

Plasma Adiponectin Levels Are Associated with Insulin Resistance, But Do Not Predict Future Risk of Coronary Heart Disease in Women

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Context: Low adiponectin levels predict type 2 diabetes, and one prospective study in men reported its independent prediction of vascular events. Many observers thus already consider adiponectin to be a major part of the “common soil” underpinning diabetes and vascular disease.

Objective: The objective of this study was to assess the association between adiponectin and incident coronary heart disease (CHD) risk in the British Women's Heart and Health Study.

Design: This was a prospective (4 yr) case (n = 167) control (n = 334) study nested within the 4286 women in British Women's Heart and Health Study.

Setting: The study was performed in a primary care setting.

Participants: The study consisted of women (n = 4286) randomly selected from 23 British towns between 1999 and 2001, who were 60–79 yr of age at baseline.

Main Outcome Measures: Association of adiponectin with CHD

risk factors and incident CHD events were the main outcome measures.

Results: Among both cases and controls, adiponectin positively correlated with age and high-density lipoprotein cholesterol and inversely correlated with waist to hip ratio, fasting insulin, fasting glucose, homeostasis model assessment of insulin resistance scores, C-reactive protein, and triglycerides. However, despite adequate power and these associations with CHD risk factors, adiponectin did not predict CHD events in unadjusted or adjusted analyses. The relative risk ratio for a doubling of adiponectin was 0.93 (95% confidence interval, 0.78, 1.11).

Conclusions: It is premature to consider adiponectin as a root for vascular disease in women despite its association with insulin resistance and diabetes. Additional prospective studies are required to determine whether there is a true sex difference in the effect of adiponectin on CHD. (*J Clin Endocrinol Metab* 90: 5677–5683, 2005)

ADIPONECTIN IS A hormone produced and secreted by adipocytes that regulates the metabolism of glucose. Adipose tissue is an important endocrine organ that produces a number of hormones (leptin, TNF- α , plasminogen activator inhibitor-1, resistin, and adiponectin) with essential roles in the regulation of insulin sensitivity and glucose metabolism as well as other physiological functions (1, 2). Adiponectin is exclusively produced by adipocytes, and unlike the other adipocyte hormones, adiponectin production and concentrations decrease in obese subjects (1, 2). Plasma adiponectin levels in humans range from 0.5–30 $\mu\text{g}/\text{ml}$, which is 1000-fold higher than the concentrations of other hormones, such as insulin and leptin (3). Besides inhibiting inflammatory pathways, recombinant adiponectin increases insulin sensitivity, improves glucose tolerance, and enhances lipid clearance in numerous animal models (3, 4). This in-

sulin-sensitizing effect appears to be mostly attributable to enhanced suppression of glucose production, but beneficial effects on muscle may also exist (2–4).

In population-based human studies, adiponectin inversely associates with body mass index (BMI), insulin resistance, triglyceride levels, blood pressure, C-reactive protein (CRP), and diabetes risk and positively associates with high-density lipoprotein cholesterol (HDL-c) levels (5–9). Current evidence demonstrates that insulin resistance and related markers predict coronary heart disease (CHD) occurrence (10–12). Given that adiponectin is probably an upstream determinant of insulin action (2–4), and high levels favor better endothelial function, lower inflammation, and protect against diabetes occurrence (2, 5–9), many have suggested the potential for adiponectin to form a major part of the mechanistic link between insulin resistance and CHD and, thus, its important potential as a therapeutic agent in the management of individuals with obesity and insulin resistance (2, 13, 14).

An inverse association has been found between adiponectin and prevalent CHD in cross-sectional studies (13, 15, 16), but these findings may reflect reverse causality. Two prospective studies have reported conflicting results. The first, of American Indians, comprised 124 cases and 248 controls and found no association (17), whereas the second, of men only, studied 226 cases and 532 controls and found an inverse

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Abbreviations: BMI, Body mass index; CHD, coronary heart disease; CI, confidence interval; CRP, C-reactive protein; HDL-c, high-density lipoprotein cholesterol; HOMA, homeostasis model assessment of insulin resistance; HRT, hormone replacement therapy; LDL-c, low-density lipoprotein cholesterol.

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association (14). The results from this latter study have been widely cited and used to suggest that adiponectin is the major mechanistic link (“common soil”) between diabetes and increased CHD risk (2). We present a third prospective study, in women only, of the association between adiponectin and CHD risk. Given the limited evidence of an effect of adiponectin on CHD in prospective population-based studies, there is a clear need for additional relevant studies. Furthermore, because adiponectin levels vary between the sexes, being considerably higher in females compared with males (2), and there are important sex differences in the effect of diabetes on CHD (18) together with the fact that the one fully published prospective study to date is in men only (14), it is necessary to examine the association between adiponectin and CHD in women.

Subjects and Methods

The British Women’s Heart and Health Study is a prospective cohort study of 4286 women who were randomly selected from 23 British towns between 1999 and 2001 and who were 60–79 yr of age at baseline (19). Women with CHD at baseline ($n = 694$; 16.2%) were excluded. Incident cases of CHD were identified by medical record reviews at 2-yr intervals and through routine death registration to January 2004. An incident case was defined as either 1) death with an underlying or contributing cause of CHD (International Classification of Disease 10 codes I20–I25 and I51.6); or 2) a myocardial infarction (defined according to World Health Organization criteria), first diagnosis of angina, or coronary artery bypass or angioplasty. There were 167 incident cases of CHD (101 nonfatal and 66 fatal). Two controls were randomly selected, within 5-yr age groups of the cases, from women without CHD at the baseline assessment. Multiple center ethical approval was obtained, and all women gave written informed consent.

At the baseline examination, blood samples were taken after a minimum 6-h fast. Serum adiponectin concentrations (in serum stored at -80°C for a median of 4 yr) were determined using ELISA (R&D Systems, Abingdon, UK). Fasting concentrations of CRP, insulin, glucose, total cholesterol, HDL-c, low-density lipoprotein cholesterol (LDL), and triglyceride levels were determined using standard laboratory methods (19). C-Reactive protein was assayed by a high-sensitivity immunonephelometric assay on a ProSpec protein analyzer (Dade-Behring, Deerfield, IL). The homeostasis model assessment of insulin resistance (HOMA) was calculated from fasting insulin and glucose (19). All blood samples were taken between 0800 and 1800 h, with the time of sampling (to nearest 1 min) recorded.

Participants were asked to bring all of their medications to the baseline assessment, and these were coded according to the British National Formulary. The use of aspirin, statin, and antihypertensive medications (any of the following: thiazide diuretics, β -blockers, calcium channel blockers and drugs affecting the renin-angiotensin system, and other antihypertensive drugs) at the time of the baseline assessment was determined from these data. Past and current use of hormone replacement therapy (HRT) at baseline was determined from the medications assessment and questionnaire data. A Dinamap 1846SX vital sign monitor (Critikon, Basingstoke, UK) was used to measure blood pressure. The mean of the two measurements was used in all analyses. Hypertension was defined as a blood pressure of 160/90 mm Hg or greater and/or any subject taking any of the antihypertensive medications listed above. BMI and waist and hip circumferences were determined using standard procedures (19). Information on adult and childhood occupational social class, smoking (never, past, or current), alcohol consumption (daily/most days, weekends only, once/twice per month, special occasions only, never), and physical activity were determined as described previously (19).

Statistical analyses

Box and whisker plots of adiponectin levels are presented for cases and controls. Geometric means of adiponectin levels and other characteristics are presented for cases and controls. Differences between cases

and controls were assessed using an unpaired t test for continuous variables and a χ^2 test for categorical variables. Spearman’s rank correlation coefficients were used to assess the associations of continuous covariates with adiponectin. Multiple logistic regression was used to assess the association of adiponectin with CHD, with adjustment for potential confounding and mediating factors. Because individual adiponectin levels exhibit a diurnal variation, with a decline overnight and a consequent nadir in the morning, we also adjusted for timing of blood sampling. Geometric means and their 95% confidence intervals (CI) were used for positively skewed variables (adiponectin, CRP, glucose, insulin, HOMA scores, and triglycerides) with logged values used in the regression models. Adiponectin was entered as a continuous variable (log adiponectin) in these regression models. Because regression coefficients for logged exposure variables are difficult to interpret, these effect estimates were expressed as the risk ratio of CHD for a doubling of adiponectin, as in a recently reported similar study in men only (14). Tests for linear trends were estimated from these models, with log CRP entered as a continuous variable. Nonlinear associations were assessed by entering quarters of the adiponectin distribution first as a series of three indicator variables and then as a continuous score and computing a likelihood ratio test comparing these two nested models. In the nested case-control study design, the odds ratio derived from logistic regression directly estimates the incidence rate ratio and, hence, the risk ratio (20, 21). We repeated our analyses using conditional logistic regression and found the same, although less precise, results.

A random effects meta-analysis was used to combine the confounder-adjusted effect of a doubling of adiponectin from our study with a similar effect estimate from the one previously published prospective study in men only (14); the third study to assess this association is published as a letter only, with insufficient information to include in this pooling. A random effects model was chosen *a priori*, because our study is of women only, and the previous published study is of men only. Evidence of heterogeneity between the effect estimates in the two studies was assessed by computing the Q statistic (22). All analyses were conducted in Stata version 8.0 (StataCorp, College Station, TX).

Results

Table 1 shows adiponectin levels and other characteristics among cases and controls. Adiponectin levels were similar among cases and controls (Table 1 and Fig. 1). Cases had higher fasting insulin, glucose (borderline statistical significance at the conventional 5% level, $P = 0.06$), HOMA scores, and LDL-c and lower HDL-c. Triglyceride levels were similar in cases and controls, as were systolic and diastolic blood pressures. However, the prevalence of hypertension (taking account of blood pressure medication as well as blood pressure levels) was greater at baseline in cases compared with controls. Cases were more likely to have been smokers and less likely to have used HRT, but indicators of socioeconomic position were not associated with case status. Both BMI and waist to hip ratio were not significantly greater among cases than controls.

Among both cases and controls, adiponectin positively correlated with age and HDL-c and inversely correlated with waist to hip ratio, fasting insulin, fasting glucose, HOMA scores, CRP, and triglycerides (Table 2). Adiponectin was inversely correlated with BMI in controls only and was not correlated with total cholesterol, LDL-c, or systolic or diastolic blood pressure in either cases or controls (Table 2). Adiponectin levels were socially patterned in control women and showed similar, but less precise, associations in cases; among controls women from childhood and adulthood manual social classes had adiponectin levels that were 12% (95% CI, 1, 32) and 13% (95% CI, 2, 32) lower, respectively, than those of nonmanual social class women. Cigarette smoking, alcohol consumption, physical activity, and use of statins,

TABLE 1. Levels of adiponectin and other characteristics among cases and controls

	Means (\pm SD) or no. (%)		P
	Cases of incident CHD (n = 165)	Controls (n = 334)	
Adiponectin (μ g/ml) ^a	14.54 (13.45,15.71)	15.09 (14.25,15.98)	0.5
Age (yr)	70.3 (5.5)	70.1 (5.3)	0.7
BMI (kg/m ²)	28.2 (5.3)	27.4 (4.5)	0.07
Waist to hip ratio	0.828 (0.57)	0.819 (0.68)	0.08
Insulin (μ U/ml) ^a	7.90 (7.02,8.89)	6.78 (6.34,7.25)	0.02
Glucose (mmol/liter) ^a	6.20 (5.96,6.46)	5.97 (5.85,6.09)	0.06
HOMA score ^a	2.15 (1.98,2.34)	1.80 (1.67,1.94)	0.02
CRP (mg/liter) ^a	2.44 (2.05,2.91)	1.97 (1.73,2.24)	0.05
Total cholesterol (mmol/liter)	6.79 (1.38)	6.62 (1.16)	0.1
LDL-c (mmol/liter)	4.31 (1.23)	4.09 (1.07)	0.04
HDL-c (mmol/liter)	1.55 (0.45)	1.67 (0.46)	0.007
Triglycerides (mmol/liter) ^a	1.80 (1.68,1.94)	1.70 (1.62,1.79)	0.2
Systolic blood pressure (mm Hg)	152.1 (23.2)	149.7 (26.4)	0.3
Diastolic blood pressure (mm Hg)	81.0 (11.3)	80.2 (12.1)	0.5
Hypertensive n (%) ^b	128 (78.1)	231 (69.4)	0.004
Taking statin [no. (%)]	5 (3.1)	20 (6.0)	0.03
Taking aspirin [no. (%)]	15 (9.2)	28 (8.4)	0.09
Ever used HRT [no. (%)]	30 (18.2)	86 (25.7)	0.06
Smoking [no. (%)]			
Never	78 (47.3)	192 (57.5)	
Past	59 (35.8)	107 (32.0)	0.01
Current	28 (17.0)	35 (10.5)	
Adult manual social class [no. (%)]	92 (55.8)	180 (53.9)	0.7
Childhood manual social class [no. (%)]	138 (83.6)	262 (78.4)	0.2
<2 h/wk of vigorous or moderate activity n (%)	39 (23.9)	68 (20.4)	0.3
Daily consumption 1–2 U alcohol [no. (%)]	19 (13.0)	51 (16.4)	0.3

^a Geometric mean and 95% CI of geometric mean.^b Blood pressure at examination 160/90 mm Hg or higher and/or taking antihypertensive medication.

aspirin, or HRT were not associated with adiponectin levels (all $P > 0.4$).

In multivariable analyses there was no association between adiponectin and CHD (Table 3). The age-adjusted relative risk ratio for a doubling of adiponectin was 0.93 (95% CI, 0.78, 1.11), and adjustment for any of the potentially confounding or mediating did not substantively alter this (Table 3). Additional adjustment for childhood and adulthood social classes did not alter the null association, nor did additional adjustment for HRT use, aspirin, BMI, or waist to hip ratio (data not shown). When we examined the effect of adiponectin by quarters of its distribution, there was very

weak (not statistically significant) evidence that those in the highest quarter of the adiponectin distribution had reduced CHD risk compared with those in the lowest quarter (Fig. 2). The age-adjusted relative risk of CHD comparing those in the highest quarter of the distribution to those in the lowest quarter was 0.63 (95% CI, 0.36, 1.08). This did not change with adjustment for potential confounding factors; additional adjustment for components of the metabolic syndrome attenuated the association to 0.80 (95% CI, 0.46, 1.41).

The effect of adiponectin did not differ between women in the lowest half of the fasting glucose distribution (0.83; 95% CI, 0.64, 1.08) and those in the highest half of the distribution

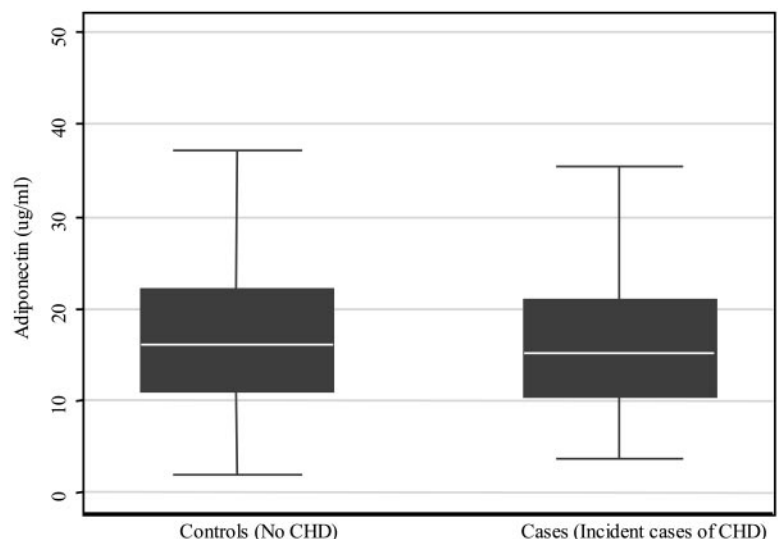


FIG. 1. Box and whisker plot of adiponectin levels among cases and controls. The horizontal bar within each box is the median value, the upper hinge of each box is the 75th percentile, and the lower hinge is the 25th percentile; the extremes of the whiskers represent the full range of values.

TABLE 2. Correlation of adiponectin levels with covariates among cases and controls

	Cases of incident CHD (n = 167)		Controls (n = 334)	
	Spearman's rank correlation coefficient with adiponectin	P	Spearman's rank correlation coefficient with adiponectin	P
Age	0.17	0.03	0.11	0.05
BMI	−0.06	0.4	−0.27	<0.001
Waist to hip ratio	−0.26	<0.001	−0.30	<0.001
Insulin	−0.33	<0.001	−0.42	<0.001
Glucose	−0.16	0.04	−0.22	<0.001
HOMA score	−0.32	<0.001	−0.43	<0.001
CRP	−0.19	0.02	−0.19	<0.001
Total cholesterol	0.03	0.7	−0.06	0.3
LDL-c	0.06	0.5	−0.06	0.3
HDL-c	0.43	<0.001	0.41	<0.001
Triglycerides	−0.40	<0.001	−0.40	<0.001
SBP	−0.08	0.3	−0.03	0.6
DBP	−0.05	0.6	0.05	0.3

DBP, Diastolic blood pressure; SBP, systolic blood pressure.

(1.04; 95% CI, 0.81, 1.34; for interaction between adiponectin and fasting glucose, $P = 0.7$), nor did the effect differ between those in the lowest half of fasting insulin distribution (0.90; 95% CI, 0.67, 1.19) and those in the highest half of the distribution (1.03; 95% CI, 0.81, 1.33; for interaction between adiponectin and fasting insulin, $P = 0.8$). When all analyses were repeated using a more strict definition of a case (including only those with World Health Organization criteria myocardial infarction, coronary artery by-pass, angioplasty, or fatal CHD; $n = 104$), the results were essentially the same as those presented here, although less precise; the age-adjusted association of adiponectin with this more strict definition of CHD was 0.96 (95% CI, 0.78, 1.19). Timing of blood sampling was not associated with incident CHD ($P = 0.9$), and adjustment for timing of blood sampling made no difference to any of the results.

In a random effects meta-analysis combining the confounder-adjusted result from our study (Table 3) with a similar confounder-adjusted result from one previously published study (0.70; 95% CI, 0.58, 0.87; Ref. 14) we obtained a pooled effect of 0.81 (95% CI, 0.61, 1.07). However, there was statistical evidence of heterogeneity between these two studies ($Q = 4.39$; 1 df; $P = 0.04$).

Discussion

Consistent with other studies (5–9), we have found adiponectin to be inversely associated with adiposity, insulin resistance, triglycerides, and CRP. However, we found no association between adiponectin and CHD risk in this study of women. The lack of an association with CHD risk is consistent with one previous prospective study of American

Indian men and women (17), but not with a prospective study among American men (14). Of note, a recent prospective case-referent study (276 cases, of which 234 were cerebral infarct) observed no association between adiponectin and stroke risk (23). Because the pathophysiology and epidemiology of cerebral infarct and CHD are similar (24), and the majority of cases in that study were cerebral infarct, this provides additional evidence that adiponectin may be less associated with atherosclerosis than currently considered. Our findings are also consistent with a recent study of adolescents that found adiponectin to be associated with insulin resistance, but not endothelial function (25).

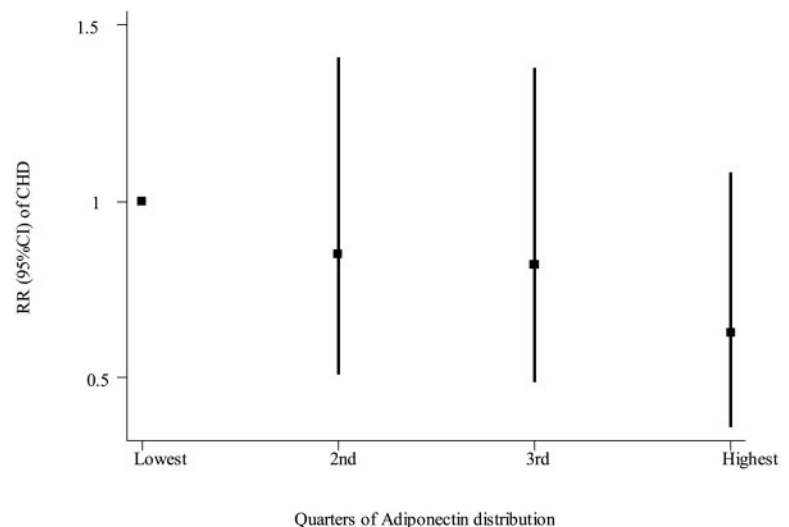
We used a single assessment of adiponectin, and it is possible that our results may be biased toward the null by regression dilution bias. However, previous studies have shown intraindividual adiponectin levels to be stable over time, with an intraclass correlation coefficient of 0.85 for levels measured 1 yr apart within the same individual (26). We excluded participants with diagnosed CHD at baseline (including those who reported a doctor diagnosis, but for whom this was not verified in medical records). However, we cannot be certain that some controls did not have asymptomatic and undiagnosed disease. A greater proportion of the controls compared with cases were taking aspirin and statin at baseline. This finding confirms the established effectiveness of these medications in the primary prevention of CHD, but may also indicate that some of the control women for whom there was no clinical evidence of CHD were deemed in some respect to be at high risk and therefore in need of statin and aspirin treatment. Adjustment for statin

TABLE 3. Multivariable associations of adiponectin with incident cases of CHD (n = 167 cases)

	Relative risk ratio (95% CI) for a doubling of adiponectin	P linear trend	P nonlinear association
Model 1: age adjusted ^a	0.93 (0.78, 1.11)	0.43	0.52
Model 2: confounder adjusted ^b	0.93 (0.77, 1.11)	0.43	0.52
Model 3: adjusted for confounders and potential mediators ^c	0.99 (0.82, 1.19)	0.90	0.71

^a Model 1: adjusted for age (continuous in years).
^b Model 2: as model 1 plus smoking (three-level categorical variable), physical activity (three-level categorical variable), alcohol consumption (five-level categorical variable).
^c Model 3: as model 2 plus hypertension status (binary) statins (binary), fasting levels of HDL-c, triglyceride (logged), glucose (logged), insulin (logged), and CRP (logged; all continuous variables).

FIG. 2. Adjusted relative risk of CHD by quarters of adiponectin distribution.



and aspirin use did not alter our finding of no association between adiponectin and CHD.

Given the established link between adiponectin and insulin resistance and dyslipidemia from both biological and epidemiological studies (2), and established links between dyslipidemia and insulin resistance and CHD (10–12), the lack of an association between adiponectin and CHD is counterintuitive. One possibility is that this and previous null studies (17, 23) lacked the power to find a weak association. We had 97% power to detect an odds ratio of 0.7 for a doubling of adiponectin; this is the reported effect in a recent prospective study of men (14). Furthermore, we had 95% power to detect a $0.85 \mu\text{g/ml}$ (equivalent to 0.5 sd) difference in the geometric mean of adiponectin levels between cases and controls and 80% power to detect a difference of $0.425 \mu\text{g/ml}$ (equivalent to 0.25 sd); both of these are weaker effects than those reported in the one positive published study to date (14).

Our results provide weak statistical evidence that in this population of older women there may be a threshold effect of adiponectin, with reduced risk of CHD among those in the top quarter of the distribution compared with those in the bottom quarter. However, we had no *a priori* hypothesis to believe that a difference would exist only between those in the top and bottom ends of the distribution, and the one previous study in men showing an association between adiponectin and CHD found a linear association, with risk decreasing monotonically across each fifth of the distribution (14). It is possible that adiponectin also influences other unmeasured biological factors that have the opposite effect on CHD risk to that of insulin resistance and dyslipidemia, and thus competing biological pathways produce an overall null effect, or that a confounding factor masks the association between adiponectin and CHD. The known biological effects and correlates of adiponectin (2), for example, lower levels among the more obese and insulin resistant, would all serve to produce an inverse association. Although unlikely, we cannot rule out the possibility that there are as yet unknown biological effects of adiponectin that would predict a positive association with CHD in women and, when combined with

its correlations with obesity and insulin resistance, result in an overall null effect.

There are a number of differences between our study and that reported by Pischon *et al.* (14), which reported a significant inverse association between adiponectin and CHD in men. In the study by Pischon *et al.* (14), follow-up covered a 6-yr period, whereas in our study, follow-up was for a 4-yr period. There is no information in the report by Pischon *et al.* (14) concerning a time difference in the effect of adiponectin on CHD, but this is most likely because there are no biological reasons to believe that the effect should vary with time. We used an ELISA to measure adiponectin levels, whereas in the study by Pischon *et al.* (14) a competitive RIA was used. Our laboratory has experience of measuring total adiponectin with RIA in previous studies of pregnant women and adolescents, and we have found comparable associations of adiponectin measured by either RIA or ELISA to adiposity and metabolic parameters (25, 27). Hence, we believe it is difficult to explain differences between our results and those of Pischon *et al.* (14) on the basis of assay differences.

Finally, and possibly of most importance, because the study by Pischon *et al.* (14) was in men only, and our study is in women only, it is possible that the effect of adiponectin varies in men and women. This is supported by the evidence of statistical heterogeneity between equivalent effect estimates from that study and ours. Adiponectin levels are, on the average, considerably higher in women compared with men (2), and women and men have marked differences in body fat distribution, with evidence that this difference explains the sex difference in atherosclerosis (28, 29). The relative effects of diabetes and hyperglycemia on CHD are greater in women compared with men (18). Because adiponectin is secreted by adipocytes and is closely involved in glucose metabolism, and given sex differences in these risk factors, it is perhaps not surprising that its effect on CHD might differ between women and men. Higher levels of adiponectin in women compared with men and the greater effect of hyperglycemia on CHD in women compared with men may reflect a relative resistance to the effect of adiponectin in women. However, this possibility requires ad-

ditional investigation in prospective studies of women and men who have undergone identical procedures (rather than comparing effects from two different cohorts, one of women and one of men, as we have done here) and that have sufficient power to detect a possible sex difference. Finally, recent data from animal studies suggest that the molecular forms of adiponectin may differ between males and females, with women having greater concentrations of the high molecular weight form of adiponectin compared with men, but lesser amounts of the other molecular forms (30). Whether such differences help explain any sexual dimorphism in the adiponectin-CHD relationship needs to be examined further. The ability to distinguish between adiponectin fractions in human populations is not easy, and our ELISA is unable to distinguish between lower weight trimer-dimer forms of adiponectin and high molecular weight complexes. We are therefore unable to determine whether there is a specific association between particular forms of adiponectin and CHD in women.

In conclusion, we found no association between adiponectin levels and CHD risk in a prospective study of women. Despite associations with established CHD risk factors in this and other studies, the contradictory findings of an association with incident CHD from the three prospective studies and one prospective study of stroke outcomes to date suggest that it would be premature to assume that adiponectin was causally related to CHD in both sexes and could provide a common mechanism between insulin resistance and CHD, or that it could provide a useful predictor in population CHD screening, as has been suggested (31). In particular, additional work is required to determine whether there is an important sex difference in the effect of adiponectin on CHD risk and to establish whether different forms of adiponectin vary in their effect on CHD risk in either women or men.

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References

- Havel PJ 2002 Control of energy homeostasis and insulin action by adipocyte hormones: leptin, acylation stimulating protein, and adiponectin. *Curr Opin Lipidol* 13:51–59
- Haluzik M, Parizkova J, Haluzik MM 2004 Adiponectin and its role in the obesity-induced insulin resistance and related complications. *Physiol Res* 53: 123–129
- Stefan N, Stumvoll M 2002 Adiponectin—its role in metabolism and beyond. *Horm Metab Res* 34:469–474
- Wang Y, Xu A, Knight C, Xu LY, Cooper GJ 2002 Hydroxylation and glycosylation of the four conserved lysine residues in the collagenous domain of adiponectin. Potential role in the modulation of its insulin-sensitizing activity. *J Biol Chem* 277:19521–19529
- Cnop M, Havel PJ, Utzschneider KM, Carr DB, Sinha MK, Boyko EJ, Retzlaff BM, Knopp RH, Brunzell JD, Kahn SE 2003 Relationship of adiponectin to body fat distribution, insulin sensitivity and plasma lipoproteins: evidence for independent roles of age and sex. *Diabetologia* 46:459–469
- Kazumi T, Kawaguchi A, Sakai K, Hirano T, Yoshino G 2002 Young men with high-normal blood pressure have lower serum adiponectin, smaller LDL size, and higher elevated heart rate than those with optimal blood pressure. *Diabetes Care* 25:971–976
- Matsubara M, Maruoka S, Katayose S 2002 Decreased plasma adiponectin concentrations in women with dyslipidemia. *J Clin Endocrinol Metab* 87:2764–2769
- Spranger J, Kroke A, Mohlig M, Bergmann MM, Ristow M, Boeing H, Pfeiffer AF 2003 Adiponectin and protection against type 2 diabetes mellitus. *Lancet* 361:226–228
- Lindsay RS, Funahashi T, Hanson RL, Matsuzawa Y, Tanaka S, Tataranni PA, Knowler WC, Krakoff J 2002 Adiponectin and development of type 2 diabetes in the Pima Indian population. *Lancet* 360:57–58
- Sattar N, Gaw A, Scherbakova O, Ford I, O'Reilly DS, Haffner SM, Isles C, Macfarlane PW, Packard CJ, Cobbe SM, Shepherd J 2003 Metabolic syndrome with and without C-reactive protein as a predictor of coronary heart disease and diabetes in the West of Scotland Coronary Prevention Study. *Circulation* 108:414–419
- Pyorala M, Miettinen H, Halonen P, Laakso M, Pyorala K 2000 Insulin resistance syndrome predicts the risk of coronary heart disease and stroke in healthy middle-aged men: the 22-year follow-up results of the Helsinki Policemen Study. *Arterioscler Thromb Vasc Biol* 20:538–544
- Bonora E, Formentini G, Calcaterra F, Lombardi S, Marini F, Zenari L, Saggiani F, Poli M, Perbellini S, Raffaelli A, Cacciatori V, Santi L, Targher G, Bonadonna R, Muggeo M 2002 HOMA-estimated insulin resistance is an independent predictor of cardiovascular disease in type 2 diabetic subjects: prospective data from the Verona Diabetes Complications Study. *Diabetes Care* 25:1135–1141
- Kumada M, Kihara S, Sumitsuji S, Kawamoto T, Matsumoto S, Ouchi N, Arita Y, Okamoto Y, Shimomura I, Hiraoka H, Nakamura T, Funahashi T, Matsuzawa Y 2003 Osaka CAD Study Group. Coronary artery disease: association of hypoadiponectinemia with coronary artery disease in men. *Arterioscler Thromb Vasc Biol* 23:85–89
- Pischoon T, Girman CJ, Hotamisligil GS, Rifai N, Hu FB, Rimm EB 2004 Plasma adiponectin levels and risk of myocardial infarction in men. *JAMA* 291:1730–1737
- Kojima S, Funahashi T, Sakamoto T, Miyamoto S, Soejima H, Hokamaki J, Kajiwarai I, Sugiyama S, Yoshimura M, Fujimoto K, Miyao Y, Suefuji H, Kitagawa A, Ouchi N, Kihara S, Matsuzawa Y, Ogawa H 2003 The variation of plasma concentrations of a novel, adipocyte derived protein, adiponectin, in patients with acute myocardial infarction. *Heart* 89:667
- Hotta K, Funahashi T, Arita Y, Takahashi M, Matsuda M, Okamoto Y, Iwahashi H, Kuriyama H, Ouchi N, Maeda K, Nishida M, Kihara S, Sakai N, Nakajima T, Hasegawa K, Muraguchi M, Ohmoto Y, Nakamura T, Yamashita S, Hanafusa T, Matsuzawa Y 2000 Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. *Arterioscler Thromb Vasc Biol* 20:1595–1599
- Lindsay R, Resnick H, Ruotolo G 2005 Adiponectin and coronary heart disease: the Strong Heart Study. *Arterioscler Thromb Vasc Biol* 25:e15–e16
- Lee WL, Cheung AM, Cape D, Zinman B 2000 Impact of diabetes on coronary artery disease in women and men: a meta-analysis of prospective studies. *Diabetes Care* 23:962–968
- Lawlor DA, Ebrahim S, Davey Smith G 2002 The association between components of adult height and type II diabetes and insulin resistance: British Women's Heart and Health Study. *Diabetologia* 45:1097–1106
- Rothman K, Greenland S 1998 Case control studies. In: Rothman K, Greenland S, eds. *Modern epidemiology*, 2nd Ed. Philadelphia: Lippincott Williams & Wilkins; 93–114
- Prentice RL, Breslow NE 1978 Retrospective studies and failure time models. *Biometrika* 65:153–158
- Deeks JJ, Altman DG, Bradburn MJ 2001 Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis. In: Egger M, Davey Smith G, Altman D, ed. *Systematic reviews in health care: meta-analysis in context*. London: BMJ Books; 285–312
- Soderberg S, Stegmayr B, Stenlund H, Sjöström LG, Agren A, Johansson L, Weinehall L, Olsson T 2004 Leptin, but not adiponectin, predicts stroke in males. *J Intern Med* 256:128–136
- Lawlor DA, Davey Smith G, Leon DA, Sterne JA, Ebrahim S 2002 Secular trends in mortality by stroke subtype in the 20th century: a retrospective analysis. *Lancet* 360:1818–1823
- Singhal A, Jamieson N, Fewtrell M, Deanfield J, Lucas A, Sattar N 2005

- Adiponectin predicts insulin resistance but not endothelial function in young healthy adolescents. *J Clin Endocrinol Metab* 90:4615–4621
26. **Pischon T, Hotamisligil GS, Rimm EB** 2003 Adiponectin: stability in plasma over 36 hours and within-person variation over 1 year. *Clin Chem* 49:650–652
27. **Ramsay JE, Jamieson N, Greer IA, Sattar N** 2003 Paradoxical elevation in adiponectin concentrations in women with preeclampsia. *Hypertension* 42:891–894
28. **Larsson B, Bengtsson C, Bjorntorp P, Lapidus L, Sjostrom L, Svardsudd K, Tibblin G, Wedel H, Welin L, Wilhelmsen L** 1992 Is abdominal body fat distribution a major explanation for the sex difference in the incidence of myocardial infarction. *Am J Epidemiol* 135:266–273
29. **Lawlor DA, Ebrahim S, Whincup P, Sterne J, Papacosta O, Wannamethee G, Dhanjil S, Griffin M, Nicolaides AN, Davey Smith G** 2004 Sex differences in body fat distribution and carotid intima media thickness: cross sectional survey using data from the British regional heart study. *J Epidemiol Community Health* 58:700–704
30. **Xu A, Chan KW, Hoo RL, Wang Y, Tan KC, Zhang J, Chen B, Lam MC, Tse C, Cooper GJ, Lam KS** 2005 Testosterone selectively reduces the high molecular weight form of adiponectin by inhibiting its secretion from adipocytes. *J Biol Chem* 280:18073–18080
31. **Ridker PM, Brown NJ, Vaughan DE, Harrison DG, Mehta JL** 2004 Established and emerging plasma biomarkers in the prediction of first atherothrombotic events. *Circulation* 109:IV6–IV19

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