Weight Gain and Obesity are Associated with Dyslipidemia, Hyperuricemia, and Liver Dysfunction in Japanese Young Male Workers

Takero Kaido,*[,a] Yasushi Honda,[b] and Kuniaki Kitamura[c]

[a]Osaka Prefecture College of Nursing, 3–7–30 Habikino, Habikino City, Osaka 583–8555, Japan, [b]Institute of Health and Sports Sciences, University of Tsukuba, 1–1–1 Tennodai, Tsukuba City, Ibaraki 305–8574, Japan, and [c]National Printing Bureau, 2–2–4 Toranomon, Minato-ku, Tokyo 105–8445, Japan

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The purpose of this cohort study was to identify the predictors of lifestyle-related disorders, such as dyslipidemia, hyperuricemia, and liver dysfunction in Japanese young male workers. As candidates for the predictors, we chose obesity at entry and weight gain. The study subjects were 166 Japanese male workers aged 28 to 35 years at two printing plants in Tokyo who showed no blood abnormalities on 6 chemistry items, *i.e.*, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), uric acid (UA), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma glutamyl transferase (GGT); the subjects completed a self-administered questionnaire survey in 1993, and underwent blood examinations in 2000. Covariates we included in the models were age, drinking habit, smoking habit and regular exercise. Linear regression models revealed that weight gain was consistently associated with the above 6 blood chemistry items at endpoint, whereas obesity was not a better predictive variable than weight gain except for UA. Logistic regression models showed that the odds ratios (ORs) of each 5% weight gain were 1.47 [95% confidence interval (CI): 0.94–2.28] for high TC, 1.27 (0.88–1.84) for high UA, 2.61 (1.32–5.18) for high ALT, and 1.88 (1.14–3.11) for high GGT. The ORs of obesity were 3.05 (0.98–9.50) for high TC, 3.88 (1.40–10.8) for high UA, 4.94 (1.05–23.22) for high ALT, and 1.78 (0.43–7.31) for GGT. In conclusion, for a period during which workers do not undergo blood tests, weight gain, in combination with obesity, may be used as a predictor of the later occurrence of blood abnormalities.

Key words —— weight gain, obesity, young adult, dyslipidemia, hyperuricemia, liver dysfunction

INTRODUCTION

Several cross-sectional studies demonstrated that Japanese men in their 40s (or even 30s) had the highest prevalence of blood test abnormalities, such as dyslipidemia, hyperuricemia and liver dysfunction.[1,2] According to a national nutritional survey in 1990, for example, the prevalence of high total cholesterol (TC) (≥ 220 mg/dl) for male subjects aged 40–49 years was 31.2%, and that of high uric acid (UA) (≥ 7 mg/dl) and high alanine aminotransferase (ALT) (≥ 40 IU/l) were 15.7% and 21.8%, respectively.[1] However, Japanese workers usually undergo health checkups including blood chemistry tests for the first time in their mid-30s or at 40 years of age. This suggests that, from the standpoint of primary prevention, we need studies on how earlier stage lifestyle factors affect blood abnormalities in a later stage (mid-30s to early 40s).

Therefore, in this study, we investigated associations of an earlier status of lifestyle-related factors and subsequent occurrence of lifestyle-related abnormalities. As the lifestyle-related factors, we chose weight gain and obesity, because weight and height are commonly measured attributes at annual health-checkups even for very young workers.

Although some longitudinal studies already showed that weight gain and obesity were related to increased risk of hypercholesterolemia,[3] hyperuricemia (or gout),[4] and hyperinsulinemia,[5,6] subjects aged 35 years and under were often not included in

*To whom correspondence should be addressed: Osaka Prefecture College of Nursing, 3–7–30 Habikino, Habikino City, Osaka 583–8555, Japan. Tel.: +81-729-50-2111; Fax: +81-729-50-2131; E-mail: kaido@osaka-hsu.ac.jp

these studies, or age was controlled as a confounding factor because the age of study subjects ranged from young adults to middle or old age. Furthermore, few studies focused on the consequences of the initial levels of lifestyle-related factors among young men.

MATERIALS AND METHODS

The study subjects were Japanese male workers aged 28 to 35 years at two printing plants in Tokyo. All the subjects underwent blood examinations including 7 blood chemistry items, *i.e.*, TC, high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), aspartate aminotransferase (AST), ALT, gamma glutamyl transferase (GGT) and UA in addition to annual health checkups in fiscal 1993. First, we selected 294 male workers who had returned self-administered questionnaires; the response rate was 95.4%. Of these, 285 subjects had health checkup information for fiscal 2000. Second, we excluded 9 subjects who had a missing value at entry for at least one of three lifestyle-related factors, *i.e.*, smoking habit, drinking habit, and regular physical exercise. Third, of the remaining 276 subjects, we also removed 4 subjects who were taking medication for liver diseases at entry, and 106 subjects who showed at least one type of blood abnormality among all the blood chemistry items at the initial examination with the exception of TG, because the subjects were not instructed to undergo blood chemistry tests in fasting status at the fiscal 1993 health checkup. Consequently, we had 166 male workers for study subjects who showed no sign of blood abnormality at entry. The mean age was 30.6 and the standard deviation was 2.14.

In the present study, we investigated three types of biochemical abnormality, *i.e.*, dyslipidemia, hyperuricemia, and liver dysfunction. Definitions of abnormality were as follows: Dyslipidemia was defined as high TC (≥ 220 mg/dl) or low HDL-C (< 35 mg/dl at entry, and < 30 mg/dl at endpoint); Hyperuricemia was defined as UA > 7.0 mg/dl[7]; Liver dysfunction was defined as high ALT (> 40 IU/l), high AST (> 36 IU/l at entry, and > 40 IU/l at endpoint), or high GGT (> 40 IU/l at entry, and > 60 IU/l at endpoint).

In the present study, obesity (coded 1 for yes, 0 for no) was defined as body mass index (BMI) ≥ 25 kg/m^2. Relative change of BMI (in percentage), an index of weight gain, was calculated with the following formula: Relative change of BMI = [BMI at endpoint (2000) – BMI at entry (1993)]/(BMI at entry)*100. The proportion of obese study subjects at entry was 15.1%.

Three lifestyle-related factors were surveyed by means of a self-administered questionnaire at entry. Because the size of the present study was not large enough to examine detailed effects of lifestyle-related factors on abnormality in blood tests, we used dichotomous classifications, which were based on the criteria conducted in the national nutrition survey.[1] Smoking habit (coded 1 for yes, 0 for no) was defined here as current smoking. Habit of drinking (coded 1 for yes, 0 for no) was defined as drinking at least 3 times a week and consuming one of the following type of alcoholic beverages per time: sake (Japanese rice wine), 180 ml or more; beer, 633 ml or more; whiskey, 60 ml or more. The criteria for regular physical exercise (coded 1 for yes, 0 for no) were as follows: Duration of exercise was 30 min or longer; frequency of exercise was at least twice a week; history of taking physical exercise was longer than or equal to 1 year. The proportions of subjects with covariates were 61.5% for smoking habit, 29.5% for habit of drinking, and 41.0% for regular physical exercise.

A linear regression model as well as a logistic regression model was used in this study, because we intended to evaluate the differences of blood chemistry data within normal levels. However, a logistic regression model was not applied to two blood chemistry items, *i.e.*, HDL-C and AST, because few cases were newly found at the 2000 health checkup, as described in the Results section. The covariates included in the 2 models were age, obesity, relative change of BMI, habit of drinking, habit of smoking, and regular physical exercise.

All analyses were carried out by the Statistical Analysis System (SAS Release 8.2). *p*-Values less than 0.05 were regarded as statistically significant.

This study was conducted in accordance with ethical standards formulated in the guidelines for epidemiologic studies issued by the Japanese Ministry of Education, Science, Sports and Culture and by the Ministry of Health, Labour and Welfare.

RESULTS

Dyslipidemia Study

At the 2000 health checkup, 20 subjects (12.0%) with TC being ≥ 220 mg/dl were found among

Table 1. Multiple Linear Regression Analysis of TC at Endpoint (2000) as a Function of Age, TC at Entry (1993), Obesity, Relative Change of BMI, Habit of Drinking, Habit of Smoking, and Regular Physical Exercise ($R^2 = 0.589$)

	estimated coefficient	standard error	*t*-value	*p*-value
Age at entry	1.37	0.72	1.90	0.060
TC at entry	0.83	0.06	12.83	< 0.001
Obesity at entry				
(1 for yes, 0 for no)	3.93	4.37	0.90	0.370
Relative change of BMI (%)	1.09	0.25	4.34	< 0.001
Habit of drinking at entry				
(1 for yes, 0 for no)	−0.14	3.40	−0.04	0.967
Habit of smoking at entry				
(1 for yes, 0 for no)	0.69	3.20	0.22	0.830
Regular exercise at entry				
(1 for yes, 0 for no)	0.84	3.14	0.27	0.790

Table 2. Odds Ratios and their 95% Confidence Intervals (95%CI) of Covariates by Logistic Regression Analysis for High Total Cholesterol ($\geq$ 220 mg/dl)

Covariates	Odds ratio (95%CI)	*p*-value
Age at entry		
Increase of 1 year	1.28 (1.02–1.60)	0.036
Obesity at entry		
No	1	
Yes	3.05 (0.98–9.50)	0.055
Relative change of BMI		
Increase of 5%	1.47 (0.94–2.28)	0.089
Habit of drinking at entry		
No	1	
Yes	2.02 (0.68–5.95)	0.203
Habit of smoking at entry		
No	1	
Yes	0.62 (0.21–1.79)	0.373
Regular exercise at entry		
No	1	
Yes	1.20 (0.43–3.34)	0.732

166 subjects. However, there was no subject with low HDL-C (< 30 mg/dl) at the 2000 health checkup.

Table 1 shows the estimated regression coefficients of the covariates by multiple linear regression analysis. TC at entry and relative change of BMI were significantly associated with TC at endpoint, whereas obesity at entry showed no significant association. Age at entry also showed marginal statistical significance ($p = 0.060$).

Table 2 shows the odds ratios (ORs) of the covariates by logistic regression analysis. Age was significantly associated with an increased risk of high TC ($\geq$ 220 mg/dl). In addition, obesity and relative change of BMI showed positive association with relatively low *p*-values ($p = 0.055$ for obesity, and $p = 0.089$ for relative change of BMI).

Table 3 shows the estimated regression coefficients of the covariates by multiple linear regression analysis of HDL-C. Age, HDL-C at entry, and relative change of BMI were significantly associated with HDL-C at endpoint, whereas obesity at entry showed negative association with a *p*-value of 0.109.

Table 3. Multiple Linear Regression Analysis of HDL-C at Endpoint (2000) as a Function of Age, HDL-C at Entry (1993), Obesity, Relative Change of BMI, Habit of Drinking, Habit of Smoking, and Regular Physical Exercise ($R^2 = 0.604$)

	estimated coefficient	standard error	*t*-value	*p*-value
Age at entry	1.06	0.38	2.82	0.006
HDL-C at entry	0.88	0.07	13.16	< 0.001
Obesity at entry				
(1 for yes, 0 for no)	−3.75	2.32	−1.61	0.109
Relative change of BMI (%)	−0.44	0.13	−3.39	< 0.001
Habit of drinking at entry				
(1 for yes, 0 for no)	2.87	1.79	1.60	0.111
Habit of smoking at entry				
(1 for yes, 0 for no)	−2.34	1.70	−1.38	0.170
Regular exercise at entry				
(1 for yes, 0 for no)	0.29	1.67	0.17	0.863

Table 4. Multiple Linear Regression Analysis of UA at Endpoint (2000) as a Function of Age, UA at Entry (1993), Obesity, Relative Change of BMI, Habit of Drinking, Habit of Smoking, and Regular Physical Exercise ($R^2 = 0.601$)

	estimated coefficient	standard error	*t*-value	*p*-value
Age at entry	0.029	0.030	0.97	0.333
UA at entry	0.931	0.068	13.76	< 0.001
Obesity at entry				
(1 for yes, 0 for no)	0.509	0.183	2.78	0.006
Relative change of BMI (%)	0.020	0.011	1.87	0.063
Habit of drinking at entry				
(1 for yes, 0 for no)	0.075	0.143	0.53	0.600
Habit of smoking at entry				
(1 for yes, 0 for no)	0.085	0.134	0.63	0.527
Regular exercise at entry				
(1 for yes, 0 for no)	−0.006	0.131	−0.05	0.962

Hyperuricemia Study

Among 166 subjects, there were 27 subjects (16.3%) with UA being > 7.0 mg/dl at the 2000 health checkup.

As shown in Table 4, a multiple linear regression analysis revealed that the regression coefficient of UA at entry and that of obesity were statistically significant. In addition, relative change of BMI showed positive association with a relatively low *p*-value ($p = 0.063$). However, habit of drinking showed no significant association.

As shown in Table 5, obesity was positively and significantly associated with an increased risk of hyperuricemia, whereas relative change of BMI and habit of drinking showed no significant association.

Liver Dysfunction Study

Among 166 subjects, there were 11 subjects (6.6%) with ALT being > 40 IU/l and 20 subjects (12.0%) with GGT being > 60 IU/l at the 2000 health checkup, whereas only 2 subjects (1.2%) with high AST (> 40 IU/l) were found.

Table 6 shows the results of multiple linear regression analysis of ALT at endpoint. ALT at entry and relative change of BMI were significantly associated with ALT at endpoint. In addition, obesity and habit of drinking also showed positive association with relatively low *p*-values ($p = 0.057$ for obesity, and $p = 0.060$ for habit of drinking).

Table 7 shows the ORs for high ALT (> 40 IU/l) by logistic regression analysis. Obesity and relative change of BMI were positively and significantly associated with an increased risk of high ALT. Habit of drinking also showed a positive association

Table 5. Odds Ratios and their 95% Confidence Intervals (95%CI) of Covariates by Logistic Regression Analysis for Hyperuricemia (> 7 mg/dl)

Covariates	Odds ratio (95%CI)	*p*-value
Age at entry		
Increase of 1 year	1.11 (0.91–1.35)	0.321
Obesity at entry		
No	1	
Yes	3.88 (1.40–10.77)	0.009
Relative change of BMI		
Increase of 5%	1.27 (0.88–1.84)	0.200
Habit of drinking at entry		
No	1	
Yes	1.74 (0.68–4.50)	0.251
Habit of smoking at entry		
No	1	
Yes	0.75 (0.30–1.90)	0.551
Regular exercise at entry		
No	1	
Yes	0.62 (0.25–1.58)	0.317

Table 6. Multiple Linear Regression Analysis of ALT at Endpoint (2000) as a Function of Age, ALT at Entry (1993), Obesity, Relative Change of BMI, Habit of Drinking, Habit of Smoking, and Regular Physical Exercise ($R^2 = 0.363$)

	estimated coefficient	standard error	*t*-value	*p*-value
Age at entry	−0.16	0.35	−0.46	0.644
ALT at entry	0.72	0.10	7.53	< 0.001
Obesity at entry				
(1 for yes, 0 for no)	4.14	2.16	1.92	0.057
Relative change of BMI (%)	0.61	0.12	4.99	< 0.001
Habit of drinking at entry				
(1 for yes, 0 for no)	3.12	1.65	1.89	0.060
Habit of smoking at entry				
(1 for yes, 0 for no)	−0.00	1.56	−0.00	1.000
Regular exercise at entry				
(1 for yes, 0 for no)	−1.06	1.51	−0.70	0.486

($p = 0.051$).

Table 8 shows the results of multiple linear regression analysis of AST at endpoint. AST at entry, relative change of BMI, and habit of drinking were significantly associated with AST at endpoint. In addition, obesity also showed a positive association with a relatively low *p*-value ($p = 0.081$).

As shown in Table 9, GGT at entry, relative change of BMI, and habit of drinking were significantly associated with GGT at endpoint. However, obesity showed no significant association.

As shown in Table 10, a logistic regression analysis revealed that relative change of BMI and habit of drinking were significantly associated with an increased risk of high GGT (> 60 IU/l). However, obesity at entry showed no significant association.

DISCUSSION

In the present study, the relative change of BMI was consistently associated with the 3 types of biochemical abnormality in both of the models, except for the hyperuricemia by a logistic regression model. A similar relation was reported in a recent prospective study (longest term 4 years) of Japanese males aged 18–59 years: Weight gain (more than 2 kg) was strongly related to an increased risk for hypercho-

Table 7. Odds Ratios and their 95% Confidence Intervals (95%CI) of Covariates by Logistic Regression Analysis for High Alanine Aminotransferase (> 40 IU/l)

Covariates	Odds ratio (95%CI)	*p*-value
Age at entry		
Increase of 1 year	1.08 (0.80–1.47)	0.617
Obesity at entry		
No	1	
Yes	4.94 (1.05–23.22)	0.043
Relative change of BMI		
Increase of 5%	2.61 (1.32–5.18)	0.006
Habit of drinking at entry		
No	1	
Yes	4.50 (0.99–20.36)	0.051
Habit of smoking at entry		
No	1	
Yes	0.72 (0.17–3.05)	0.657
Regular exercise at entry		
No	1	
Yes	0.30 (0.06–1.51)	0.144

Table 8. Multiple Linear Regression Analysis of AST at Endpoint (2000) as a Function of Age, AST at Entry (1993), Obesity, Relative Change of BMI, Habit of Drinking, Habit of Smoking, and Regular Physical Exercise ($R^2 = 0.268$)

	estimated coefficient	standard error	*t*-value	*p*-value
Age at entry	0.12	0.19	0.61	0.541
AST at entry	0.58	0.10	6.02	< 0.001
Obesity at entry				
(1 for yes, 0 for no)	2.06	1.17	1.76	0.081
Relative change of BMI (%)	0.21	0.07	3.00	0.003
Habit of drinking at entry				
(1 for yes, 0 for no)	2.27	0.94	2.41	0.017
Habit of smoking at entry				
(1 for yes, 0 for no)	0.19	0.88	0.22	0.830
Regular exercise at entry				
(1 for yes, 0 for no)	−0.00	0.85	−0.00	0.997

lesterolemia, after adjustments for age and other confounding factors.[3)]

If the 3 types of biochemical abnormality are related to insulin resistance, as reported in some articles,[8–13)] then our results, in conjunction with these articles, are consistent with the following studies: A cohort study of community-resident Japanese males also reported that weight gain, determined by a regression slope of BMI over time, was correlated to the slopes of cardiovascular risk factors both in the 30–49 year group and in the 50–69 year group[14)]; in a cross-sectional study of 2272 men aged 42, 48, 54, or 60 conducted between 1984 to 1989 as baseline examinations, percentage of gained weight from age 20 to middle age, calculated as weight change (difference between measured weight at the baseline and self-reported weight at age 20) divided by the weight at age 20, was significantly associated with prevalence of insulin resistance syndrome at the baseline.[15)]

In the linear regression models, obesity at entry was not a better predictive variable than relative change of BMI, except for the hyperuricemia study. Our explanation for this is as follows: Although BMI is commonly used in determining obesity, it actually is not a very good indicator, because BMI does

Table 9. Multiple Linear Regression Analysis of GGT at Endpoint (2000) as a Function of Age, GGT at Entry (1993), Obesity, Relative Change of BMI, Habit of Drinking, Habit of Smoking, and Regular Physical Exercise ($R^2 = 0.405$)

	estimated coefficient	standard error	*t*-value	*p*-value
Age at entry	−0.89	0.71	−1.26	0.210
GGT at entry	1.77	0.21	8.35	< 0.001
Obesity at entry				
(1 for yes, 0 for no)	−4.00	4.31	−0.93	0.354
Relative change of BMI (%)	0.80	0.24	3.29	0.001
Habit of drinking at entry				
(1 for yes, 0 for no)	11.40	3.32	3.43	< 0.001
Habit of smoking at entry				
(1 for yes, 0 for no)	−0.26	3.13	−0.08	0.933
Regular exercise at entry				
(1 for yes, 0 for no)	1.67	3.01	0.56	0.578

Table 10. Odds Ratios and their 95% Confidence Intervals (95%CI) of Covariates by Logistic Regression Analysis for High Gamma Glutamyl Transferase (> 60 IU/l)

Covariates	Odds ratio (95%CI)	*p*-value
Age at entry		
Increase of 1 year	0.95 (0.74–1.22)	0.670
Obesity at entry		
No	1	
Yes	1.78 (0.43–7.31)	0.426
Relative change of BMI		
Increase of 5%	1.88 (1.14–3.11)	0.014
Habit of drinking at entry		
No	1	
Yes	11.65 (3.49–38.96)	< 0.001
Habit of smoking at entry		
No	1	
Yes	1.43 (0.42–4.84)	0.567
Regular exercise at entry		
No	1	
Yes	1.13 (0.39–3.29)	0.825

not take account of amount of bones and muscles, and because BMI was reported to be significantly influenced by age and sex.[16] On the other hand, increase of BMI during the 7 years of observation in young adulthood is speculated as being related to body fat mass increase, except that the weight gain is attributed to increases in other tissues such as muscle mass by resistance training. Thus, the relative change of BMI is a better index in young male workers for the prediction of lifestyle-related disorders, such as dyslipidemia, hyperuricemia, and liver dysfunction.

In the hyperuricemia study by a logistic regression model, the relative change of BMI was not a good predictive variable. Our speculations for this are as follows: First, when study subjects were limited to sole normouricemic subjects (n = 255), a logistic regression model revealed that the relative change of BMI was significantly associated with an increased risk of hyperuricemia [OR = 1.33, 95% confidence interval (CI): 1.01–1.74], whereas obesity at entry showed no association (OR = 1.52, 95%CI: 0.74–3.13). Sample size of the present study (n = 166) may be too small to detect association between the relative change of BMI and risk of hyperuricemia, because odds ratios of the relative change

of BMI for hyperuricemia were close to each other. Second, some prospective studies recently reported that increased serum uric acid (or hyperuricemia) was associated with an increased risk of developing hyperinsulinemia.[5,6] Thus, the complex mechanism of developing hyperuricemia may affect the ORs of obesity at entry (OR = 1.52 for the study with 255 normouricemic subjects, OR = 3.88 for the present study).

Consequently, the results of the present study indicate that weight gain, in combination with obesity, may be used as a predictor of the later occurrence of blood abnormalities, *i.e.*, dyslipidemia, hyperuricemia, and liver dysfunction, for a period during which male workers do not undergo blood chemistry tests.

Alcohol intake has been associated with hyperuricemia or gout, because ethanol induces purine degradation in the liver and decreases renal urate excretion. In our study, habit of drinking showed no significant association with hyperuricemia in both of the models. The reason is unclear. From previous studies, however, it may be because the effect of habitual drinking is weak for young males or because our study subjects did not consume large enough amounts of alcohol to cause hyperuricemia. For example, a cross-sectional study showed that alcohol consumption was not associated with prevalence of hyperuricemia for the 30–39 year age group after controlling for covariates, whereas alcohol consumption was significantly associated with prevalence of hyperuricemia for both the 40–59 year age group and the group aged 60 years and over[17]; an experimental study demonstrated that a small amount of ethanol ingestion caused uric acid elevation in subjects who had a habit of consuming more than 60 g ethanol every day.[18]

Although regular exercise ameliorates the metabolic abnormalities found in patients with insulin resistance,[19] taking regular exercise showed no meaningful association with the 3 types of abnormality in the present study. Since accumulation of physical activity in intermittent, short bouts has been recommended instead of exercise,[20] a subclass of physical activity, it is desirable to examine the association between the total amount of activity performed by young male subjects, measured as weekly caloric expenditure or total time of physical activity, and the later occurrence of lifestyle-related diseases.

The present study is subject to some limitations. First, we were unable to assess the comparability of biochemical measurements between the two years, *i.e.*, at entry and at endpoint. However, it is probable that the relationship between two biochemical measurements by different methods is linear. Thus, the lack of comparability may be limited, because the regression models showed significant association regarding the relative change of BMI. Second, we were also unable to investigate changes of lifestyle factors during the study period. The relative change of BMI in the present study may reflect some lifestyle modification, *e.g.*, quitting smoking and decrease in activity. Third, although it was speculated that the 3 types of biochemical abnormality were related to insulin resistance in the present study, the study subjects did not undergo measurement of insulin resistance (*e.g.*, fasting insulin and glucose levels). It is desirable to investigate the association between insulin resistance and lifestyle-related diseases in young male workers. Finally, in the liver dysfunction study, subjects with viral hepatitis were not eliminated, because we examined neither hepatitis B antigen nor hepatitis C antibody in the study subjects' blood.

In conclusion, our findings imply that weight gain should be taken into account at the annual health checkups, especially for young male workers who are not undergoing biochemical tests, even if subjects are not classified as obese (BMI $\geq$ 25 kg/m^2).

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