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Relationship between Major Depression and High Serum Cholesterol in Japanese Men

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NAKAO, M. and EIJI, Y. *Relationship between Major Depression and High Serum Cholesterol in Japanese Men.* Tohoku J. Exp. Med., 2004, **204** (4), 273-287 —— Although it has been argued that those with lower levels of serum cholesterol are likely to be depressive, the findings are inconsistent. The present study attempted to clarify the relationship between major depression and serum total cholesterol in a working population. Subjects were 987 Japanese men working at an institute, aged 20 to 64 years. In addition to blood examinations and physical measurements, clinical structured interviews of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) were used to detect major depression. The prevalence of major depression was higher in the hypercholesterolemics (serum total cholesterol levels ≧ 5.69 mmol/liter) than in the normocholesterolemics (3.10-5.69 mmol/liter) (6.1% vs 1.8%, $p < 0.05$). Notably, there was no case with major depression among the hypocholesterolemics (< 3.10 mmol/liter). Through a multiple regression analysis, serum total cholesterol levels were positively predicted by the following four variables: major depression, age, body mass index, and skipping breakfast (all $p < 0.01$). Concerning those diagnosed with major depression, serum total cholesterol levels remained higher in the following year ($p < 0.05$), comparing to those without such diagnosis. Therefore, depression is associated with higher serum cholesterol levels in a population of Japanese male workers. The irregularity of eating behavior may be one of the factors mediating high serum cholesterol levels and major depression. ——— cholesterol; depression; working population; eating behavior

It has been argued that low serum cholesterol is associated with depression. For example, subjects with low serum cholesterol were likely to be depressive in a mega-study ($n > 1000$) with older population (Morgan et al. 1993). In a patient study, it was also reported that those with major depression had lower serum cholesterol than those without major depression (Olusi and Fido 1996). However, a meta-analysis assessing the hazards of reducing serum cholesterol has refuted the con-

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nection between lowering cholesterol and increased depression in middle-aged populations (Law et al. 1994).

A recent study with adolescent psychiatric inpatients indicated that serum cholesterol was rather higher in suicidal patients than non-suicidals (Apter et al. 1999). The positive relationship between high serum total cholesterol levels and increased risk of suicide has also been observed in a general population as well

TABLE 1. *Description of major studies on the relationship*

Authors	Country	Setting	No. of subjects	Male Sex(%)	Mean age or range	Depression assessment
1. Inverse relationship						
Morgan et al. (1993)	U.S.A.	General population	1020	100	50-89	BDI
Dealberto et al. (1993)	France	General population	787	43	60-69	CES-D (dichotomized)
Lindberg et al. (1994)	Sweden	Employed workers	905	71	41(men) 38(women)	A 5-point scale (dichotomized)
Olusi et al. (1996)	Kuwait	Psychiatric inpatients	100	64	20-39(n = 58) 40-59(n = 32) 60-79(n = 10)	DSM-IV for major depression
Horsten et al. (1997)	Sweden	General population	300	0	31-65	9-item questionaire derived by Pearlin
Agargun et al. (1998)	Turkey	Psychiatric outpatients (panic disorders, PD)	16	38	18-65	DSM-III-R for major depression (MD)
Suarez (1999)	U.S.A.	General population	121	0	18-27	NEO-PI depression Subscale
Steegmans et al. (2000)	Nether lands	General population	255	100	40-70	BDI (dichotomized)

(Continued)

(Tanskanen et al. 2000). In addition, our recent study demonstrated the positive relationship between serum total cholesterol concentration and depression in a Japanese young population (Nakao et al. 2001a) (Table 1).

These controversial findings might be partly resulted by unhealthy lifestyles due to depression. Concerning serum cholesterol concentration, it has been recognized that behavioral risk factors of coronary artery diseases including obesity, physi-

between depression and serum cholesterol levels

Cholesterol assessment	Statistical methods	Main results
4 levels (low, normal, borderline, and high)	Mann-Whitney's U-test, low vs. all other levels in each age groups	Increased scores in men with low cholesterol levels aged 70-79 and 80-89 years.
5 levels (low, low-med, med, high-med, and high)	Chi-square test in each sex (low vs. all other levels)	Higher prevalence of depression in those with low cholesterol level in both sexes. The similar results found when limiting to those without anti-hypercholesterolemc medication.
Continuous	Student's *t*-test in each sex	Lower serum cholesterol levels in middle-aged men experiencing depression more frequently. No such association in middle-aged women.
Continuous	Student's *t*-test, (sex-, age- and weight-matched healthy controls)	Lower serum cholesterol levels in both sexes and in all age groups.
10 levels	Multiple regression analysis (education, smoking, menopause, and waist/hip ratio)	Higher depression scores in middle-aged women at the lowest 10th cholesterol cholesterol level. No univariate association between depression scores and serum cholesterol levels
Continuous	One-way ANOVA among age-, sex-, and weight-matched PD(+)MD(+), PD(+)MD(−), and the normal controls	A significant variation in serum cholesterol levels across the three groups (PD(+)MD(−) > Normal controls = PD(+)MD(+)).
Continuous analysis	Multiple regression (age, body mass index, and physical activities)	Inverse association of the NEO depression scale scores with serum cholesterol in young women.
2 levels	Logistic regression analysis (age, calorie intake, and alcohol)	Higher risk of having depression symptoms in middle-aged men with low cholesterol levels.

(TABLE 1, Continued)

Authors	Country	Setting	No. of subjects	Male Sex(%)	Mean age or range	Depression assessment
2. No significant relationship						
Strandberg et al. (1993)	Finland	General population	621	Unclear	75-85	SDS DSM-II
Brown et al. (1994)	U.S.A.	General population	3939	39	70+	CES-D
McCallum et al. (1994)	Australia	General population	2805	44	60+	CES-D
Apter et al. (1999)	Israel	Adolescent psychiatric inpatients	152	48	12-21	BDI
Shibata et al. (1999)	Japan	General population	504	39	65+	Geriatric Depression Score
Lacerda et al. (2000)	Brazil	Psychiatric outpatients	21	29	41	DSM-IV
Terao et al. (2000)	Japan	Human dock visitors	13571	74	46	Hitachi Mental scale (dichotomized)
3. Positive relationship						
Segers et al. (1976)	Belgium	General population	1694	100	38 in 819 men aged < 45 52 in 875 men aged > 44	SDS
van Doornen (1980)	Netherlands	Healthy subjects recruited for study	78	100	35-45	Rating of Statements List derived by Dijl
Nakao et al. (2001a)	Japan	University students (freshmen)	114	75	18-20	POMS Depression Scales

BDI, Beck Depression Inventory; CES-D, Centers for Epidemiologic Studies' Depression Scale; DSM, Clinical interview of depression using the Diagnostic and Statistical Manual of Psychiatric Disorders; ANOVA, Analysis of Variances; NEO-PI, Neuroticism, Extraversion, Openness-Personality Inventory; SDS, Zung's Self-rating Depression Scale; POMS, Profile of Mood States.

Cholesterol assessment	Statistical methods	Main results
Continuos	Unclear (Separate analysis in men and women)	No association between serum cholesterol levels and any depression-related variables in elderly men or women. No correlation of serum cholesterol levels with one-year change in SDS scores in either sex.
4 levels (low, normal, borderline, and high)	Multiple regression analysis (age, physical function, et al.) in each sex	No association of serum cholesterol levels with the depression scores in elderly men or women.
4 levels (quantiles)	Multiple regression analysis (age, medication) in each sex	No association of low serum cholesterol with depressive symptoms in elderly men or women.
Continuos	Correlational analysis in the total sample	No association between serum cholesterol levels and BDI either in the total sample of young persons.
Continuous	Multiple regression analysis (education and age) in each sex	No association of serum cholesterol levels with the depression scores in elderly men or women.
Continuous	One-way AVOVA among major depression, panic disorder, and anxiety disorder.	No variation in serum cholesterol levels among the three disorders.
8 levels	Logistic regression analysis (age, sex, body mass index, total protein, et al.)	No risk of depressive symptoms in those at the lowest cholesterol levels as well as at the 2nd and 3rd lowest cholesterol levels. Lower depression risk at the 4th lowest cholesterol levels.
Continuous	Correlational analysis in obese, normal, and lean subjects	Positive correlation between SDS scores and serum cholesterol levels only in obese men aged < 45 years. No such association in any other groups.
Continuos	Correlational analysis in the total sample	Positive correlation between depression scale scores and serum cholesterol levels in middle-aged men.
2 levels (Persistent vs temporary high cholesterol	Logistic regression analysis (all POMS scales, sex, and body mass index)	Higher POMS deppression scale scores in young persons with persistent hypercholesterolemia than those with temporary-elevated hypercholesterolemia and the normal controls (n = 11).

cal inactivity, and cigarette smoking are closely associated with lipids and lipoprotein (Takemura et al. 2000; Olson et al. 2001). Because appetite loss is one of important symptoms of major depressive episodes (American Psychiatric Association 1994), some depressive patients may be less likely to keep regular eating, making their cholesterol levels varying (Bahar et al. 2003).

Thus the present study attempted to accomplish two research tasks. One was to clarify the specific relationship between serum total cholesterol levels and the clinical diagnosis of major depression in current workers, assuming that severe depressive persons who could not work and elderly persons were excluded from the sample. The second task was to assess the effects of age, body mass index, eating pattern (skipping breakfast), and other health-related lifestyles on the relationship between cholesterol and major depression. To perform these research tasks, employees undergoing annual health checkups in a Japanese institute were assessed using a self-completed questionnaire of lifestyle, and then interviewed for the diagnosis of major depression according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (American Psychiatric Association 1994).

Materials and Methods

Study subjects

The subjects were 987 Japanese male workers who attended health examinations at a research institute in the suburbs of Tokyo in June, 2001. Those whose ages were above 65 years (0.4%) were excluded from analyses. Female participants (31%) were also excluded from analysis because it has been reported that depression is more common in women than in men (Katon et al. 1982; Regier et al. 1988; Nakao et al. 2001b) and that serum cholesterol levels are influenced by gender-related factors including menstrual conditions (Faix et al. 1993; Legato 2000). Approximately 10% of the workers were from overseas and excluded because of difficulties in the interview and the self-rating questionnaire.

The characteristics of the subjects are summarized in Table 2. The job categories were researchers (68%), research assistants (18%), and office workers (14%). Although the health examinations were mandatory to all the employees, the attendance rate was 85%, which was consistent over the past 5 years. The distributions of age and job categories were comparable between the subjects and those who did not attend the health checkups ($p > 0.05$, chi-square test) (Table 2).

The health checkups were performed in a clinic of the institute at the expense of the institute. Because the subjects did not include blue-collar workers required for special examinations related to their jobs, the procedures were common and similar to those used in regular employer-sponsored health checkups which were done under contract by clinical staff in a medical company conducting examinations for more than one thousand enterprises around Tokyo annually.

The study was approved by the Ethical Committee at the Teikyo University School of Medicine. Within one week before the health checkups all of the participants received a letter informing them that non-mandatory psychological interviews were to be performed for the present study, but no one refused to be interviewed at the health checkups.

Assessments of serum cholesterol levels and health-related lifestyle

The subjects completed a questionnaire on health-related lifestyles (eating breakfast, alcohol intake, smoking status, and regular exercise) in the past month before starting the health examinations. Each item was rated on three or four categorical scales.

At the health examinations, physical measurements of body height, body weight, and blood pressure were performed. Serum levels of total cholesterol, triglyceride and high density lipoprotein (HDL) cholesterol were also examined. According to the reference values used for the

TABLE 2. *Basic characteristics of the male subjects and comparison between those with major depression (n= 24) and those without major depression (n = 963)*

Mean (S.D.) or *n* (%)	Total (*n* = 987)	Major depression		
		(+)	(–)	*p*[a]
Age, years	35 (10)	36 (10)	35 (10)	NS[b]
Body Mass Index, kg/m^2	23.0 (3.2)	23.1 (3.1)	23.0 (3.2)	NS
Serum cholesterol, mmol/liter				
Total cholesterol	4.89 (0.83)	5.33 (0.81)	4.89 (0.83)	< 0.01
Triglyceride	1.87 (1.13)	2.01 (1.27)	1.62 (1.13)	NS
High Density Lipoprotein	1.40 (0.36)	1.38 (0.36)	1.40 (0.36)	NS
Breakfast				< 0.005
Everyday	637 (65%)	11 (46%)	626 (65%)	
Sometimes (3-4 times/week)	148 (15%)	1 (4%)	147 (15%)	
Never or almost never	201 (20%)	12 (50%)	189 (20%)	
No information	1 (0.1%)	0 (0%)	1 (0.1%)	
Alcohol drinking, *n* (%)				NS
Never	248 (25%)	7 (29%)	241 (25%)	
1-3 days/week	446 (45%)	6 (25%)	440 (46%)	
4-6 days/week	128 (13%)	4 (17%)	124 (13%)	
Every day	158 (16%)	7 (29%)	151 (16%)	
No information	6 (1%)	0 (0%)	6 (0.6%)	
Smoking status, *n* (%)				< 0.05
Never	655 (66%)	13 (54%)	642 (67%)	
Quitted	118 (12%)	3 (13%)	115 (12%)	
Currently smoking	209 (21%)	8 (33%)	201 (21%)	
No information	5 (0.5%)	0 (0%)	5 (0.5%)	
Exercise, *n* (%)				< 0.005
Regularly	210 (21%)	4 (17%)	206 (21%)	
Sometimes	260 (26%)	3 (13%)	257 (27%)	
Never	514 (52%)	17 (71%)	497 (52%)	
No information	3 (0.3%)	0 (0%)	3 (0.3%)	

[a] *p* values were based on *t*-test (age, body mass index, serum cholesterol levels) or chi-square test (the others).

[b] NS, not significant ($p > 0.05$).

health examinations (Mitsubishi Kagaku Bio-Clinical Laboratories, Inc., Tokyo), hypercholesterolemics were defined as those with serum total cholesterol level ≧ 5.69 mmol/liter (≧ 220 mg/100 ml), which has been validated in a Japanese population (Uji and Okabe 1995), and clinically used most frequently in diagnosing hypercholesterolemia. Similarly, hypocholesterolemics were defined as those with serum total cholesterol level < 3.10 mmol/liter (< 120 mg/100 ml).

Assessments of major depression

Because the gold standard for diagnosing depression is careful application of standardized clinical criteria (The Canadian Task Force on the Periodic Health Examination 1994), structured clinical interviews for detecting major depression

were performed by the same interviewer in an independent interview room, according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (American Psychiatric Association 1994). The process was as follows: after simply asking recent physical and mental conditions, the interviewer asked each subject whether he had "depressive mood" lasting during the same 2 weeks, and then asked whether he had "loss of interest or pleasure" during the same period. To minimize the interview time, the interviewer finished the DSM-IV interview when the subject had neither "depressed mood" nor "loss of interest or pleasure," based on the DSM-IV depressive-mood algorithm of the Primary Care and International Version (American Psychiatric Association 1996). Only those who answered "yes" in both or either of the two questions subsequently interviewed according to the full DSM-IV criteria for major depressive episodes and major depression (American Psychiatric Association 1994).

The interviewer was a male physician specializing both in psychiatry and in internal medicine. Because the research assistants helped the subjects fill out the self-rating questionnaire beforehand, the interviewer was blinded to such information. In the present study, 12 subjects reporting suicidal ideation were picked up from those assessed as positive for major depression. Although the data were additional (Nakao and Yano 2003), the re-assessed subjects definitely met the criteria of major depression through the second structured clinical interviews of the DSM-IV two weeks after the health checkups, with high scores on the 17-item Hamilton Depression Scale (median: 12.5, range: 10-23) as well as high t-scores on the depression scale of the Profile of Mood States (median: 77, range: 54-85) (Hamilton 1967; McNair et al. 1971).

Causal relationship between serum cholesterol levels and major depression

To examine the causal relationship of serum total cholesterol levels with the prevalence of major depression, the same examinations were performed in the following year (June, 2002). Out of the 987 subjects, 732 (74%) attended the following year's health examination, and serum total cholesterol levels and depressive states were reassessed at the examination. The prevalence of major depression for 2002 was compared between those with hypercholesterolemia in 2001 and those without hypercholesterolemia in 2001. Conversely, serum total cholesterol levels for 2002 were compared between those with major depression in 2001 and those without it.

Data analysis

The data were coded and recorded in the database by three statistical assistants independent of the present study. All analyses were performed using the SAS statistical package (SAS Institute Inc. 1988). P value of < 0.05 level was accepted as significant.

Serum total cholesterol levels were classified by two ways. First, they were clinically divided into three categories of hyper-, normo-, and hypocholesterolemias, according to the reference values (i.e., $\geqq 5.69$, 3.10-5.69, and < 3.10 mmol/liter) used for the health examinations (Mitsubishi Kagaku Bio-Clinical Laboratories, Inc., Tokyo). Second, the serum cholesterol levels were statistically divided into quartiles, because the sample size of the hypocholesterolemics was relatively small in the present study. The chi-square test was used to find the group differences in the prevalence of major depression.

Student's t-test was used to compare serum total cholesterol levels between those with major depression and those without major depression. The multiple regression analysis was then performed to determine the independent effects of major depression, age, body mass index, and health-related lifestyles on serum total cholesterol levels.

RESULTS

Prevalence of major depression

In the total sample, 24 cases (2.4%) were

identified as having major depression (Table 3). Although the data were not shown in the table, the prevalence of major depression was comparable among the three job categories, and there were no significant differences in age and body mass index between the major depressive subjects and the non-major-depressive subjects (Student's *t*-test).

Concerning eating breakfast, the prevalence of major depression was higher ($p < 0.005$) in the subjects skipping breakfast (eating breakfast not every day) than in those eating breakfast every day (Table 2). The prevalence of major depression was also significantly associated with smoking status and exercise. It was not significantly associated with alcohol drinking (Table 2).

Serum total cholesterol levels

The prevalence of hypercholesterolemics was 14.9%, and the prevalence of hypocholesterolemics was 0.5%. Pearson's correlation coefficiency between age and serum total cholesterol levels was 0.38 ($p < 0.0001$), and the coefficiency between body mass index and serum total cholesterol levels was 0.28 ($p < 0.0001$).

The average serum total cholesterol levels (standard deviation) were 4.91 (0.86) mmol/liter among those skipping breakfast; they were 4.89 (0.78) mmol/liter among those eating breakfast everyday. The values were comparable between the two groups. Serum total cholesterol levels were higher ($p < 0.01$) in those drinking alcohol 4 days per week or more frequent (5.02 [0.78] mmol/liter) than in those less than 4 days per week (4.84 [0.83] mmol/liter). Smoking status and exercise were not significantly associated with serum total cholesterol levels.

Relationship between serum total cholesterol levels and major depression

The prevalence of major depression was higher ($p < 0.01$) in the hypercholesterolemics (6.1%) than in the normocholesterolemics (1.8%). There was no case with major depression among the hypocholesterolemic subjects. Concerning the quartiles of serum total cholesterol levels, major depression was the most frequently seen ($p < 0.05$) in the highest cholesterol group (Table 3).

The box-and-whisker plots of serum total cholesterol levels are shown in Fig. 1, comparing the major depressive subjects with the non-major-depressive subjects. The average serum total cholesterol levels (standard deviation) were 5.30 (0.85) mmol/liter in the major depressive subjects; they were 4.84 (0.83) mmol/liter in the non-

TABLE 3. *Relationship between serum total cholesterol levels and prevalence of major depression in men*

Serum total cholesterol levels (mmol/liter)	*n*	Diagnosis of major depression, *n* (%)
Total	987	24 (2.4%)
Clinical classification		
Hypercholesterolemia (≧ 5.69)	147	9 (6.1%)*
Normocholesterolemia (3.10-5.69)	835	15 (1.8%)
Hypocholesterolemia (< 3.10)	5	0 (0%)
Statistical classification		
3rd quartile or more (≧ 5.33)	257	13 (5.1%)*
Median to 3rd quartile (4.81-5.33)	246	3 (1.2%)
1st quartile to median (4.32-4.81)	243	4 (1.6%)
less than 1st quartile (< 4.32)	241	4 (1.7%)

*$p < 0.05$ between cholesterol levels by the chi-square test.

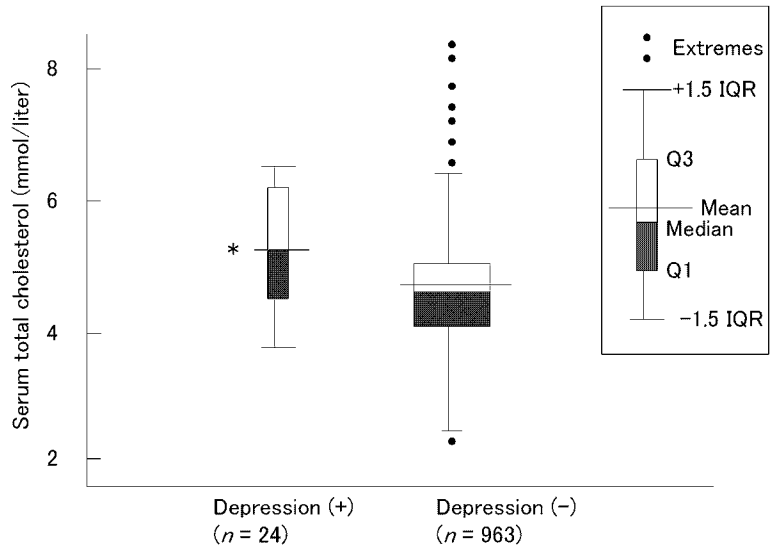

Fig. 1. Box-and-whisker plots of serum total cholesterol levels in the subjects with major depression and those without major depression.
Q1, the value of the first quartile (25%) in the sample.
Q3, the value of the third quartile (75%) in the sample.
IQR = interquartile range (the distance between Q1 and Q3).
According to the rule of the SAS graphic system (SAS Institute Inc. 1988), the upper (or lower) limit of whisker is defined as either the maximal (or minimal) value or the value distant from Q3 (or Q1) by 1.5 IQR. When there are values over Q3 (or below Q1) by more than 1.5 IQR, each of them is plotted as extremes. In the present study, therefore, the upper and lower limits of the whiskers mean the maximum and minimum points in the major depressive group because no extremes existed; they mean ± 1.5 IQR from Q3 (Q1) in the non-major depressive group because there were 8 extremes (7 upper values and one lower value). All data were included for analysis ($^{*}p < 0.01$, between the major depressive subjects and the non-major-depressive subjects by Student's *t*-test).

major-depressive subjects. The values were significantly different ($p < 0.01$) between the two groups (Fig. 1).

The results of the multiple regression analysis indicated that serum cholesterol levels were positively and independently predicted by major depression ($p < 0.01$) (Table 4). Age and body mass index positively predicted serum total cholesterol levels ($p < 0.0001$ for both). Eating breakfast negatively predicted serum total cholesterol levels ($p < 0.0001$). Smoking status, alcohol drinking, and exercise were not significant (Table 4).

Causal relationship between serum total cholesterol and major depression

Concerning the 732 subjects receiving the health examination in both years, the prevalence of major depression for 2002 was 4.2% in the 119 subjects diagnosed with hypercholesterolemia in 2001; it was 2.3% in the remaining 613 subjects. The prevalence of major depression for 2002 was comparable between the two groups. When the analysis was limited to the 712 subjects without major depression in 2001, the prevalence of major depression for 2002 was 2.7% in the 111 hypercholesterolemics in 2001; it was 1.8% in the 601 non-hypercholesterolemics in 2001 ($p > 0.05$ between the two groups). When the analysis was limited to the 20 subjects with major depression in 2001, the prevalence of major depression for 2002 was 25.0% in both the 8 hypercholesterolemics and 12 non-hypercholesterolemics in 2001 ($p > 0.05$ between the two groups).

The average serum total cholesterol levels (S.D.) for 2002 were 5.4 (1.0) mmol/liter in the 20

TABLE 4. *Predictors of serum cholesterol levels in men: the results of multiple regression analysis (n = 973)*[a]

Variables	Unstandardized Regression coefficient	Standard error	Standardized regression coefficient	*p* value
Major depression[b]	15.529	5.740	0.078	< 0.01
Age, years	1.241	0.104	0.381	< 0.0001
Body mass index, kg/m^2	1.987	0.292	0.199	< 0.0001
Eating of breakfast[c]	–8.004	1.995	–0.122	< 0.001
Alcohol drinking[d]	–2.030	2.093	–0.029	NS[e]
Smoking status[f]	0.263	2.233	0.003	NS
Exercise[g]	0.201	1.822	0.003	NS

[a] There were 14 missing data of alcohol drinking, smoking status, eating of breakfast or exercise.
[b] (Positive) = 1; (Negative) = 0.
[c] (Regular) = 1; (Sometimes or never) = 0.
[d] (≧ 4 days/week) = 1; (≦ 3 days/week) = 0.
[e] NS, not significant ($p > 0.05$).
[f] (Currently smoking) = 1; (Never or quitted) = 0.
[g] (Every day) = 1; (Sometimes or never) = 0.

subjects diagnosed with major depression in 2001; they were 5.0 (0.9) mmol/liter in the 712 subjects without such diagnosis in 2001. The values for 2002 were higher ($p = 0.03$) in those with major depression in 2001 than in those without major depression in 2001.

However, such significant differences were not found between the two groups when the analysis was separately conducted in the 119 hypercholesterolemics in 2001 and the 613 non-hypercholesterolemics in 2001 (data were not shown).

Finally, the course of major depression was classified into four groups: i.e. normal group (no major depression in both years, $n = 698$), onset group (no major depression in 2001 and major depression in 2002, $n = 14$), persistent group (major depression in both years, $n = 5$), and improving group (major depression in 2001 and no major depression in 2002, $n = 15$). From 2000 to 2001, the average serum total cholesterol levels (S.D.) were changed as follows: 4.88 (0.84) to 4.99 (0.86) (normal group), 5.13 (0.68) to 5.07 (0.83) (onset group), 5.18 (0.87) to 5.66 (1.21) (persistent group), and 5.22 (0.83) to 5.33 (0.94) (improving group). Serum cholesterol levels significantly increased from 2000 to 2001 only in the persistent group ($p = 0.03$, paired *t*-test).

DISCUSSION

In the present study, the prevalence of major depression was significantly higher in the hypercholesterolemic subjects than in the normocholesterolemic subjects. No major depression was found in the hypocholesterolemic subjects. When the subjects were classified into quartiles of serum total cholesterol, the results were parallel to these lines. Regarding serum cholesterol levels as a continuous variable, the values were significantly higher in the major depressive subjects than in those without major depressive subjects; the values in the following year were still significantly higher in the former group than in the latter group.

Because hypercholesterolemics were reported to be more depressed among young Japanese university students in our own study conducted before (Nakao et al. 2001a), it is interesting that the similar association of depression was found among the Japanese male adults with hypercholesterolemia. Although several literature have reported the inverse relationship between cholesterol and depression since the publication of the study by Morgan (1993), the pioneer study did

not show that subjects with high serum cholesterol levels were less depressive. Additionally, the significant findings in the previous study were limited to the elderly persons (Morgan et al. 1993) and have been criticized by difference of eating behavior which may cause association between low cholesterol and depression (Horsten et al. 1997). Concerning the non-elderly male subjects in a general population, for example, results of two studies (Segers and Mertens 1976; van Doornen 1980) agreed while three (Lindberg et al. 1994; Steegmans et al. 2000; Terao et al. 2000) disagreed with our findings of the positive relationship between cholesterol and depression. Because all of the five studies have been completed using self-rating questionnaires (Segers and Mertens 1976; van Doornen 1980; Lindberg et al. 1994; Steegmans et al. 2000; Terao et al. 2000), it is not clear what proportion of reported depression was clinically significant. Thus our findings reinforce the idea that the relationship between low cholesterol and depression is still inconclusive, and rather suggest that it is possible to observe the positive association between cholesterol and depression, which may depend on age, severity of depression, and other factors.

Concerning physiological mechanism, decrease in serum cholesterol was reported to be related to both the improvement in depression and the increase in an arterial oxygen tension (PaO_2) in a previous study (Glueck et al. 1993). The authors suggested that cholesterol lowering facilitates correction of metabolic defects such as high serum viscosity with attendant reduced red blood cell oxygenation and resultant segmental cerebral hypoxia (Seplowitz et al. 1981), which may be associated with symptoms of depression. However, it was not likely that severe intravascular changes in the brain occurred among those who were healthy enough to do intelligent jobs in the present study. Furthermore, the prevalence of major depression for 2002 was comparable between those with hypercholesterolemia and those without such disorder in 2001. Thus it might be less likely that increased cholesterol caused depression in the present study.

Concerning health-related lifestyle, serum total cholesterol levels were not significantly associated with smoking, alcohol intake, and lack of exercise in the final model of the multiple regression model in the present study. The remaining lifestyle factor, eating behavior, might be a clue connecting major depression with cholesterol elevation. Skipping breakfast was an independent predictor for serum total cholesterol levels, and closely associated with major depression in the present study. Although lack of food intake in the morning itself might decrease body weight, the body mass index was positively associated with serum total cholesterol levels in the present study. Thus eating-behaviors might be likely to be irregular and bulimic in the daytime or at night in some cases of workers with major depression as the consequence of accelerated increased stress perception to daily works (Takeuchi et al. 2004), although this idea is far from conclusion. Further studies are needed to mention the issue of eating-behaviors in the future.

The major limitation of the present study was the generalizability of the results. The data were obtained in the setting of one research institute, and the results might be generalized only to the Japanese male laboratory workers. It is possible that the positive relationship between serum total cholesterol levels and major depression in men may be the phenomenon in hidden cases with mild type of major depression who are able to work at present.

Second, depressive symptoms were diagnosed only through clinical interviews without the use of standardized psychological questionnaires. For practical reasons, only pre-existing materials used in the health examinations (i.e., the reporting of life-style and physician's interview) were utilized in the present study. To prevent inconsistency of the diagnoses, the same physician who was expert in the DSM-IV assessments evaluated all the subjects. The diagnosis of major depression was made without the knowledge of cholesterol level of each subject that information bias was

unlikely.

Third, information of psychotropic medication was also lacked in the pre-existing materials and asked directly by the physician. Although at least five subjects were identified as taking anti-depressants currently in the interview (not shown in the table), they were not excluded in the analysis because we were not sure about the exact number of cases with medication. However, it has been reported that a long-term use of anti-depressants including tricyclics could induce weight gain (Harris and Ashford 1991), and thus it is important to assess kinds and duration of medications on physical and psychological conditions in the future studies.

Finally, major depression has a variety of clinical features, and the analysis might be needed for subtypes of major depression. For example, appetite loss is typical in the major depressive cases, but they often complain of bulimic symptoms in their clinical course. Also, decreased thyroid function might play an important role in the relationship between major depression and hypercholesterolemia, because hypothyroidism has been reported to be associated with depression (Engum et al. 2002) and could be caused by relative increase in reverse T3 levels due to skipping breakfast. Hypothyroidism accounts for about 2% of all cases of hyperlipidemia and is second only to diabetes mellitus as a cause of secondary hyperlipidemia. However, the nature of the present study did not permit us to specify the subtypes of major depression such as bulimic type or hypothyroid type; minimal intervention was required to fulfil the whole study over the two years, with the limiting time and cost in the examination. This issue should be addressed with more sample size of major depression in a clinical population in the future.

In summary, major depression appears to be related to higher cholesterol levels in Japanese male laboratory workers. Among a variety of lifestyle factors, eating behavior as a consequence of depression may lead to cholesterol changes. Because it has been reported that depression is associated with cerebrovascular diseases including heart diseases, both detection and treatment of depression in hypercholesterolemic patients may be important for the prevention of cardiovascular events in future.

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