

CDH13 Genotype–Dependent Association of High–Molecular Weight Adiponectin With All-Cause Mortality: The J-SHIP Study

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OBJECTIVE

Despite its anti-inflammatory and antiatherogenic effects, adiponectin is potentially associated with adverse clinical outcomes, such as all-cause mortality. As plasma adiponectin levels are strongly influenced by single nucleotide polymorphisms in the gene encoding T-cadherin (*CDH13*), we conducted a longitudinal study to investigate the possible link between the *CDH13* genotype, plasma adiponectin levels, and all-cause mortality.

RESEARCH DESIGN AND METHODS

This longitudinal study evaluated 2,020 Japanese subjects. Baseline clinical parameters were obtained from subjects' personal health records as evaluated at annual medical check-ups. Plasma high–molecular weight adiponectin (HMWA) levels were measured by an ELISA assay, and genotyping was performed by a TaqMan probe assay.

RESULTS

Mean follow-up duration was 6.5 years. Kaplan-Meier analysis showed that HMWA levels were positively associated with mortality ($P < 0.001$). HMWA levels were associated with older age, lower body weight, lower plasma triglyceride and glucose levels, and higher plasma HDL cholesterol. However, the Cox regression analysis showed that the positive association between HMWA and all-cause mortality was independent of these covariates (hazard ratio [HR] 1.92, $P = 0.006$). The *CDH13* rs4783244 genotype was strongly associated with baseline HMWA levels (per-allele effect size 1.65 $\mu\text{g/mL}$, $P < 0.001$). In a separate analysis by the *CDH13* genotype, the HR for all-cause mortality was linearly increased with the number of G alleles (P value for HMWA–*CDH13* genotype interaction = 0.023).

CONCLUSIONS

Higher plasma HMWA level was an independent prognostic factor for all-cause mortality in a general population. The *CDH13* genotype may be a factor that affects not only the plasma level of HMWA but also the prognostic significance of HMWA.

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Adiponectin is an adipocyte-derived secretory protein that has peripheral insulin-sensitizing activity (1). Adiponectin also exerts systemic anti-inflammatory effects via suppression of the growth and proliferation of macrophage progenitors, as well as the inflammation caused by fully differentiated macrophages (1). Further, cross-sectional studies in various populations have reported that a higher plasma adiponectin level is associated with a lower frequency of type 2 diabetes (2), metabolic syndrome (3), and thinner carotid arterial wall thickness (4). The results of these experimental studies and population-based cross-sectional association studies indicate that adiponectin is a cardioprotective factor in humans.

In contrast, several longitudinal epidemiological studies have reported that a higher plasma adiponectin level was associated with an increased incidence of cardiovascular disease (CVD) (5,6) and mortality (7–12). The underlying mechanism of the inverse association between these cross-sectional association studies and longitudinal prospective studies, the “adiponectin paradox,” is unclear and prevents a complete understanding of the biological role of adiponectin. A number of possibilities warrant investigation including reverse causality stemming from a compensatory increase of adiponectin to subclinical CVD risks and adiponectin resistance (13).

Recent advances in DNA array technology have enabled the high-throughput analysis of single nucleotide polymorphisms (SNPs). Genome-wide association studies (GWAS) have successfully identified SNPs of the *CDH13* gene that have a strong association with plasma adiponectin levels (14,15). The *CDH13* gene encodes T-cadherin, a receptor for hexameric and high-molecular weight forms of adiponectin (HMWA) (16). Although earlier studies (17,18) and recent GWAS in European subjects (19,20) reported a strong susceptibility of SNPs in the *ADIPOQ* gene that encodes adiponectin, GWAS of adiponectin in East Asian subjects, namely Korean (15) and Japanese (21), identified SNPs in the *CDH13* locus, such as rs4783244.

Because plasma adiponectin levels in subjects homozygous for the allele that with an association with higher adiponectin levels (affected allele) were ~1.5 times higher than those homozygous for the allele without (unaffected allele) (21), genetic variation might be partially involved in the adiponectin paradox.

To clarify our hypothesis, we analyzed the possible interaction of the *CDH13* genotype in the association of plasma levels of HMWA and all-cause mortality in Japanese middle-aged to elderly community residents.

RESEARCH DESIGN AND METHODS

This longitudinal study enrolled community-dwelling Japanese subjects living in Nomura Town, Ehime Prefecture, a mostly rural town with 11,000 inhabitants. Study subjects were recruited through a community-based annual medical check-up process in 2002 as part of the Shimanami Health Promoting Program (J-SHIP) (3,22,23), which was a longitudinal epidemiological study evaluating factors relating to CVD, dementia, and death. Among a total of 2,721 residents who agreed to participate in the J-SHIP study and completed baseline clinical measurements, 2,020 persons for whom an overnight fasting plasma sample was provided (>11 h) for HMWA measurement ($n = 2,084$), for whom *CDH13* genotype was determined ($n = 2,042$), and for whom mortality during this study period could be followed up were enrolled in this analysis. All study procedures were approved by the ethics committee of Ehime University Graduate School of Medicine, and all subjects provided signed informed consent prior to participation.

Baseline Measurements

Baseline clinical characteristics evaluated at medical checkups, including anthropometric measurements, blood pressure (BP), and basic plasma markers, were obtained from personal health records. Additional characteristics, including medication and history of CVD, were obtained by individual interviews using a structured questionnaire. Hypertension was defined as any or all of the following: systolic BP (SBP) ≥ 140

mmHg, diastolic BP ≥ 90 mmHg, and current use of antihypertensive medication. Subjects with a fasting blood glucose level of >126 mg/dL or currently using antihyperglycemic medication were defined as having type 2 diabetes. Renal function was evaluated based on the estimated glomerular filtration rate (eGFR), which was calculated from the plasma creatinine values using the following formula specifically developed by the Japanese Society of Nephrology for the estimation of the glomerular filtration rate in Japanese: $194 \times \text{creatinine}^{-1.094} \times \text{age}^{-0.287} \times 0.739$ (if female).

Follow-up of All-Cause Mortality

Vital status was ascertained until 30 November 2009 by checking a residential registration certification, which is under local government control. Since the registration of a person's death is obligatory under the Family Registration Law in Japan, the local government's vital statistics database enabled the follow-up of all-cause mortality. Further, as the notification of a change of address is obligatory under the residential registration certificate system, we were informed of subjects who moved outside of the cohort area and treated them as a censored case.

Measurement of Plasma HMWA Levels

Plasma samples were obtained from each subject after a period of overnight fasting of at least 11 h. Samples were immediately frozen and stored at -80°C until analysis. Plasma concentrations of HMWA were determined using an ELISA assay (Fujirebio, Tokyo, Japan) (3,24), which consisted of HMWA-specific capture antibody (IH7) and HMWA-specific horseradish peroxidase-conjugated detection antibody (POD-IH7). The specificity of this monoclonal antibody has previously been described (25). Standardized HMWA concentrations were determined by human HMWA purified by gelatin-cellulofine column chromatography. Intra- and interassay coefficient variations of the adiponectin assay were 4.4% and 9.7%, respectively.

Genotyping

DNA was extracted from peripheral blood using a QIAamp DNA blood kit

(Qiagen, Hilden, Germany). The SNP rs4783244 in the *CDH13* gene was genotyped by a TaqMan probe assay using commercially available primers and probes purchased from the Assay-on-Demand system (Life Technologies, Carlsbad, CA). Fluorescence of PCR products was measured using an ABI PRISM 7900HT sequence detector (Life Technologies, Tokyo, Japan).

Statistical Analysis

Differences in the numeric variables of baseline data were assessed by ANOVA, and differences in frequency were assessed by a χ^2 test. Overall survival ratio was calculated by Kaplan-Meier analysis. Covariate-adjusted hazard ratio (HR) for total mortality was analyzed by Cox proportional hazards regression analysis. Combined HR was calculated under a random effects model. A *P* value <0.05 was considered statistically significant.

RESULTS

Baseline clinical characteristics of study subjects are shown in Table 1. Mean HMWA level in female subjects (7.62 ± 4.56 $\mu\text{g/mL}$) was nearly double that in male subjects (4.12 ± 2.93 $\mu\text{g/mL}$, *P* < 0.001). Subjects were therefore divided by HMWA quartile within each sex and then combined to avoid

potential sex differences (Table 1). Table 1 also summarizes the differences in clinical parameters among HMWA quartiles. Age was strongly and positively associated with HMWA quartile, while BMI showed a significant inverse association. Plasma levels of HDL cholesterol, triglyceride, and glucose were also significantly different among HMWA quartiles. In a simple comparison, SBP and eGFR were significantly associated with HMWA quartile; however, these associations disappeared after adjustment for age and BMI.

Mean follow-up duration was 6.5 years, during which time 84 subjects died.

Figure 1A shows the Kaplan-Meier plot for all-cause mortality by HMWA quartile, with the highest quartile being strongly associated with all-cause mortality. For clarification of whether the prognostic significance of HMWA was independent of possible covariates, Cox regression analysis was performed by a forward covariate selection method. Table 2 summarizes the HR of the 4th quartile of HMWA, as well as 10 $\mu\text{g/mL}$ increases in HMWA, in relation to total mortality. In any model adjusted for relevant clinical parameters (Table 2 [models 1–3]), higher plasma HMWA levels were independently associated with total mortality.

The G allele of the *CDH13* rs4783244 genotype was strongly associated with baseline plasma HMWA level (Fig. 2). Although obese subjects, defined as having a BMI >25 kg/m^2 , showed significantly lower HMWA levels in both sexes (male obese 3.25 ± 2.22 , nonobese 4.49 ± 3.12 , *P* < 0.001; female 6.37 ± 3.68 , 8.18 ± 4.86 , *P* < 0.001), the association between *CDH13* genotype and HMWA was independent of obesity status (Fig. 2). Per-allele effect size of the genotype calculated by a regression analysis adjusted for age, sex, and BMI was 1.65 $\mu\text{g/mL}$ (*P* < 0.001).

Nevertheless, the prognostic significance of HMWA on total mortality was independent of the *CDH13* genotype (Table 2 [model 4]). In a separate analysis by the genotype, however, HR for all-cause mortality was linearly increased with the number of G alleles (Fig. 1B), and the association between HMWA and poor prognosis was seen only in the GG genotype carries. The term of interaction between the *CDH13* genotype and plasma HMWA level was identified as a significant factor for all-cause mortality (*P* = 0.023) in the Cox regression analysis adjusted for the same covariates as are adjusted for in model 3 of Table 2. These results

Table 1—Clinical parameters of HMWA quartiles

	Total subjects	HMWA quartile				<i>P</i>	
		Quartile 1	Quartile 2	Quartile 3	Quartile 4	ANOVA (crude)	Trend (adjusted)
<i>n</i>	2,020	501	507	507	505		
HMWA ($\mu\text{g/mL}$)	6.09 ± 4.33	2.34 ± 1.07	4.21 ± 1.51	6.36 ± 2.05	11.43 ± 4.60		
Age (years)	62.4 ± 12.3	57.9 ± 11.9	60.9 ± 12.4	63.3 ± 11.7	67.6 ± 11.0	<0.001	
Sex (male %)	44.2	44.3	43.8	43.4	44.2	0.998	
BMI (kg/m^2)	23.5 ± 3.2	24.6 ± 3.2	23.8 ± 3.2	23.3 ± 2.9	22.2 ± 3.0	<0.001	
SBP (mmHg)	139 ± 22	140 ± 22	136 ± 21	139 ± 23	142 ± 22	0.001	0.995
Total cholesterol (mg/dL)	203 ± 35	205 ± 36	204 ± 35	201 ± 33	203 ± 34	0.302	0.093
HDL cholesterol (mg/dL)	62 ± 16	56 ± 14	60 ± 14	63 ± 15	68 ± 16	<0.001	<0.001
Triglyceride (mg/dL)	113 ± 74	139 ± 92	115 ± 69	107 ± 64	91 ± 58	<0.001	<0.001
eGFR (mL/min/1.73 m^2)	80 ± 17	82 ± 18	80 ± 17	81 ± 17	78 ± 17	<0.001	0.266
Glucose (mg/dL)	98 ± 21	102 ± 24	98 ± 23	98 ± 22	95 ± 15	<0.001	<0.001
Antihyperglycemic medication (%)	3.4	3.8	2.8	4.1	3.0	0.575	
Type 2 diabetes (%)	7.4	10.6	6.9	6.7	5.4	0.011	
<i>CDH13</i> genotype (G allele %)	65.8	51.7	65.3	68.3	77.9	<0.001	

Data are means \pm SD unless otherwise indicated. Quartile of HMWA was calculated within each sex and then combined to avoid potential sex differences. Statistical significance in numeric variables was assessed by ANOVA, while differences in frequency were assessed by a χ^2 test. Trends in numeric variables among the HMWA quartile were assessed by regression analysis adjusted for age and BMI. The eGFR was calculated from plasma creatinine values using the following formula: $194 \times \text{creatinine}^{-1.094} \times \text{age}^{-0.287} \times 0.739$ (if female). Type 2 diabetes was defined as a fasting plasma glucose level >126 mg/dL or the current use of medication to lower blood glucose levels. G-allele frequency of the *CDH13* rs4783244 genotype is shown.

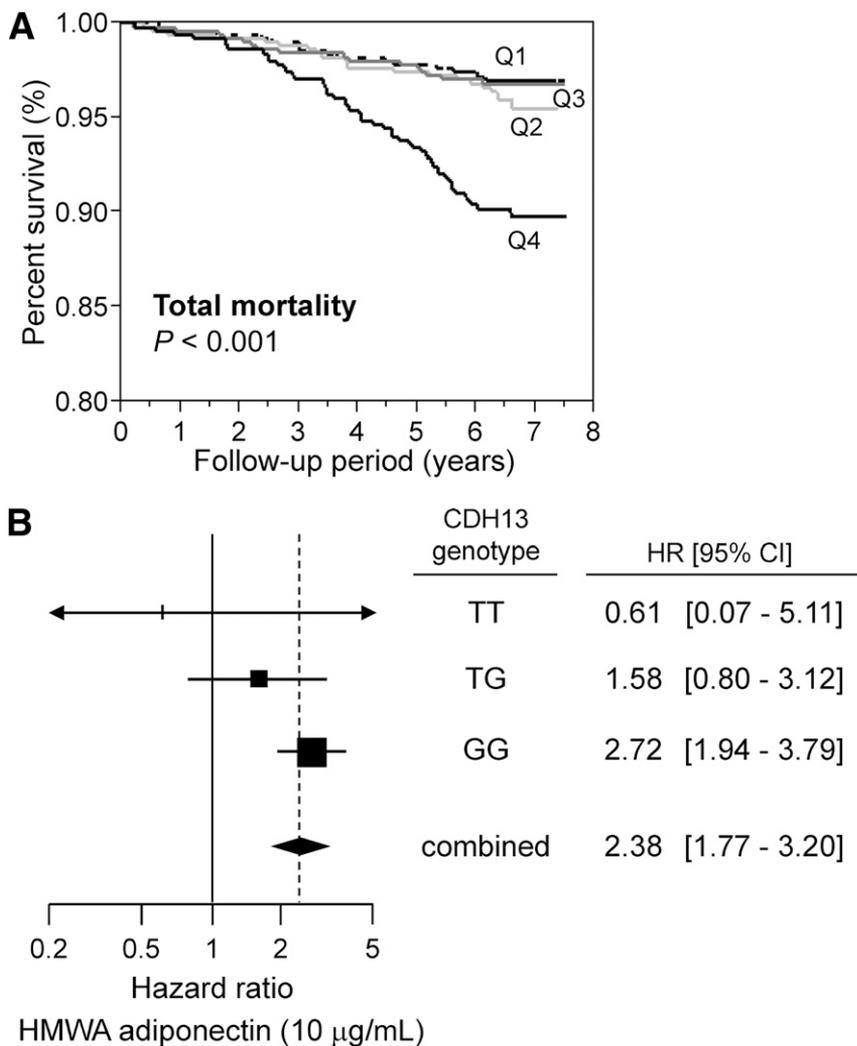


Figure 1—HMWA and all-cause mortality. **A:** Kaplan-Meier plot of survival by HMWA quartile (Q1–Q4). Subjects were divided by HMWA quartile within each sex and then combined to avoid potential sex differences. **B:** HR of HMWA with total mortality and CDH13 rs4783244 genotype. HR of HMWA (continuous variable [per 10 $\mu\text{g}/\text{mL}$]) for each CDH13 rs4783244 genotype was calculated by a Cox regression analysis adjusted for age and sex. Diamond represents the combined odds ratio calculated by a random-effects model.

indicate that the poor prognostic significance of HMWA was genotype dependent.

CONCLUSIONS

In this longitudinal study in a general population, we observed that higher plasma HMWA levels were significantly associated with all-cause mortality. Further, the association between HMWA and mortality showed a high degree of variation among CDH13 rs4783244 genotypes. To our knowledge, this is the first study showing a genotype-dependent association of HMWA with all-cause mortality.

Our results confirmed the increased risk of all-cause mortality in subjects with a higher baseline HMWA level. Several previous studies reported a similar relationship in general populations (5, 8–10), as well as in patients with type 2 diabetes (7), coronary artery disease (6,11), and chronic heart failure (12). Higher plasma HMWA in a general population is a complex phenotype that may represent a clustering of subclinical risk statuses, namely, reduced renal and cardiac function, obesity, insulin resistance and metabolic disorders, atherosclerosis, systemic inflammation, weight loss in elderly, and anemia. However, these studies were conducted

mainly in European subjects (7,9–12) or in European and African American subjects (5,6,8), with no positive results being reported from East Asian subjects. In contrast, it has been reported that the Japanese population has distinct anthropometric characteristics, including a lower frequency of obesity compared with developed Western countries (26), and considerably lower plasma adiponectin levels (27), even in comparison with Japanese Americans living in Hawaii (28). In populations with lower HMWA levels, our results demonstrate the cross-validity of the prognostic significance of HMWA.

We also found an inverse association between HMWA and all-cause mortality between CDH13 TT and CDH13 GG genotype carriers, with the HR of the CDH13 TT genotype failing to reach statistical significance, presumably due to the smaller subsample size. Although the CDH13 gene is known to encode T-cadherin, a receptor for HMWA, the functionality of each CDH13 rs4783244 genotype or other unidentified responsible SNPs in linkage disequilibrium have not been clarified. However, T-cadherin knockout mice were reported to show dramatically increased plasma adiponectin levels due to impaired linkage between adiponectin and target cells (29). It is therefore possible that the G allele of the CDH13 genotype causes secondary hyperadiponectinemia by altering the amount or functionality of T-cadherin. This genetically dependent adiponectin resistance and consequent reduction in adiponectin’s anti-inflammatory and antiatherogenic effects may explain the increased mortality ratio in subjects with higher HMWA levels. Because differences in HMWA levels for each CDH13 rs4783244 genotype were similar between nonobese and obese subjects (Fig. 2), the production of adiponectin and formation of high-molecular weight isoforms might not be a factor in the genotype-specific mortality ratio.

According to the HapMap database (<http://hapmap.ncbi.nlm.nih.gov/>), frequency of the CDH13 rs4783244 genotype is similar across all ethnic groups. However, GWAS in European subjects (19,20) identified only the

Table 2—HR of plasma HMWA levels on total mortality

Model	Factors adjusted for	HMWA			
		10 $\mu\text{g}/\text{mL}$		4th quartile	
		HR (95% CI)	P	HR (95% CI)	P
1	Age, sex	2.03 (1.34–2.96)	0.001	1.78 (1.19–2.68)	0.006
2	Age, sex, BMI	1.85 (1.20–2.76)	0.006	1.63 (1.08–2.48)	0.021
3	Age, sex, BMI, SBP, TC, HDLC, glucose, CVD, eGFR, current smoking, current medication	1.91 (1.20–2.96)	0.007	1.59 (1.03–2.46)	0.035
4	Age, sex, BMI, SBP, TC, HDLC, glucose, CVD, eGFR, current smoking, current medication, CDH13 genotype	1.83 (1.12–2.91)	0.017	1.51 (0.97–2.37)	0.068

HR was calculated by a cox regression analysis. CVD indicates previous history of CVDs (namely, stroke and myocardial infarction). Medication includes antihypertensive drugs and antihyperglycemic drugs. HDLC, HDL cholesterol; TC, total cholesterol.

ADIPOQ gene as susceptible loci for plasma adiponectin levels. Although more large-scale GWAS might identify the *CDH13* gene as another susceptible loci, it is probable that genetic polymorphisms in the *ADIPOQ* gene have a larger effect than those in the *CDH13* genotype in European populations regardless of the type of adiponectin complex (30). Because the *ADIPOQ* gene encodes adiponectin, our “genetic adiponectin resistance” hypothesis involving the *CDH13* gene as a means of explanation might not be easily extrapolated to other populations. However, our results provide novel supporting evidence that adiponectin resistance is a key mechanism of the adiponectin paradox,

which is lacking in other proposed mechanisms such as renal dysfunction and decreased adiponectin clearance, weight loss, or sarcopenia in the elderly and compensatory rise in adiponectin due to subclinical risks (reverse causality) (13). Our present results also excluded the possibility of confounding effects of decreased renal function.

Several limitations of this study warrant mention. First, we could not evaluate a cause-specific mortality, particularly cardiovascular mortality. Results of long-term analysis for cardiovascular mortality would strengthen our findings. Second, we did not analyze other molecular isoforms of adiponectin. As T-cadherin is a receptor for HMWA and the HMW isoform is

considered an active form, further investigations regarding isoform specificity will be necessary. Third, this study contained ~2,000 study subjects. Replication studies, particularly in East Asian populations, with a larger sample size are therefore needed to confirm our present findings.

In summary, our longitudinal study demonstrated that the prognostic significance of HMWA is genotype specific. Our findings may provide the insight necessary to help solve the adiponectin paradox and further highlight the importance of genetic factors in understanding the contribution of adiponectin levels to adverse clinical outcomes.

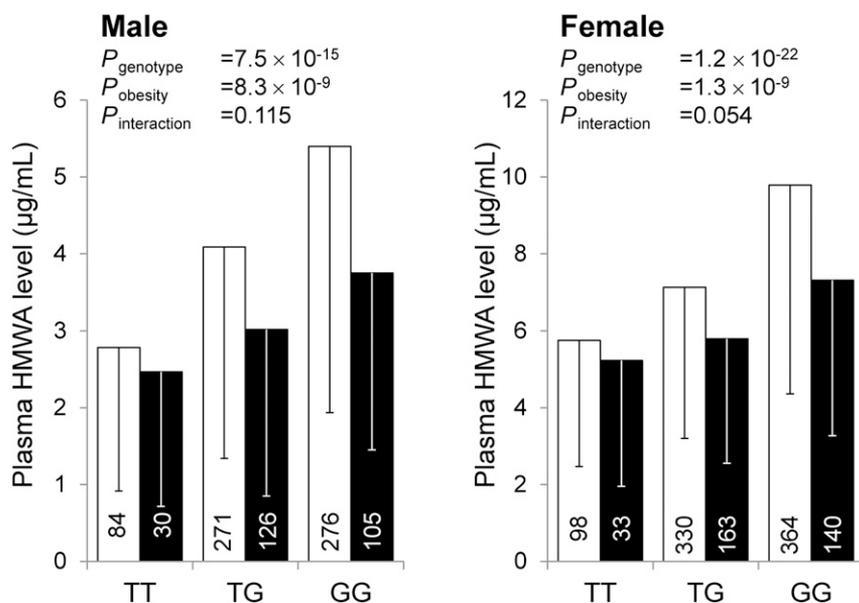


Figure 2—Mean HMWA level and CDH13 rs4783244 genotype. Values are means \pm SD. Statistical significance was assessed by ANOVA. Number of subjects for each genotype is shown in the column. Obesity was defined as a BMI >25 kg/m². White bars, nonobese; black bars, obese.

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References

1. Turer AT, Scherer PE. Adiponectin: mechanistic insights and clinical implications. *Diabetologia* 2012;55:2319–2326
2. Li S, Shin HJ, Ding EL, van Dam RM. Adiponectin levels and risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA* 2009;302:179–188
3. Tabara Y, Osawa H, Kawamoto R, et al. Reduced high-molecular-weight adiponectin and elevated high-sensitivity C-reactive protein are synergistic risk factors for metabolic syndrome in a large-scale middle-aged to elderly population: the Shimanami Health Promoting Program Study. *J Clin Endocrinol Metab* 2008;93:715–722
4. Iglseider B, Mackevics V, Stadlmayer A, Tasch G, Ladurner G, Paulweber B. Plasma adiponectin levels and sonographic phenotypes of subclinical carotid artery atherosclerosis: data from the SAPHIR Study. *Stroke* 2005;36:2577–2582
5. Kizer JR, Benkeser D, Arnold AM, et al. Total and high-molecular-weight adiponectin and risk of coronary heart disease and ischemic stroke in older adults. *J Clin Endocrinol Metab* 2013;98:255–263
6. Kizer JR, Barzilay JI, Kuller LH, Gottdiener JS. Adiponectin and risk of coronary heart disease in older men and women. *J Clin Endocrinol Metab* 2008;93:3357–3364
7. Singer JR, Palmas W, Teresi J, Weinstock R, Shea S, Luchsinger JA. Adiponectin and all-cause mortality in elderly people with type 2 diabetes. *Diabetes Care* 2012;35:1858–1863
8. Kizer JR, Benkeser D, Arnold AM, et al. Associations of total and high-molecular-weight adiponectin with all-cause and cardiovascular mortality in older persons: the Cardiovascular Health Study. *Circulation* 2012;126:2951–2961
9. Poehls J, Wassel CL, Harris TB, et al.; Health ABC Study. Association of adiponectin with mortality in older adults: the Health, Aging, and Body Composition Study. *Diabetologia* 2009;52:591–595
10. Laughlin GA, Barrett-Connor E, May S, Langenberg C. Association of adiponectin with coronary heart disease and mortality: the Rancho Bernardo study. *Am J Epidemiol* 2007;165:164–174
11. Cavusoglu E, Ruwende C, Chopra V, et al. Adiponectin is an independent predictor of all-cause mortality, cardiac mortality, and myocardial infarction in patients presenting with chest pain. *Eur Heart J* 2006;27:2300–2309
12. Kistorp C, Faber J, Galatius S, et al. Plasma adiponectin, body mass index, and mortality in patients with chronic heart failure. *Circulation* 2005;112:1756–1762
13. Sattar N, Nelson SM. Adiponectin, diabetes, and coronary heart disease in older persons: unraveling the paradox. *J Clin Endocrinol Metab* 2008;93:3299–3301
14. Wu Y, Li Y, Lange EM, et al. Genome-wide association study for adiponectin levels in Filipino women identifies CDH13 and a novel uncommon haplotype at KNG1-ADIPOQ. *Hum Mol Genet* 2010;19:4955–4964
15. Jee SH, Sull JW, Lee JE, et al. Adiponectin concentrations: a genome-wide association study. *Am J Hum Genet* 2010;87:545–552
16. Hug C, Wang J, Ahmad NS, Bogan JS, Tsao TS, Lodish HF. T-cadherin is a receptor for hexameric and high-molecular-weight forms of Acrp30/adiponectin. *Proc Natl Acad Sci USA* 2004;101:10308–10313
17. Vozarova de Courten B, Hanson RL, Funahashi T, et al. Common polymorphisms in the adiponectin gene ACDC are not associated with diabetes in Pima Indians. *Diabetes* 2005;54:284–289
18. Pollin TI, Tanner K, O'connell JR, et al. Linkage of plasma adiponectin levels to 3q27 explained by association with variation in the APM1 gene. *Diabetes* 2005;54:268–274
19. Heid IM, Henneman P, Hicks A, et al. Clear detection of ADIPOQ locus as the major gene for plasma adiponectin: results of genome-wide association analyses including 4659 European individuals. *Atherosclerosis* 2010;208:412–420
20. Ling H, Waterworth DM, Stirnadel HA, et al. Genome-wide linkage and association analyses to identify genes influencing adiponectin levels: the GEMS Study. *Obesity (Silver Spring)* 2009;17:737–744
21. Morisaki H, Yamanaka I, Iwai N, et al. CDH13 gene coding T-cadherin influences variations in plasma adiponectin levels in the Japanese population. *Hum Mutat* 2012;33:402–410
22. Onuma H, Tabara Y, Kawamura R, et al. Plasma resistin is associated with single nucleotide polymorphisms of a possible resistin receptor, the decorin gene, in the general Japanese population. *Diabetes* 2013;62:649–652
23. Osawa H, Tabara Y, Kawamoto R, et al. Plasma resistin, associated with single nucleotide polymorphism -420, is correlated with insulin resistance, lower HDL cholesterol, and high-sensitivity C-reactive protein in the Japanese general population. *Diabetes Care* 2007;30:1501–1506
24. Nakano Y, Tajima S, Yoshimi A, et al. A novel enzyme-linked immunosorbent assay specific for high-molecular-weight adiponectin. *J Lipid Res* 2006;47:1572–1582
25. Aso Y, Yamamoto R, Wakabayashi S, et al. Comparison of serum high-molecular weight (HMW) adiponectin with total adiponectin concentrations in type 2 diabetic patients with coronary artery disease using a novel enzyme-linked immunosorbent assay to detect HMW adiponectin. *Diabetes* 2006;55:1954–1960
26. World health statistics 2013 [internet], 2013. Geneva, World Health Org. Available from http://www.who.int/gho/publications/world_health_statistics/en/index.html.
27. Kadowaki T, Sekikawa A, Okamura T, et al. Higher levels of adiponectin in American than in Japanese men despite obesity. *Metabolism* 2006;55:1561–1563
28. Nakamura Y, Ueshima H, Okuda N, et al.; INTERLIPID Research Group. Relation of dietary and other lifestyle traits to difference in serum adiponectin concentration of Japanese in Japan and Hawaii: the INTERLIPID Study. *Am J Clin Nutr* 2008;88:424–430
29. Denzel MS, Scimia MC, Zumstein PM, Walsh K, Ruiz-Lozano P, Ranscht B. T-cadherin is critical for adiponectin-mediated cardioprotection in mice. *J Clin Invest* 2010;120:4342–4352
30. Dastani Z, Hivert MF, Timpson N, et al.; DIAGRAM+ Consortium; MAGIC Consortium; GLGC Investigators; MuTHER Consortium; DIAGRAM Consortium; GIANT Consortium; Global B Pgen Consortium; Procardis Consortium; MAGIC investigators; GLGC Consortium. Novel loci for adiponectin levels and their influence on type 2 diabetes and metabolic traits: a multi-ethnic meta-analysis of 45,891 individuals. *PLoS Genet* 2012;8:e1002607