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ScienceDirect
Metabolism Clinical and Experimental 57 (2008) 811–818
Metabolism
Clinical and Experimental
www.metabolismjournal.com

Adiponectin and noncardiovascular death: a nested case-control study

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Received 5 September 2007; accepted 7 January 2008

Abstract

This study is to evaluate the associations between adiponectin level and noncardiovascular death and to test a hypothesis that adiponectin level reflects the degree of systemic wasting that precedes death. A nested case-control study was conducted involving 5243 subjects, drawn from 12 490 subjects of the Jichi Medical School Cohort Study, whose blood samples had been drawn between 1992 and 1995. Over an average of 10.8 years of follow-up, 103 cases with noncardiovascular death and 565 controls without history/event/death of any cardiovascular disease were identified. Odds ratios (ORs) were estimated relative to the lowest quintile of adiponectin level. The risks for noncardiovascular death of the second lowest quintile and the highest quintile of adiponectin level were significantly higher than that of the lowest quintile when adjusted for age and sex (model 1) (OR, 2.38 [95% confidence interval (CI), 1.12-5.06] and 2.16 [1.01-4.80]). All the statistical significances disappeared when adjusted further for body mass index and C-reactive protein level (model 2). When excluding cases with cancer death, the odds for death in the highest 2 quintiles were significantly higher than those in the lowest quintile in model 1 (OR, 2.80 [95% CI, 1.04-7.59] and 3.74 [1.38-10.18]). The significant difference between the highest vs the lowest quintile remained significant in model 2 and even after adjusting further for smoking, diabetes, and total cholesterol level (model 3) (OR, 3.28 [95% CI, 1.02-10.51] and 3.98 [1.21-13.13]). Adiponectin levels had linear associations with the risks of noncardiovascular noncancer death in models 1, 2, and 3 (OR per 1 SD increase in log-adiponectin, 1.72 [95% CI, 1.23-2.40], 1.89 [1.23-2.91], and 2.01 [1.29-3.15]). Adiponectin is an independent indicator of noncardiovascular mortality that may relate with systemic wasting.

1. Introduction

Adiponectin, also designated *Acrp30*, *AdipoQ*, *apM1*, and *GBP28*, is a plasma protein of approximately 30 kd and is the most abundant gene product in adipose tissue [1]. Adiponectin is noted for its direct causal link to insulin sensitivity and for its anti-inflammatory property [2,3]. Lower plasma adiponectin levels are reported to be associated with development of obesity, type 2 diabetes mellitus, metabolic syndrome, dyslipidemia, and hypertension [4-11]. In short, adiponectin is associated with many of the traditional cardiovascular risk factors. Further evidence has shown that hypoadiponectinemia was associated with atherosclerotic cardiovascular events such as myocardial infarction and brain infarction [12-14]. Moreover, recent studies further indicated that adiponectin had a protective role against cancer, showing that hypoadiponectinemia increased incidences of various types of cancer [15-20]. Taking all of the evidence into account, a positive association between hypoadiponectinemia and mortality was highly anticipated.

However, recent epidemiologic studies have shown results to the contrary. Some prospective studies revealed that hyperadiponectinemia, but not hypoadiponectinemia, was associated with all-cause mortality [21-23]. The reason for this contradiction is not known; but it is inferred from the data that adiponectin plays some role in its association with death not as a protector of atherosclerosis, but as a marker of wasting [21,24]. Release of adiponectin from fat tissue is increased under conditions of malnutrition [25,26]. Plasma adiponectin concentration rises in the inflammatory state [27]. It is thus hypothesized that adiponectin can act as a mirror, reflecting the degree of systemic wasting, and thus can predict death.

To test this hypothesis, the association between predeath plasma adiponectin concentration and noncardiovascular death needs to be longitudinally evaluated. Cardiovascular

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doi:10.1016/j.metabol.2008.01.024

death involves both atherosclerotic and wasting components in its underlying pathophysiology, and thus is not suitable for evaluating the role of adiponectin as a predictor of predeath wasting state. Inconclusive results of past epidemiologic studies support it: cardiovascular death is reported to be associated with both hypoadiponectinemia [28] and hyperadiponectinemia [21-23]. Exclusion of cardiovascular deaths from all deaths diminishes the influence of atherosclerosis and increases the extent to which wasting plays parts in the development of mortality. Furthermore, exclusion of cancer death is crucial in evaluating the association between adiponectin and predeath wasting. Adiponectin possesses an anticarcinogenic property [15-20], and this property can make the association between adiponectin and cancer death complicated. It is thus difficult to assess the adiponectin-wasting association in cancer death cases. However, as far as we know, there is no in-depth study evaluating the association between adiponectin level and noncardiovascular deaths, and adiponectin level and noncardiovascular noncancer deaths. We therefore conducted a nested case-control study assessing the associations in the community setting.

2. Subjects and methods

2.1. Study population

The Jichi Medical School Cohort Study began in 1992. Its primary objective was to clarify the relationship between potential risk factors and cardiovascular diseases in 12 rural districts in Japan [29]. The baseline data of this cohort study were obtained between April 1992 and July 1995. If several sets of data were obtained for a single subject during that period, the first set was used as baseline. The baseline data were collected as part of a national mass-screening program. In Japan, mass screening for cardiovascular diseases has been conducted since 1982 in accordance with the Health and Medical Service for the Aged Act of 1981. Local government offices in each community issued invitations to eligible residents for the mass screening, and personal invitations also were sent to all potential subjects by mail. As a result, 12 490 subjects were eligible (4913 men and 7577 women) across all ages (19-93 years of age). The overall response rate among the 12 communities was 65.0%. Written informed consent to participate in the study was obtained individually from all respondents of the mass screening.

Among the 12 490 subjects, 5243 subjects (42.0%) whose blood samples remained stored in 2007 were extracted as potential study participants. Among these potential subjects, 252 individuals who had stroke or myocardial infarction and 756 matched controls without any of the 2 diseases during follow-up were extracted (a case to control ratio of 1 to 3) for another case-control study. Matching was for sex, community, and age. For this particular study, the control group without stroke and myocardial infarction was extracted. Within the control sample, individuals who did not sign the agreement to participate in the study, those who had a history of cardiovascular event at baseline, and those who died of any other cardiovascular diseases than stroke or myocardial infarction (ie, any type of heart failure, rupture of aortic aneurysm, and pulmonary embolism) during follow-up were excluded. In the end, 668 subjects without history/event/death of any cardiovascular disease at baseline and during follow-up remained and were analyzed as study participants. During the follow-up, 103 (15.4%) subjects died of noncardiovascular causes (cases) and 565 (84.6%) subjects remained living (controls). Verification steps for cardiovascular events and causes of deaths are described later.

2.2. Measurement of baseline variables

Body weight was recorded with the subject clothed, and 0.5 kg in summer or 1 kg during the other seasons was subtracted from the recorded weight. Body mass index (BMI) was calculated as weight (in kilograms)/height^2 (in square meters). Systolic blood pressure and diastolic blood pressure were measured with a fully automated sphygmomanometer, BP203RV-II (Nippon Colin, Komaki, Japan), placed on the right arm of a seated subject who had rested in the sitting position for 5 minutes before measurement. Information about medical history and life style was gathered by means of a written questionnaire.

Blood samples were drawn from the antecubital vein of seated subjects, with minimal tourniquet use. Specimens were collected in siliconized vacuum glass tubes containing a 1/10 volume of 3.8% trisodium citrate for blood glucose and no additives for lipids. Tubes were centrifuged at 3000*g* for 15 minutes at room temperature. After separation, the serum samples were stored at 4°C in refrigerated containers if analysis was to be performed within a few days. Otherwise, the samples were frozen until analysis. Plasma samples were quick frozen then stored at −80°C until laboratory examination could be performed.

Total cholesterol and triglycerides were measured using an enzymatic method (Wako, Osaka, Japan; interassay coefficient of variation [CV], 1.5% for total cholesterol and 1.7% for triglyceride). High-density lipoprotein cholesterol was measured using the phosphotungstate precipitation method (Wako; interassay CV, 1.9%). Blood glucose was measured via an enzymatic method (Kanto Chemistry, Tokyo, Japan; interassay CV, 1.9%). High-sensitivity C-reactive protein (CRP) levels were measured using nephelometry, a latex particle-enhanced immunoassay (NA Latex CRP Kit; Dade Behring, Tokyo, Japan). The value in the calibrator was assigned from the *Certified Reference Material 470* (IRMM, Geel, Belgium), an international plasma protein reference manual. Its interassay and intraassay CVs were 1.18% and 1.36%, respectively. The assay is sensitive enough to detect 0.03 mg/L of CRP. Plasma adiponectin concentrations were measured by solid-phase enzyme-linked immunosorbent assay (adiponectin ELIZA kit; Otsuka Pharmaceutical, Tokyo, Japan). The interassay CV was less than 10%. The ideal measurement range was between 0.375 and 12.0 mg/dL.

The maximal detectable range was >23.4 pg/mL. Both high-sensitivity CRP and adiponectin were measured in 2007. The other biochemical markers were measured concurrent with sample collection.

In this study, blood samples of 520 (77.8%) subjects were drawn after overnight fasting. *Diabetic subjects* were defined as those with currently treated diabetes, plasma glucose ≥126 mg/dL after overnight fasting, or casual blood glucose ≥200 mg/dL.

2.3. Follow-up

Subjects were followed through December 31, 2006. Causes of death were identified using death certificates collected at the respective local public health centers, with permission from the Ministry of General Affairs and the Ministry of Health, Labour, and Welfare (Japan). Individuals who moved out of the communities during the observation period were followed until their date of emigration. Data on emigration of study subjects were obtained every year from their corresponding municipal governments.

To check the status of cardiovascular events, repeated examinations, which also were part of the national mass-screening program, were used to follow most subjects every year. Those examined were asked whether they had experienced a cardiovascular disease after enrolling. Subjects who did not come to the screening examination were contacted by mail or phone. Public health nurses visited the subjects to obtain pertinent information when necessary. In all, 100% of the subjects were contacted. Those with a history of cardiovascular disease were asked in which hospital they had been treated and when the disease was diagnosed. Medical records at hospitals in the areas also were checked to determine if these subjects had been treated. If an incident was suspected, forms were filled out and pertinent electrocardiography, computer tomography, and/or magnetic resonance imaging images were obtained for diagnostic confirmation. Diagnoses were determined independently by means of a diagnosis committee composed of 1 radiologist, 1 neurologist, and 2 cardiologists.

No sampling or measurement of any variable was conducted during follow-up.

2.4. Statistical analysis

Statistical analyses were carried out using SPSS for Windows, version 11.5 (SPSS Inc, Tokyo, Japan). Continuous variables were compared between cases and controls using unpaired *t* tests. Categorical variables were compared using χ^2 analysis or the Fisher exact test. Levels of adiponectin, triglyceride, and high-sensitivity CRP were not normally distributed; consequently, they were $\log_{10}$-transformed in all analyses. The association between adiponectin and death was examined by means of logistic regression analysis. Goodness of fit was confirmed by the Hosmer and Lemeshow method. For logistic regression analysis, adiponectin levels were categorized into quintiles, using results from all study subjects, so that quintile 1 contains the lowest 20% and quintile 5 covers the highest 20% of the adiponectin levels. Three separate models were generated for regression analysis: model 1 was adjusted for age and sex; model 2 was adjusted for age, sex, BMI, and high-sensitivity CRP; and model 3 was adjusted for age, sex, BMI, high-sensitivity CRP, diabetes, current smoking status, and total cholesterol. For each model, the odds ratio (OR) and its 95% confidence interval (95% CI) of each of quintiles 2 to 5 vs quintile 1, as well as of combined quintiles 2 to 5 vs quintile 1, were calculated. The OR and 95% CI were also calculated in changes of OR per SD increase in $\log_{10}$-adiponectin to test for linear trends. All analyses were 2-tailed. The value $P < .05$ was considered statistically significant.

3. Results

The mean follow-up period was 10.8 years (11.50 years [SD, 1.31] in controls and 7.26 years [SD, 3.24] in death cases). Among the 668 study subjects, 42 (40.8%) died of cancer, 14 (13.6%) of pneumonia, 11 (10.7%) of chronic lung diseases, 10 (9.7%) of senility, 8 (7.8%) of accident, 7 (6.8%) of suicide, 6 (5.8%) of chronic liver diseases, 2 (1.9%) of chronic renal failure, 2 (1.9%) of hemorrhage of unknown origin, and 1 (1.0%) of unknown cause. Measurements of adiponectin and high-sensitivity CRP were conducted for 14.2 years (SD, 1.05) in controls and 14.2 years (SD, 1.06) in cases after initial sample collection.

Comparisons of characteristics between those with noncardiovascular death and those without are shown in Table 1. The proportion of men was significantly greater in cases than controls (64.1% vs 50.6%, $P = .012$), as were current smokers (39.8% vs 22.7%, $P < .001$) and those with diabetes (11.7% vs 6.2%, $P = .046$). The mean age was significantly higher in cases than controls (70.2 [SD, 7.9] vs 64.6 [8.4] years, $P < .001$), as were adiponectin levels (9.0 vs 8.0 mg/L, $P = .034$) and high-sensitivity CRP (556.5 vs 376.2 mg/L, $P = .002$). Body mass index was lower in cases than in controls (21.4 [SD, 3.0] vs 22.7 [SD, 2.9] kg/m^2, $P < .001$).

Fig. 1 shows the noncardiovascular (A), cancer (B), and noncardiovascular noncancer (C) mortality rates divided by quintiles of adiponectin levels. In all of the 3 causes of death, the mortality rates were lowest in the lowest adiponectin quintile. In Fig. 1A, the noncardiovascular mortality rates had 2 peaks at quintile 2 and quintile 5 showing an N-shaped curve. In Fig. 1B, the cancer mortality rates had the peak at quintile 2 and bottoms at quintiles 1, 4, and 5. Fig. 1C shows a monotonous upward line indicating a linear trend toward an increased risk of noncardiovascular noncancer death at higher adiponectin levels.

Table 2 shows multivariable-adjusted OR for noncardiovascular death in each quintile of adiponectin level. The risks for noncardiovascular death of quintiles 2 and 5 were significantly higher than that of quintile 1 in model 1 (OR,

Table 1
Baseline characteristics of noncardiovascular death cases and matched controls

	Cases (n = 103)	Control (n = 565)	*P* value
Age, mean (SD), y	70.2 (7.9)	64.6 (8.4)	<.001
Male sex	66 (64.1)	286 (50.6)	.012
BMI, mean (SD), kg/m^2	21.4 (3.0)	22.7 (2.9)	<.001
Current smoker	41 (39.8)	128 (22.7)	<.001
Current drinker	48 (46.6)	271 (48.0)	.51
Diabetes [a]	12 (11.7)	35 (6.2)	.046
Systolic blood pressure, mean (SD), mm Hg	131.2 (23.6)	132.3 (22.4)	.69
Diastolic blood pressure, mean (SD), mm Hg	76.2 (13.7)	78.7 (13.2)	.10
Total cholesterol, mean (SD), mg/dL	186.7 (37.7)	191.3 (32.4)	.19
High-density lipoprotein cholesterol, mean (SD), mg/dL	48.4 (13.9)	49.8 (12.3)	.31
Triglyceride, geographic mean (IQR), mg/dL [b]	104.7 (79.5-131.3)	95.9 (67.0-126.8)	.09
Adiponectin, geographic mean (IQR), mg/L [b]	9.0 (6.4-13.0)	8.0 (5.6-12.4)	.034
High-sensitivity CRP, geographic mean (IQR), ng/mL [b]	556.5 (251.5-977.0)	376.3 (171.3-738.8)	.002

Data are expressed as number (percentage) unless otherwise indicated. SD indicates standard deviation; IQR, interquartile range.
[a] Cases with fasting plasma glucose ≥126 mg/dL or postprandial glucose ≥200 or history of treated diabetes were included.
[b] Data were $\log_{10}$-transformed for analysis.

2.38 [95% CI, 1.12-5.06] and 2.16 [1.01-4.80], respectively). In addition, when combining the upper 4 quintiles (quintiles 2 to 5), the risk of the combined category was higher than quintile 1 in model 1 (OR, 2.03 [95% CI, 1.06-3.91]). However, all the statistical significances seen in model 1 disappeared in model 2 and model 3. There was no linear association between adiponectin levels and risks for noncardiovascular death in any of the models.

The results of the same multivariate analysis using subjects who died of cancer are shown in Table 3. The odds for cancer death of subjects in quintile 2 were higher than those in quintile 1 in model 1 and model 2, but the differences were statistically marginal (OR, 2.68 [95% CI, 0.97-7.36] and 2.84 [0.95-8.49], respectively). No linear trend was recognized in any of the models.

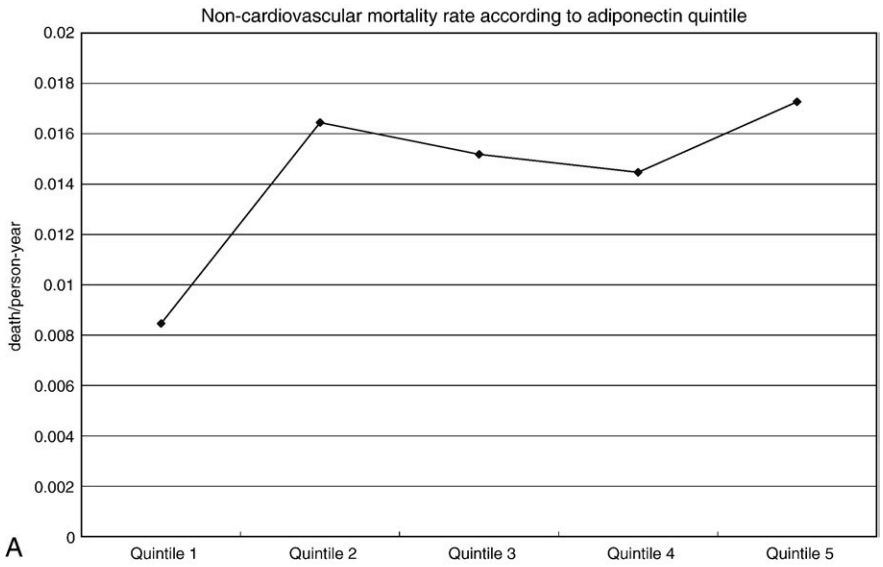
The multivariable-adjusted ORs for noncardiovascular noncancer death are shown in Table 4. In model 1, the odds for death among subjects in quintiles 4 and 5 and the combined quintiles 2 to 5 were significantly higher than those in quintile 1 in model 1 (OR, 2.80 [95% CI, 1.04-7.59], 3.74 [1.38-10.18], and 2.41 [1.02-5.69], respectively). The significant differences of quintile 4 and combined quintiles 2 to 5 vs quintile 1 were lost in models 2 and 3, but the significant differences of quintile 5 vs quintile 1 remained (OR, 3.28 [95% CI, 1.02-10.51] in model 2 and 3.98 [1.21-13.13] in model 3). Adiponectin levels had linear associations with the risks of noncardiovascular noncancer death in models 1, 2, and 3 (OR per 1 SD increase in log-adiponectin, 1.72 [95% CI, 1.23-2.40], 1.89 [1.23-2.91], and 2.01 [1.29-3.15], respectively).

4. Discussion

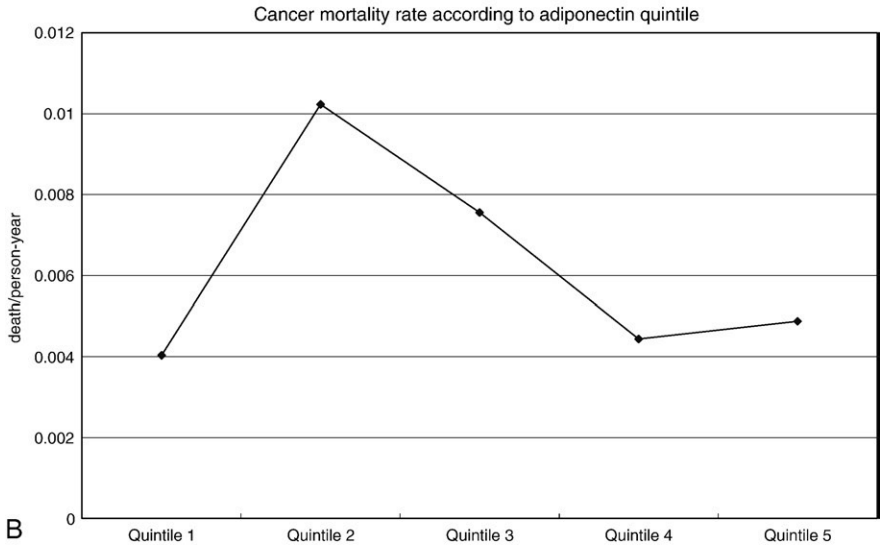
This study demonstrated that the second lowest quintile and the highest quintile of adiponectin concentrations were positively associated with noncardiovascular deaths; but these associations were largely dependent on other variables, particularly on BMI and CRP. The study identified that the peak of risks for noncardiovascular death at the second lowest quintile of adiponectin was largely due to the increased risk for cancer death at the quintile. The second peak seen at the highest quintile derived mainly from the maximum risk for noncardiovascular noncancer death at this quintile. A linear and independent association between adiponectin levels and risks for noncardiovascular noncancer death was observed.

Adiponectin is known to be a modulator of energy homeostasis. Plasma adiponectin concentration increases in response to caloric deprivation and body weight loss; it improves insulin action and enhances lipid oxidation probably through activation of adenosine monophosphate kinase [25-27]. Infection, chronic degenerative diseases, and senility, all of which are the major causes of noncardiovascular noncancer death, shift the systemic energy balance toward the negative side; and the perturbations in energy balance usually precede death. The positive association between hyperadiponectinemia and noncardiovascular noncancer death seen in this study is partially explained by this mechanism. Another explanation is the role of inflammation. Adiponectin inhibits the inflammatory processes regulating monocyte adhesion, macrophage transformation, and the proliferation of smooth muscle cells in blood vessels [27]. Rathmann and Herder [24] hypothesized that adiponectin was released from adipose tissue as a counterregulator against systemic inflammation or the proinflammatory state. This can be another explanation for the pathological effect of hyperadiponectinemia on noncardiovascular noncancer death suggested by the results of this study. Traditional inflammatory cytokines such as tumor necrosis factor–α and

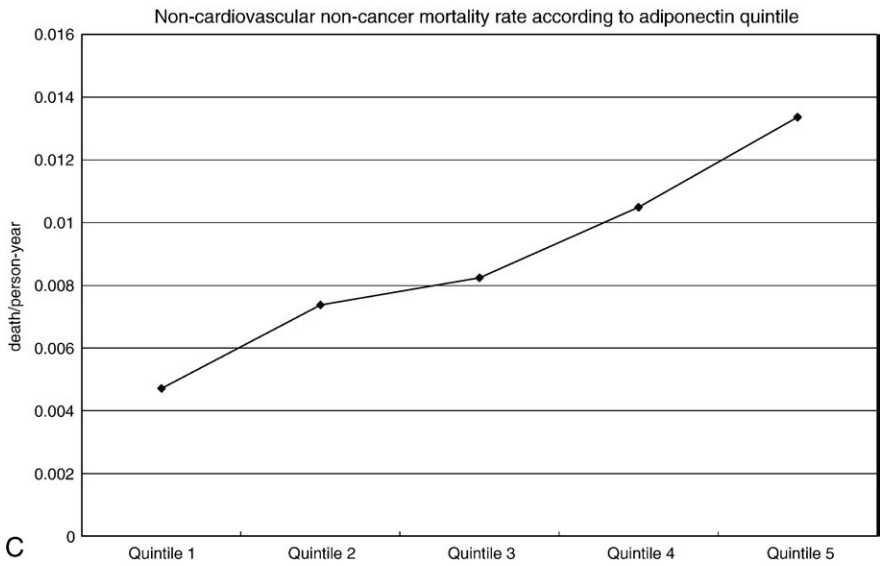
Fig. 1. The noncardiovascular (A), cancer (B), and noncardiovascular noncancer (C) mortality rate according to adiponectin quintile. Quintile 1, <5.1 mg/L; quintile 2, 5.1 to 7.2 mg/L; quintile 3, 7.2 to 9.6 mg/L; quintile 4, 9.6 to 13.3 mg/L; and quintile 5, >13.3 mg/L.


Non-cardiovascular mortality rate according to adiponectin quintile
death/person-year
0.02
0.018
0.016
0.014
0.012
0.01
0.008
0.006
0.004
0.002
0
Quintile 1
Quintile 2
Quintile 3
Quintile 4
Quintile 5

A


Cancer mortality rate according to adiponectin quintile
death/person-year
0.012
0.01
0.008
0.006
0.004
0.002
0
Quintile 1
Quintile 2
Quintile 3
Quintile 4
Quintile 5

B


Non-cardiovascular non-cancer mortality rate according to adiponectin quintile
death/person-year
0.016
0.014
0.012
0.01
0.008
0.006
0.004
0.002
0
Quintile 1
Quintile 2
Quintile 3
Quintile 4
Quintile 5

C

Table 2
Multivariable-adjusted ORs for noncardiovascular death, relative to adiponectin level (103 cases and 565 controls)

	Range, mg/L	Cases	Controls	Model 1 [a]			Model 2 [b]			Model 3 [c]		
				HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
Quintile 1	<5.1	13	123	1.00			1.00			1.00		
Quintile 2	5.1-7.2	24	110	2.38	1.12-5.06	.024	2.15	0.98-4.74	.06	1.89	0.83-4.30	.13
Quintile 3	7.2-9.6	21	111	1.82	0.84-3.95	.13	1.52	0.67-3.49	.32	1.50	0.64-3.54	.35
Quintile 4	9.6-13.3	21	115	1.76	0.80-3.88	.16	1.44	0.61-3.40	.40	1.41	0.58-3.46	.45
Quintile 5	13.3<	24	106	2.16	1.01-4.80	.046	1.66	0.67-4.16	.28	2.10	0.82-5.39	.12
Quintiles 2-5	≥5.1	90	442	2.03	1.06-3.91	.034	1.72	0.86-3.45	.12	1.68	0.83-3.43	.15
Per SD increase in log				1.24	0.96-1.59	.10	1.19	0.89-1.59	.25	1.25	0.92-1.68	.15

HR indicates hazard ratio.
[a] Adjusted for age and sex.
[b] Adjusted for model 1 + BMI and high-sensitivity CRP.
[c] Adjusted for model 2 + current smoking status, diabetes, and total cholesterol.

interleukin-1 were not measured in this study. It is possible that they also are predictors of noncardiovascular or noncardiovascular noncancer death. Further studies are needed to compare the predictive power between adiponectin and other inflammatory cytokines.

Both the negative energy balance and inflammation lead to the state called *wasting*. The higher predeath adiponectin levels in cases with noncardiovascular death and cases with noncardiovascular noncancer death probably reflect the wasting state in which the cases had been embedded before death. Past cross-sectional studies revealed that higher levels of adiponectin were associated with liver cirrhosis, rheumatoid arthritis, inflammatory bowel disease, and systemic lupus erythematosus, all of which are conditions predisposed to wasting [30-33]. Moreover, the robustness of statistical significance of the linear association between adiponectin levels and noncardiovascular noncancer deaths regardless of the multifactorial adjustment including BMI and CRP indicates that the wasting-predictive property of adiponectin is independent of conventional indicators of wasting. Adiponectin may possess its own mechanism by which it is associated with wasting. This is further supported by past studies that reported that hyperadiponectinemia predicted death independent of BMI in patients with heart diseases and chronic kidney diseases [21,23,34,35]. These studies suggest that adiponectin is a more sensitive marker of wasting than BMI. Because BMI is not a precise indicator of the amount of body fat, the interpretation of these studies should be made with caution.

In terms of cancer death, interpretation of the results of this study is more complex. Past cross-sectional and longitudinal studies showed that hypoadiponectinemia was associated with incidences of colorectal [15], gastric [16], endometrial [17], breast [18], and renal carcinoma [20]. The method(s) by which hypoadiponectinemia increases the risk of cancers is largely unknown. One possible mechanism is that hyperinsulinemia accompanied by hypoadiponectinemia reduces circulating levels of insulinlike growth factor–1, which increases cellular proliferation and inhibits apoptosis [36,37]. Probably because of this anticarcinogenic property of adiponectin, the association between adiponectin level and cancer death was nonlinear as was expected. The relationship between adiponectin levels and risks of cancer death supposedly rests on the balance between the anticancer effect of adiponectin and its property of reflecting the degree of wasting. The lowest risk for cancer death in the lowest quintile of adiponectin levels is probably due to the low wasting condition. The peak of the risks seen in the second lowest quintile group may reflect a complex condition in which the carcinogenic effect of hypoadiponectinemia overwhelms the beneficial effect of low wasting status in the quintile. The other bottoms of risks seen in the highest

Table 3
Multivariable-adjusted ORs for cancer death according to adiponectin level (42 cases and 565 controls)

	Range, mg/L	Cases	Controls	Model 1 [a]			Model 2 [b]			Model 3 [c]		
				OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value
Quintile 1	<5.1	6	123	1.00			1.00			1.00		
Quintile 2	5.1-7.2	14	110	2.68	0.97-7.36	.06	2.84	0.95-8.49	.06	2.68	0.84-8.53	.10
Quintile 3	7.2-9.6	10	111	1.69	0.58-4.96	.34	1.79	0.57-5.64	.32	1.82	0.55-6.03	.33
Quintile 4	9.6-13.3	6	115	0.90	0.27-3.02	.87	0.94	0.26-3.37	.92	0.97	0.26-3.66	.96
Quintile 5	13.3<	6	106	0.93	0.27-3.20	.90	0.79	0.20-3.07	.73	1.07	0.26-4.45	.92
Quintiles 2-5	≥5.1	36	442	1.63	0.65-4.10	.30	1.70	0.62-4.66	.30	1.73	0.61-4.90	.30
Per SD increase in log				0.84	0.60-1.18	.32	0.79	0.55-1.14	.21	0.91	0.61-1.34	.62

[a] Adjusted for age and sex.
[b] Adjusted for model 1 + BMI and high-sensitivity CRP.
[c] Adjusted for model 2 + current smoking status, diabetes, and total cholesterol.

Table 4
Multivariable-adjusted ORs for noncardiovascular noncancer death according to adiponectin level (61 cases and 565 controls)

	Range, mg/L	Cases	Controls	Model 1 [a]			Model 2 [b]			Model 3 [c]		
				OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value
Quintile 1	<5.1	7	123	1.00			1.00			1.00		
Quintile 2	5.1-7.2	10	110	1.92	0.68-5.44	.22	1.47	0.50-4.36	.49	1.52	0.50-4.59	.46
Quintile 3	7.2-9.6	11	111	1.80	0.64-5.05	.26	1.21	0.39-3.71	.74	1.24	0.40-3.87	.71
Quintile 4	9.6-13.3	15	115	2.80	1.04-7.59	.043	2.05	0.69-6.08	.20	1.98	0.64-6.11	.24
Quintile 5	13.3<	18	106	3.74	1.38-10.18	.010	3.28	1.02-10.51	.046	3.98	1.21-13.13	.023
Quintiles 2-5	≥5.1	54	442	2.41	1.02-5.69	.045	1.69	0.69-4.11	.25	1.73	0.70-4.26	.24
Per SD increase in log				1.72	1.23-2.40	.002	1.89	1.23-2.91	.004	2.01	1.29-3.15	.002

[a] Adjusted for age and sex.
[b] Adjusted for model 1 + BMI and high-sensitivity CRP.
[c] Adjusted for model 2 + current smoking status, diabetes, and total cholesterol.

and the second highest quintile groups are probably due to the anticarcinogenic effect of hyperadiponectinemia that overwhelms the effect of high wasting status.

Moderate alcohol intake was reported to be associated with higher adiponectin concentrations [38] and therefore can be a confounder of the association between adiponectin and noncardiovascular death. Among all the cases with noncardiovascular death, 6 (5.8%) died of chronic liver diseases, 2 (1.9%) died of primary liver cancer, and 3 (2.9%) died of liver failure due to cancer of unknown origin. In total, only 11 (10.7%) cases died of diseases that could be caused directly by alcohol intake. Moreover, it is uncertain how much proportion of the death cases was truly associated with alcohol intake. Taking into account the fact that more than 80% of patients with liver cirrhosis and more than 95% of those with hepatocellular carcinoma are caused by hepatitis viruses in Japan [39,40], we consider the confounding effect of alcohol intake to be minimal in this study.

This study is not without limitations. The prolonged interval between blood collection and measurement might have some effect on the measurement of results. However, past studies in which plasma adiponectin levels have been measured shortly after plasma collection have shown that mean levels of adiponectin in healthy Japanese populations range between 7.9 and 11.4 [4,41-43]. This range is in agreement with the mean adiponectin level detected among the controls in our study (8.0 [interquartile range, 5.6-12.4]), suggesting adequate stability of adiponectin levels in frozen, stored samples over time. Lack of information on the longitudinal change of body weight or BMI during follow-up is another limitation. Because body weight was measured at baseline and no repeated measurement was conducted, it is difficult to ascertain that those who had died were wasting before their death. The fact that BMI at baseline was significantly lower in cases than in controls suggests that cases at baseline were already in a predeath wasting state. Considering the pathophysiology of most of the noncardiovascular deaths, we presumed that cases were wasting away throughout the follow-up periods. This presumption should be supported by data from repeated BMI measurements in future studies. The third limitation is that the small number of outcome cases decreased statistical power to detect difference of risks among adiponectin quintiles. The subjects of this study were extracted originally as the controls for another nested case-control study evaluating the association between adiponectin and cardiovascular diseases [44]. This methodological turnabout decreased the number of total study participants, leading to the limited number of death cases despite the long follow-up period.

Plasma adiponectin concentration is one of the major indicators of systemic atherosclerosis. Our study showed that adiponectin is also an independent indicator of noncardiovascular death, which potentially relates with systemic wasting. Further studies are needed to confirm the usefulness of adiponectin concentration as a predictor of wasting and death.

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