, 0.2 mmol/l of each deoxynucleoside triphosphate, 2.5 mmol/l $MgCl_2$ and 1 U of rTaq DNA polymerase (Toyobo Co., Ltd, Osaka, Japan) in polymerase buffer. The amplification protocol consisted of initial denaturation at 95°C for 5 min, followed by 35 cycles of denaturation at 95°C for 30 s, annealing at 60°C for 30 s and extension at 68°C for 30 s; a final extension was conducted at 68°C for 2 min. Further details are provided elsewhere.[13]

Data analysis

Quantitative data were compared among three groups by one-way analysis of variance and the Tukey–Kramer *post hoc* test, and between two groups by the unpaired Student's *t*-test. Allele frequencies were estimated by the gene-counting method, and the χ^2 test was used to identify any significant departure from Hardy–Weinberg equilibrium. In the analyses to examine the association between genotypes and lipid or glucose metabolisms, participants who were being treated with lipid-lowering medications or oral hypoglycemic agents or insulin were excluded. Unless indicated otherwise, a *P*-value of <0.05 was considered to be statistically significant. The data were analyzed with the Statistical Analysis System (SAS), release 8.2.

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Results

Genotype frequencies for the preproghrelin Leu72Met polymorphism were CC (Leu72Leu) 0.634, CA (Leu72Met) 0.327 and AA (Met72Met) 0.04. These frequencies are consistent with those expected under Hardy–Weinberg equilibrium. There were no significant differences in the genotype distributions of preproghrelin Leu72Met polymorphism between men and women, or among the different age groups (Table 1).

As shown in Table 2, although there were no differences in current body weight and body weight at 18 years of age between genotypes, middle-aged men who were 72Met allele carriers showed both a higher body weight change from body weight at 18 years of age ($P=0.013$, CC vs CA/AA) and higher waist circumference ($P=0.038$, CC vs CA/AA) than noncarriers. Among the middle-aged men in the present study, the Leu72Leu genotype was associated with the lowest BMI (trend, $P=0.049$), and the 72Met allele carriers tended to have a higher WHR ($P=0.062$, CC vs CA/AA) than subjects with the Leu72Leu genotype. However, no differences in anthropometric measurements among Leu72Met genotypes were observed in older men, or in female cohorts (Table 3).

In order to assess the association of the Leu72Met polymorphism with overweight or obesity, genotype and allele frequencies were compared among normal-weight ($BMI<25\,kg/m^2$) and overweight/obese ($BMI\geqslant25\,kg/m^2$) groups (Table 4). Although there were no significant differences in the genotype distribution according to BMI in women and older men, a significantly higher frequency of CA, AA or CA/AA was found in the higher BMI group than in the normal-weight group among middle-aged men.

No significant association was observed between the three genotypes and serum lipid, fasting glucose, insulin, HbA1c or HOMA-IR levels in men and women (Table 5). The preproghrelin Leu72Met genotypes showed similar allele frequencies in diabetic individuals and in non-diabetic controls (data not shown).

Table 1 Distribution of Leu72Met genotype of preproghrelin gene of the subjects

	n	CC		CA		AA		CA/AA	
		n	%	n	%	n	%	n	%
Total	2228	1412	63.4	728	32.7	88	4.0	816	36.6
Men*†	1121	709	63.3	371	33.1	41	3.7	412	36.8
Women	1107	703	63.5	357	32.3	47	4.3	404	36.5
Age (years)‡§									
40–49	562	364	64.8	177	31.5	21	3.7	198	35.2
50–59	556	357	64.2	177	31.8	22	4.0	199	35.8
60–69	560	359	64.1	180	32.1	21	3.8	201	35.9
70–79	550	332	60.4	194	35.3	24	4.4	218	39.6

*CC, CA, AA, men vs women, $\chi^2=0.6159$, $P=0.7350$; †CC, CA/AA, men vs women, $\chi^2=0.0160$, $P=0.8995$; ‡CC, CA, AA, age groups, $\chi^2=2.9716$, $P=0.8124$; §CC, CA/AA, age groups, $\chi^2=2.9149$, $P=0.4049$.

Table 2 Anthropometric variable of men according to age group and Leu72Met polymorphism of preproghrelin gene

	Middle aged (n = 563)								*Older (n = 556)*							
	CC		*CA*		*AA*		*CA/AA*		*CC*		*CA*		*AA*		*CA/AA*	
	Mean	*s.e.*	*Mean*	*s.e.*	*Mean*	*s.e.*	*Mean*	*s.e.*	*Mean*	*s.e.*	*Mean*	*s.e.*	*Mean*	*s.e.*	*Mean*	*s.e.*
Weight (kg)	64.6	0.5	65.6	0.7	67.5	2.0	65.8	0.6	59.7	0.5	59.1	0.6	57.2	1.9	58.9	0.6
Weight at 18 years (kg)	56.9	0.4	56.4	0.5	57.2	1.5	56.5	0.5	55.3	0.4	54.5	0.5	55.4	1.5	54.6	0.5
Weight change from 18 years (kg)	7.7	0.4	9.2	0.6	10.3	1.7	9.3	0.5*	4.6	0.5	4.9	0.7	1.8	2.1	4.6	0.7
Height (cm)	167.0	0.3	167.2	0.4	166.3	1.4	167.2	0.4	162.0	0.3	161.9	0.4	161.7	1.2	161.9	0.4
BMI (kg/m^2)	23.1	0.1	23.4	0.2	24.4	0.6	23.5	0.2†	22.7	0.2	22.5	0.2	21.9	0.6	22.4	0.2
Waist circumference (cm)	82.2	0.4	83.4	0.6	84.9	1.8	83.6	0.6‡	82.4	0.5	82.1	0.6	80.5	1.9	81.9	0.6
Hip circumference (cm)	92.2	0.3	92.7	0.4	93.4	1.1	92.8	0.3	90.0	0.3	89.6	0.4	88.7	1.1	89.5	0.3
Waist-hip-ratio	0.891	0.003	0.899	0.004	0.907	0.012	0.899	0.004§	0.913	0.003	0.914	0.005	0.904	0.014	0.913	0.004
Fat mass (kg)	20.6	0.2	21.2	0.3	20.8	1.0	21.2	0.3	21.9	0.2	22.0	0.3	22.1	0.9	22.0	0.3

Except for *, †, ‡ and §, no significant trends and differences were detected among three groups (CC, CA and AA) and between two groups (CC and CA/AA). *$P=0.013$ (CC vs CA/AA); †$P=0.049$ (trend); ‡$P=0.038$ (CC vs CA/AA); §$P=0.062$ (CC vs CA/AA). Analysis of variance and the Tukey–Kramer *post hoc* test or the unpaired Student's *t*-test between two groups. BMI = Body mass index.

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Table 3 Anthropometric variable of women according to age group and Leu72Met polymorphism of preproghrelin gene

	Middle aged (n = 553)								*Older (n = 552)*							
	CC		*CA*		*AA*		*CA/AA*		*CC*		*CA*		*AA*		*CA/AA*	
	Mean	*s.e.*	*Mean*	*s.e.*	*Mean*	*s.e.*	*Mean*	*s.e.*	*Mean*	*s.e.*	*Mean*	*s.e.*	*Mean*	*s.e.*	*Mean*	*s.e.*
Weight (kg)	53.9	0.4	53.9	0.6	54.4	1.6	54.0	0.6	50.8	0.4	50.9	0.6	52.4	1.7	51.1	0.6
Weight at 18 years (kg)	48.8	0.3	49.1	0.4	49.2	1.2	49.1	0.4	47.9	0.4	47.7	0.5	49.2	1.4	47.8	0.5
Weight change from 18 years (kg)	5.2	0.4	4.8	0.6	5.2	1.6	4.9	0.5	3.0	0.5	3.2	0.7	3.1	1.9	3.2	0.7
Height (cm)	154.0	0.3	154.1	0.4	154.4	1.0	154.1	0.3	148.5	0.3	148.6	0.4	147.9	1.2	148.5	0.4
BMI (kg/m^2)	22.7	0.2	22.7	0.2	22.8	0.7	22.7	0.2	23.0	0.2	23.0	0.2	24.1	0.7	23.2	0.2
Waist circumference (cm)	73.5	0.5	73.4	0.6	73.4	1.7	73.4	0.6	76.4	0.5	77.5	0.7	77.8	2.0	77.5	0.7
Hip circumference (cm)	91.5	0.3	91.5	0.4	90.9	1.1	91.4	0.4	89.8	0.3	89.9	0.4	90.8	1.2	90.0	0.4
Waist-hip-ratio	0.802	0.003	0.801	0.005	0.806	0.012	0.802	0.004	0.849	0.004	0.860	0.005	0.855	0.014	0.860	0.005
Fat mass (kg)	30.7	0.3	30.3	0.4	30.5	1.0	30.3	0.3	32.3	0.3	32.7	0.4	33.3	1.1	32.7	0.4

No significant trends and differences were detected among three groups (CC, CA and AA) and between two groups (CC and CA/AA). Analysis of variance and the Tukey–Kramer *post hoc* test or the unpaired Student's *t*-test between two groups. BMI = Body mass index.

Table 4 Distribution of Let72Met genotype of preproghrelin gene

	n	*CC*		*CA*		*AA*		*CA/AA*		P	P*
		n	%	n	%	n	%	n	%		
All age groups											
Men											
BMI < 25 kg/m^2	854	546	63.9	280	32.8	28	3.3	308	36.1	0.411	0.393
BMI > 25 kg/m^2	267	163	61.1	91	34.1	13	4.9	104	39.0		
Women											
BMI < 25 kg/m^2	866	558	64.4	273	31.5	35	4.0	308	35.6	0.454	0.224
BMI > 25 kg/m^2	241	145	60.2	84	34.9	12	5.0	96	39.8		
Middle ages (younger than 60 years)											
Men											
BMI < 25 kg/m^2	413	280	67.8	123	29.8	10	2.4	133	32.2	0.032	0.036
BMI > 25 kg/m^2	151	88	58.3	54	35.8	9	6.0	63	41.7		
Women											
BMI < 25 kg/m^2	446	288	64.6	139	31.2	19	4.3	158	35.4	0.694	0.395
BMI > 25 kg/m^2	108	65	60.2	38	35.2	5	4.6	43	39.8		
Older (60 years or older)											
Men											
BMI < 25 kg/m^2	441	266	60.3	157	35.6	18	4.1	175	39.7	0.692	0.394
BMI > 25 kg/m^2	116	75	64.7	37	31.9	4	3.5	41	35.3		
Women											
BMI < 25 kg/m^2	420	270	64.3	134	31.9	16	3.8	150	35.7	0.604	0.389
BMI > 25 kg/m^2	133	80	60.2	46	34.6	7	5.3	53	39.9		

P-value by the χ^2 analysis among groups CC, CA and AA. *P**-value by the χ^2 analysis between groups CC and CA/AA. BMI = Body mass index.

Discussion

We observed that the frequency of the 72Met allele of the present cohort was 36.6%. It has been demonstrated that the frequency of the 72Met allele of the preproghrelin gene is approximately 8% in the Caucasian population and approximately 2% in the black population in three different cohorts.[10] Compared with these previous studies, the frequency of the 72Met allele in our Japanese cohort was much higher than that observed in Caucasian or African populations, probably reflecting genetic/ethnic heterogeneity.

The Leu72Met polymorphism of preproghrelin was previously found in a group of obese French children and adolescents.[9] In this case, a significant association was observed between the 72Met allele and earlier age of onset of obesity. Additionally, obese Italian children and adoles-

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Table 5 Metabolic variables and Leu72Met polymorphism of preproghrelin gene

	Men									Women								
	n	CC		CA		AA		CA/AA		n	CC		CA		AA		CA/AA	
		Mean	s.e.	Mean	s.e.	Mean	s.e.	Mean	s.e.		Mean	s.e.	Mean	s.e.	Mean	s.e.	Mean	s.e.
Total cholesterol (mM)[a]	1044	5.48	0.03	5.49	0.05	5.42	0.14	5.48	0.04	996	5.83	0.03	5.92	0.05	5.83	0.14	5.91	0.05
Triglyceride (mM)[a]	1027	1.48	0.04	1.53	0.06	1.32	0.16	1.51	0.10	977	1.20	0.03	1.23	0.04	1.21	0.10	1.23	0.04
HDL-C (mM)[a]	1044	1.49	0.01	1.48	0.02	1.49	0.06	1.48	0.02	996	1.71	0.02	1.71	0.02	1.71	0.06	1.71	0.02
LDL-C (mM)[a]	1035	3.40	0.03	3.42	0.05	3.36	0.13	3.42	0.04	980	3.57	0.03	3.63	0.05	3.62	0.14	3.63	0.05
Lipoprotein (a) (mM)[a]	1034	0.39	0.02	0.37	0.03	0.35	0.07	0.37	0.02	980	0.40	0.02	0.46	0.03	0.33	0.07	0.44	0.02
Glucose (mM)[b]	1049	5.71	0.04	5.74	0.05	5.91	0.15	5.75	0.05	1051	5.51	0.03	5.52	0.05	5.20	0.13	5.49	0.04
Insulin (μU/ml)[b]	1048	8.28	0.22	8.21	0.31	7.63	0.91	8.15	0.29	1050	8.23	0.19	8.57	0.27	8.02	0.74	8.51	0.25
HbA1c (%)[b]	1064	5.21	0.02	5.26	0.03	5.41	0.10	5.28	0.03	1071	5.16	0.02	5.15	0.03	5.06	0.07	5.14	0.02
HOMA-IR[b]	1048	2.20	0.08	2.13	0.11	2.06	0.33	2.13	0.11	1050	2.07	0.06	2.20	0.09	1.88	0.26	2.16	0.09

[a]Analysis of subjects who were not under lipid treatment. Adjusted for age. [b]Analysis of subjects who were not on oral hypoglycemic agents or insulin. Adjusted for age. No significant differences were observed in any metabolic values among three different genotypes (CC, CA and AA) or between CC and CA/AA. Analysis of variance and the Tukey–Kramer *post hoc* test or the unpaired Student's *t*-test between two groups. Abbreviations: HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment for insulin resistance; LDL, low-density lipoprotein.

cents with the preproghrelin 72Met allele have also been reported to become obese earlier than homozygous patients for the wild Leu72 allele, even though 72Met allelic frequency was similar between obese and control groups.[8] These findings were not confirmed, however, in a group of extremely obese German children.[14] In addition, one report suggests that preproghrelin 72Met carrier status may be protective against fat accumulation.[10] A limited number of observations have been made on the relationship between preproghrelin Leu72Met polymorphism and overweight/obesity in middle-aged subjects, and no report has been published to date on older subjects. In a Swedish middle-aged female obese cohort, no difference of 72Met allele frequency was observed between obese subjects and controls.[7] However, the self-reported age of onset of weight problems tended to be lower among 72Met allele carrier obese subjects than among those without this allele.

In the present study, we observed a significant effect of the preproghrelin variant on overweight/obesity only in middle-aged men, as the 72Met allele was more commonly observed among overweight/obese middle-aged men. We also demonstrated that body weight change from weight at 18 years of age is associated with Leu72Met variants, given that middle-aged men with the 72Met allele had a greater body weight change than Leu72 homologous subjects. Similar trends were also observed for BMI, waist circumference and WHR in middle-aged men, but not in older men or in women when our population was subdivided into three subgroups according to preproghrelin genotype. Consequently, the 72Met allele may contribute to body weight change from adolescence to middle age in men but not in women. We observed the absence of the effect of Leu72Met genotypes on the anthropometric measurements in older man. Although we do not know the exact reasons, the effects of aging or environmental influences may overcome the genetic influence on the anthropometric measurements. The limitation of our study is that the weight at 18 years was recalled by the participants in the present study, as the documented measurements of weight at 18 years of age were not available. Although several studies have observed that adults are able to recall their earlier weights fairly accurately,[15] it is possible that the reported weight might not be accurate or under-reported. In fact, it has been reported that overweight women underestimated their earlier weights and that lean men overestimated their earlier weight.[16]

Based on recent studies, it appears that ghrelin may play a role in the glucose and lipid metabolisms. However, only limited data are currently available with regard to the effect of ghrelin polymorphism on these metabolisms. It has been reported that Leu72Met polymorphism is associated with triglyceride or lipoprotein (a) levels.[10,17] In the present study, however, we observed no association between serum lipid levels, fasting glucose, insulin, HbA1c or HOMA-IR levels and preproghrelin Leu72Met genotypes.

In the present study of a community-dwelling Japanese middle-aged to elderly cohort, we demonstrated that the 72Met allele of the preproghrelin gene is a contributing factor for midlife weight change in men but not in women or elderly men. However, Leu72Met polymorphism was not found to be associated with the metabolic variables studied.

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Underuse of Medications for Chronic Diseases in the Oldest of Community-Dwelling Older Frail Japanese

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OBJECTIVES: To test the following hypotheses: (1) the rate of polypharmacy, defined as six or more prescribing medications, is lower in the oldest old (≥85) than in younger older people (65–84); (2) beneficial medication use is lower in the oldest old; (3) the underuse of these medications in the oldest old is associated with physical or cognitive impairment or comorbid conditions.

DESIGN: A cross-sectional study of the baseline data from the Nagoya Longitudinal Study for Frail Elderly.

SETTING: Community-based.

PARTICIPANTS: One thousand eight hundred seventy-five community-dwelling older people (632 men, 1,243 women).

MEASUREMENTS: The data, which were collected at the patients' homes or from care-managing center records, included the clients' demographic characteristics, depression status as assessed using the short version of the Geriatric Depression Scale, a rating for basic activities of daily living (ADLs), prescribed medications, and physician-diagnosed chronic diseases.

RESULTS: The oldest old had less polypharmacy even after controlling for ADLs and comorbid conditions. The underuse of beneficial medications for the oldest old was observed after adjusting for ADLs, cognitive impairment, comorbid conditions, antithrombotic agents for subjects with a history of cardiovascular diseases, acetylcholinesterase inhibitors for those with dementia, and antidepressants for those with depression. However, being aged 85 and older was not associated with the underuse of hypoglycemic and antihypertensive agents by those with diabetes mellitus and hypertension, respectively.

CONCLUSION: Among community-dwelling frail older people, the rate of polypharmacy is lower in the oldest members than in the younger ones. The underuse of prescribed medications for chronic diseases/conditions of frail older people is common but not for all conditions. J Am Geriatr Soc 2006.

Key words: polypharmacy; undertreatment; elderly

It has been reported that the underuse of medications, defined as the omission of drug therapy that is indicated for the treatment or prevention of a disease or condition, is an important and increasingly recognized problem in older people.[1,2] The underprescribing of drugs seems to have a negative effect on health outcomes for older people,[3,4] but apart from concern about the risks of the excess prescribing of inappropriate or unnecessary drug therapy for older people,[5,6] there is still insufficient knowledge about the adverse consequences associated with the underprescribing of beneficial drug therapies. It is not known whether all kinds of medications are underused in older people or whether specific medications for specific chronic diseases or conditions are selectively underused in older people. In addition, knowledge about the factors that influence the underuse of medications for the common chronic diseases of older people is sparse. There is also a lack of knowledge about how functional and psychological factors influence the use of medication by physicians or how frailty and comorbidity affect drug use by older people.

The national policy in not only Japan but also Western countries is to enable elderly people to retain their independence as long as possible, to have a high quality of life, and to continue living at home as long as they can. It is essential to prevent frail older people from suffering from recurrent diseases and additional illnesses that would require them to receive care in an acute setting or to be admitted to a nursing home or to cause mortality. Therefore, preventive medication for chronic diseases/conditions is important for frail older people living in a community setting.

In the present study targeting frail, community-dwelling elderly persons (≥65), the following hypotheses were tested: (1) the rate of multiple medication use is lower in the oldest people (≥85) than in younger ones (65–84); (2) beneficial medication use for common chronic conditions such as cardiovascular disease (CVD), dementia, depression,

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diabetes mellitus, and hypertension is lower in the oldest people than in younger ones; and (3) the underuse of these medications in the oldest old is associated with physical impairment, cognitive impairment, or comorbid conditions.

METHODS

Study Design and Subjects

The present study consisted of a cross-sectional analysis of 1,875 elderly persons (632 men, 1,243 women) who participated in the Nagoya Longitudinal Study for Frail Elderly (NLS-FE). The study population was community-dwelling older people (≥65) eligible for long-term care insurance (LTCI) who lived in Nagoya City, Japan, and were provided various home care services from the Nagoya City Health Care Service Foundation for Older People, which has 17 visiting nursing stations associated with care-managing centers. Japan introduced a universal-coverage LTCI program in April 2000[7,8] that covers care for people aged 65 and older and people aged 40 and older with 15 specific diseases such as cerebrovascular disease and presenile dementia. Under the LTCI program, care levels (Level 0 to Level 5) are determined according to eligibility criteria. Older people in the community who are eligible for LTCI are frail and chronically ill, have physical and mental problems, and are easy to admit to an acute hospital or institute setting. During the registration period for the NLS-FE (November 1, 2003, to December 31, 2003), 1,875 of 3,630 elderly clients agreed to participate in this study. The NLS-FE participants were scheduled to undergo comprehensive in-home assessments at baseline and 6, 12, and 24 months by trained nurses. In the present study, the cross-sectional data from the baseline assessment were used. Informed consent for participation was obtained verbally from the patients or, for those with substantial cognitive impairment, from a surrogate (usually the closest relative or legal guardian), as well as from caregivers, according to procedures approved by the institutional review board of Nagoya University Graduate School of Medicine.

Data Collection

Three hundred twenty-eight nurses visited the clients' homes and collected the data using standardized interviews with patients or surrogates and caregivers and from care-managing center records. The data included clients' demographic characteristics, depressive symptoms as assessed using the short version of the Geriatric Depression Scale (GDS-15),[9] and a rating for seven basic activities of daily living (ADLs) (feeding, bathing, grooming, dressing, toileting, walking, and transferring), with summary scores ranging from 0 (total disability) to 20 (no disability).[10]

Information obtained from care-managing center records included the following physician-diagnosed chronic conditions: ischemic heart disease, congestive heart failure, liver diseases, cerebrovascular disease, diabetes mellitus, dementia, chronic obstructive pulmonary disease, renal disease, cancer, hypertension, pressure ulcer, depression, and diseases constituting the Charlson Comorbidity Index,[11] which represent the sum of a weighted index that takes into account the number and seriousness of preexisting comorbid conditions. In the present study, only a limited number of subjects diagnosed for depression by a physician according to the care-managing center records were observed. Therefore, the participants were considered to be depressed if their GDS-15 score was 6 or higher.

The data also included the number of prescribed medications and their corresponding therapeutic classes, including antihypertensive drugs, antiplatelets, anticoagulants, antipsychotic medications (including antidepressants), hypoglycemics, nonsteroidal antiinflammatory drugs and acetaminophen, anti-Alzheimer's disease drugs (acetylcholinesterase inhibitors), gastrointestinal medications, and insulin. The information about regular prescribed medications was recorded in interviews with patients and caregivers and taken from prescription records and classified by nurses using standard instruments. Clients eligible for LTCI have their own primary care physicians, who submit a report on their clinical status every 6 months.

Statistical Analysis

Analysis of variance with a Bonferroni correction for multiple comparisons was used to determine differences between age groups (65–74, 75–84, and ≥85) for continuous variables, and the Kruskal-Wallis test was used to test categorical variables. The chi-square test was used to compare the presence of chronic diseases/conditions or the number of prescription medications used between age groups. Univariate and multivariate logistic regression was used to determine which characteristics of older people predicted multiple medication use or the underuse of beneficial medication. For the logistic regression analysis, the ADL score (range 0–20) was categorized into three groups with approximately equal number of participants in each group: high function (≥18), mid function (12–17), and low function (≤11). The number of prescribed medications was also categorized into four groups (0, 1–2, 3–5, and ≥6). All analyses were performed using SPSS version 11.0 (SPSS, Inc., Chicago, IL).

RESULTS

Table 1 shows the characteristics of the participants according to age group. ADL score was lowest in the oldest old (≥85). The prevalence of a history of coronary heart disease, hypertension, and dementia increased, and the prevalence of diabetes mellitus decreased, with age. Polypharmacy, defined as six or more prescribed medications, decreased with age. To identify the factors influencing polypharmacy in frail older people in the community, logistic regression analysis was conducted (Table 2). Participants with congestive heart failure (odds ratio (OR) = 1.66, 95% confidence interval (CI) = 1.09–2.55), coronary heart disease (OR = 3.05, 95% CI = 2.16–4.31), and diabetes mellitus (OR = 1.51, 95% CI = 1.06–2.15) were more likely to be receiving multiple medications according to multivariate analysis. In contrast, participants with dementia were less likely to have been prescribed multiple medications (OR = 0.64, 95% CI = 0.48–0.84). The oldest old had less polypharmacy using univariate analysis (OR = 0.64, 95% CI = 0.49–0.82) and multivariate analysis (OR = 0.55, 95% CI = 0.39–0.77) controlled for sex, ADL dependency, and the presence of common chronic diseases.

Table 1. Characteristics of Community-Dwelling Frail Older People Stratified by Age

Characteristic	Total (N = 1,875)	Age 65–74 (n = 433)	Age 75–84 (n = 827)	Age ≥85 (n = 615)	*P*-value
Men/women (% of men/total)	632/1,243 (33.7)	191/242 (44.1)	275/552 (33.3)	166/449 (27.0)	<.001
Age, mean ± SD*	80.6 ± 7.7	70.5 ± 2.7	79.4 ± 2.8	89.3 ± 3.6	<.001
Activity of daily living score, mean ± SD (range 0–20)†	12.8 ± 6.6	12.6 ± 6.8	13.6 ± 6.3	11.8 ± 6.7	<.001‡
Charlson Comorbidity Index, mean ± SD†	2.0 ± 1.6	2.2 ± 1.7	1.9 ± 1.5	2.0 ± 1.5	.003§
GDS-15 score, mean ± SD (range 0–15)†	6.6 ± 3.6	6.8 ± 3.8	6.5 ± 3.6	6.5 ± 3.6	.38
Chronic diseases (% of total)					
Congestive heart failure	8.5	1.8	6.5	15.7	<.001
Coronary heart disease	12.2	7.0	12.5	15.2	<.001
Cerebrovascular disease	34.3	40.1	32.4	33.1	.03
Diabetes mellitus	12.0	16.1	12.3	8.9	.003
Dementia	34.4	24.8	31.0	45.7	<.001
Hypertension	24.3	19.4	24.5	27.3	.01
Depression (GDS-15 score ≥6)	57.2	58.4	56.7	57.1	.27
Cancer	9.1	9.1	8.8	9.6	.90
Use of medications (% of total)					
0	5.1	3.3	3.3	8.9	<.001
1–2	16.8	14.0	15.7	20.3	
3–5	41.9	41.9	43.2	40.2	
≥6	36.2	40.9	37.8	30.6	

* Analysis of variance or † Kruskal-Wallis was used for analysis; chi-square test was used for others.
‡ Aged 65–74 vs 75–84, $P = .007$; 65–74 vs ≥85, $P = .003$; 75–84 vs ≥85, $P < .001$.
§ Aged 65–74 vs 75–84, $P < .001$; 65–74 vs ≥85, $P = .02$; 75–84 vs ≥85, $P = .08$.
SD = standard deviation; GDS-15 = 15-item Geriatric Depression Scale.

Logistic regressions were conducted to evaluate the extent to which age group and the characteristics of older people were independent predictors of being prescribed essential medications. Univariate analysis showed the rates of prescription of antithrombotic agents (antiplatelet or warfarin), acetylcholinesterase inhibitors, and antidepressants in older people with a history of CVD (including coronary heart disease and stroke), dementia, and depressive symptoms, respectively, declined substantially with age (Table 3), but in participants with diabetes mellitus or hypertension, age did not influence hypoglycemic (oral hypoglycemic drugs or insulin) or antihypertension use. Being female was associated with the underuse of antithrombotic agents in older people with a history of CVD (male: OR = 1.80, 95%

Table 2. Logistic Regression Analysis for Polypharmacy

Characteristic	Univariate Odds Ratio (95% Confidence Interval)	Multivariate Odds Ratio (95% Confidence Interval)
Age (reference: 65–74)		
75–84	0.88 (0.69–1.11)	0.71 (0.53–0.95)
≥85	0.64 (0.49–0.82)	0.55 (0.39–0.77)
Male (reference: female)	1.26 (1.03–1.53)	1.05 (0.82–1.35)
Activity of daily living score (range 0–20) (reference: high function (≥18))		
Mid function (12–17)	1.26 (0.99–1.59)	1.35 (1.03–1.79)
Low function (≤11)	0.94 (0.74–1.19)	1.38 (0.99–1.89)
Presence of chronic diseases (reference: absence)		
Congestive heart failure	1.91 (1.36–2.68)	1.66 (1.09–2.55)
Coronary heart disease	2.65 (1.98–3.54)	3.05 (2.16–4.31)
Cerebrovascular disease	0.96 (0.78–1.18)	1.10 (0.84–1.43)
Dementia	0.59 (0.47–0.73)	0.64 (0.48–0.84)
Diabetes mellitus	1.59 (1.19–2.13)	1.51 (1.06–2.15)
Depression (Geriatric Depression Scale-15 score ≥6)	1.27 (1.02–1.58)	1.26 (0.99–1.59)
Hypertension	0.87 (0.69–1.08)	0.82 (0.62–1.08)

Table 3. Univariate Analysis of Characteristics Associated with Participants Receiving Medication

Characteristic	Antithrombotic Agent Use for History of CVD		Acetylcholinesterase Inhibitor Use for Dementia		Antidepressant Use for Depression		Hypoglycemic Use for Diabetes Mellitus		Antihypertensive Use for Hypertension	
	n, Odds Ratio (95% Confidence Interval)									
Age										
65–74	163,	1.00 —	83,	1.00 —	173,	1.00 —	60,	1.00 —	83,	1.00 —
75–84	290,	0.75 (0.51–1.10)	205,	1.00 (0.51–1.94)	348,	0.68 (0.34–1.35)	94,	1.56 (0.73–3.32)	196,	2.05 (0.99–4.27)
≥85	219,	0.48 (0.32–0.73)	202,	0.44 (0.21–0.93)	220,	0.40 (0.16–0.96)	48,	0.55 (0.25–1.26)	155,	1.92 (0.89–4.11)
Sex										
Female	391,	1.00 —	336,	1.00 —	465,	1.00 —	129,	1.00 —	302,	1.00 —
Male	281,	1.80 (1.32–2.46)	154,	0.79 (0.45–1.38)	276,	0.69 (0.36–1.35)	73,	0.75 (0.40–1.41)	132,	0.56 (0.31–1.03)
Activity of daily living score (range 0–20)										
High function (≥18)	167,	1.00 —	74,	1.00 —	237,	1.00 —	59,	1.00 —	160,	1.00 —
Mid function (12–17)	238,	1.14 (0.77–1.70)	180,	0.50 (0.27–0.93)	272,	0.93 (0.45–1.91)	71,	1.27 (0.56–2.88)	143,	0.88 (0.42–1.88)
Low function (≤11)	265,	0.81 (0.54–1.20)	233,	0.13 (0.06–0.28)	232,	0.88 (0.41–1.89)	72,	0.60 (0.28–1.29)	130,	0.57 (0.28–1.16)
Chronic diseases										
Congestive heart failure										
Absence	613,	1.00 —	438,	1.00 —	624,	1.00 —	189,	1.00 —	363,	1.00 —
Presence	59,	0.89 (0.52–1.54)	51,	0.22 (0.05–0.94)	63,	0.51 (0.12–2.15)	13,	0.30 (0.10–0.94)	42,	2.75 (0.64–11.78)
CVD										
Absence			221,	1.00 —	390,	1.00 —	110,	1.00 —	201,	1.00 —
Presence			268,	0.28 (0.16–0.48)	297,	0.48 (0.23–0.97)	92,	0.71 (0.38–1.31)	204,	1.12 (0.61–2.07)
Dementia										
Absence	380,	1.00 —			507,	1.00 —	130,	1.00 —	236,	1.00 —
Presence	268,	0.67 (0.49–0.93)			161,	1.49 (0.73–3.02)	65,	0.48 (0.25–0.91)	154,	0.62 (0.33–1.14)
Depression										
Absence	198,	1.00 —	120,	1.00 —			67,	1.00 —	154,	1.00 —
Presence	297,	1.26 (0.87–1.81)	161,	1.06 (0.54–2.08)			90,	0.65 (0.31–1.37)	184,	1.30 (0.64–2.62)
Diabetes mellitus										
Absence	580,	1.00 —	424,	1.00 —	597,	1.00 —			328,	1.00 —
Presence	92,	0.89 (0.57–1.40)	65,	0.96 (0.45–2.03)	90,	1.18 (0.48–2.90)			77,	0.72 (0.35–1.48)
Hypertension										
Absence	468,	1.00 —	336,	1.00 —	557,	1.00 —	125,	1.00 —		
Presence	204,	0.54 (0.38–0.76)	154,	0.50 (0.27–0.93)	184,	1.14 (0.58–2.27)	77,	1.15 (0.61–2.19)		

CVD = cardiovascular disease.

Table 4. Multivariate Analysis of Characteristics Associated with Participants Receiving Medication

Characteristic	Antithrombotic Agent Use for History of CVD (n = 480)	Acetylcholinesterase Inhibitor Use for Dementia (n = 280)	Antidepressant Use for Depression (n = 668)	Hypoglycemic Use for Diabetes Mellitus (n = 154)	Antihypertensive Use for Hypertension (n = 302)
	Odds Ratio (95% Confidence Interval)				
Age (reference 65–74)					
75–84	0.90 (0.56–1.42)	0.67 (0.25–1.82)	0.59 (0.28–1.26)	1.39 (0.54–3.54)	1.98 (0.75–5.19)
≥85	0.53 (0.32–0.90)	0.21 (0.06–0.71)	0.33 (0.12–0.91)	0.53 (0.19–1.49)	1.48 (0.55–3.98)
Sex (reference female)					
Male	1.57 (1.08–2.30)	1.20 (0.54–2.68)	0.74 (0.35–1.57)	0.93 (041–2.13)	0.79 (0.34–1.80)
Activity of daily living score (reference high function (≥18))					
Mid function (12–17)	1.17 (0.74–1.84)	0.56 (0.24–1.29)	0.91 (0.40–2.03)	1.73 (0.66–4.53)	0.94 (0.39–2.27)
Low function (≤11)	0.94 (0.58–1.54)	0.07 (0.02–0.26)	0.96 (0.40–2.31)	1.28 (0.49–3.58)	0.80 (0.29–2.20)
Presence of chronic disease (reference absence)					
Congestive heart failure	1.18 (0.61–2.27)	0.29 (0.03–2.46)	0.63 (0.14–2.82)	0.26 (0.06–1.01)	1.93 (0.41–9.14)
CVD		0.26 (0.12–0.57)	0.45 (0.21–0.97)	0.95 (0.43–2.10)	1.70 (0.75–3.86)
Dementia	0.92 (0.61–1.39)		1.88 (0.87–4.05)	0.68 (0.28–1.66)	0.73 (0.32–1.65)
Depression	1.25 (0.85–1.84)	1.75 (0.80–3.82)		0.62 (0.27–1.39)	1.54 (0.72–3.29)
Diabetes mellitus	0.56 (0.32–0.99)	0.73 (0.23–2.34)	0.85 (0.31–2.29)		0.77 (0.30–1.97)
Hypertension	0.69 (0.45–1.05)	0.37 (0.15–0.92)	1.40 (065–2.99)	1.28 (0.54–3.03)	

CVD = cardiovascular disease.