Associations of Total and High-Molecular-Weight Adiponectin with All-Cause and Cardiovascular Mortality in Older Persons: The Cardiovascular Health Study

Running title: Kizer et al.; Adiponectin and Mortality in Older Adults

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Abstract:

**Background**—Adiponectin shows opposite associations with adverse outcomes in healthy middle-aged populations (lower risk), and cohorts with prevalent cardiovascular disease (CVD), heart failure (HF) or advanced age (higher risk).

**Methods and Results**—In a population-based study of older adults, we examined the relationships of total and high-molecular-weight (HMW) adiponectin with mortality among subgroups defined by baseline cardiovascular status: no CVD, HF or atrial fibrillation (AF) (Group 1); CVD but no HF/AF (Group 2); and HF/AF (Group 3). We found significant differences in the associations with all-cause mortality across the groups. The association in Group 1 was U-shaped; increasing levels of total adiponectin up to 12.4 mg/L were associated with lower mortality after adjustment for confounders (HR=0.81 per 1-SD [0.65-0.95]), but above this cutpoint, higher levels conferred greater risk (HR=1.19 [1.12-1.27]). Further adjustment for diabetes or insulin resistance, protection against which has been proposed to mediate adiponectin’s beneficial relationships with outcome, attenuated the association in the lower range. There was no significant association in Group 2, but in Group 3, total adiponectin showed a direct adjusted association. Additional adjustment for putative metabolic/inflammatory intermediates suggested a direct association for Group 2, and magnified the one for Group 3 (HR=1.31 [1.15-1.50]). Results were similar for HMW adiponectin, and for cardiovascular mortality.

**Conclusions**—Adiponectin exhibits distinct associations with mortality in elders, which shift from U-shaped to flat to direct with greater baseline cardiovascular dysfunction, but become more consistently adverse after accounting for metabolic/inflammatory factors presumed to be favorably regulated by the adipokine. These findings advance understanding of the adiponectin paradox as relates to older adults.

**Key words:** adiponectin; aging; mortality
As the most abundant secretory product of adipocytes, the bioactive protein adiponectin has been a major focus of efforts to define the endocrine functions of adipose tissue and their role in obesity-associated disorders.\(^1\) Unlike other adipokines, adiponectin is inversely related to adiposity, and demonstrates insulin-sensitizing and anti-atherogenic properties in the laboratory.\(^{1,2}\) Yet epidemiological studies of adiponectin have shown directionally opposite relationships with adverse outcomes in different populations. Whereas adiponectin is associated with lower incidence of coronary heart disease (CHD) in healthy middle-aged cohorts,\(^{3,4}\) it has been linked to higher mortality in groups with prevalent cardiovascular disease (CVD),\(^5\) heart failure (HF),\(^6\) or older age.\(^7-9\)

These contrasting associations, known as the “adiponectin paradox,” remain a major puzzle in the field.\(^10\) While the basis for the paradox remains uncertain, the influence of prevalent CVD, and particularly HF, has come to be increasingly appreciated. The observation that adiponectin is absent from the normal vascular wall but detectable at high levels following vascular injury has led to the concept that increased adiponectin concentrations may represent a response to, and hence a marker of, more severe underlying atherosclerosis.\(^2\) In turn, recognition that natriuretic peptides stimulate adiponectin secretion provides a mechanism linking elevated adiponectin levels to more pronounced cardiac dysfunction and a poorer prognosis.\(^11\)

Previous work from our group suggested a U-shaped association between total adiponectin and mortality among long-term survivors of the Cardiovascular Health Study (CHS),\(^12\) providing a potential path to reconciling the opposite associations. We have since expanded measurement of total adiponectin to a majority of the CHS cohort, and added adiponectin’s reportedly more metabolically active high-molecular-weight (HMW) fraction.\(^13\) Here we parlayed such large-scale measurements to better characterize the shape of
adiponectin’s associations with all-cause and cardiovascular mortality, and test the hypothesis that these relationships would differ in subgroups defined by prevalent CVD, HF, and atrial fibrillation (AF) status.

Methods

Study Population

CHS is a longitudinal investigation of determinants of CVD in older adults.14 Participants were ≥65 years old and residing in the community. They were identified from Medicare eligibility lists and recruited from four field centers in the United States.14 An original cohort (n=5,201) was enrolled in 1989-90, followed in 1992-93 by an African-American cohort (n=687). As previously described, participants underwent health evaluations at site clinics according to standardized protocols.14,15

Of the 5,553 subjects who completed the 1992-93 examination (baseline for this analysis), 838 did not have samples for adiponectin measurement, and 30 had missing information on covariates, leaving 4,685 eligible individuals.

Definition of Covariates

Hypertension was defined by blood pressure ≥140/90 mm Hg, or self-report and antihypertensive therapy. Diabetes was defined by fasting glucose ≥126 mg/dl or glucose-lowering treatment. Anthropometry was performed in standardized fashion.16 Subclinical CVD was defined as reported previously.17

Laboratory measurements on fasting blood samples have been described.18-20 Homeostasis model assessment of insulin resistance (HOMA-IR),21 and estimated glomerular filtration rate (eGFR)22 were calculated using standard approaches.
Ascertainment of Outcome

Surveillance for incident CVD events, hospitalizations, and mortality involved regular telephone contacts and clinical examinations.23 Deaths were confirmed and classified by a mortality review committee as previously described.24 Ascertainment of vital status was 100% complete through June 2008.

Prevalent Cardiovascular Disorders

Prevalent CVD was defined as myocardial infarction, angina pectoris or revascularization, stroke, transient ischemic attack, or peripheral arterial disease. Along with prevalent HF and AF, prevalent CVD was ascertained through the 1992-93 examination using published methods.15, 23

Measurement of Adiponectin

Adiponectin measurements were performed on EDTA-plasma samples stored at -70°C. Total and HMW adiponectin were measured by ELISA (Millipore, Billerica, MA); inter-assay analytical coefficients of variation were 6.9% and 11.1%, respectively.

Statistical Analysis

Eligible participants were stratified a priori into 3 subgroups defined by presence of clinically manifest cardiovascular disorders at baseline: Group 1, no CVD, HF or AF; Group 2, CVD but no HF or AF; and Group 3, HF and/or AF. We tested for an interaction of adiponectin by group to confirm our decision to evaluate these subgroups separately.

Comparisons of adiponectin concentrations by covariates within groups employed Student’s t-test; within-group correlations were assessed by Pearson coefficients. Age-, sex-, and race-adjusted means of adiponectin were compared across groups using linear regression. Missing covariates (n=418) were replaced by prior values (1989-92) in the original cohort, if available, or imputed baseline data as previously described.25
The shapes of the associations of total and HMW adiponectin with all-cause and cardiovascular mortality were examined in Cox models using penalized cubic splines.\textsuperscript{26} Non-linearity of these associations was tested with a likelihood ratio test.\textsuperscript{26} Based on the strength of non-linearity and the overall shape of the association, we chose to summarize the dominant linear features using two linear splines for Group 1, and a single linear term for Groups 2 and 3. The use of linear splines for Group 1 has the advantage of allowing assessment of effect modification by relevant covariates, and of direct comparability with findings in Groups 2 and 3. To further characterize the non-linear relationship of adiponectin with mortality in Group 1, we also report hazard ratios at specific points along the cubic spline; these do not represent division of the data into quantiles but instead show how the hazard function changes across the data. The proportional hazards assumption was confirmed using Schoenfeld’s goodness-of-fit procedures.

To determine the independent associations of total and HMW adiponectin with fatal events, we examined the effect of adjusting for potential confounders, or covariates related to both adiponectin levels and outcome but not deemed to be on the causal pathway between the two. We developed sequential multivariable models, initially adjusting for age, sex and race, and subsequently for additional confounding variables, defined as candidate covariates that altered the risk estimate for adiponectin by \( \geq 10\% \). Candidate confounding variables included study center; socioeconomic factors; anthropometry; lifestyle habits; blood pressure; antihypertensive or antithrombotic treatment; estrogen therapy; self-reported health status; and eGFR, serum albumin, and N-terminal pro-brain-type natriuretic peptide (NT-proBNP). Assessment of the independent association of adiponectin with mortality was based on the adjusted risk estimates accounting for the aggregate of confounding.

To explore the associations further, we next undertook adjustment for putative mediators,
or factors potentially in the causal pathway between adiponectin and clinical events. These consisted of glycemic, lipid, and inflammatory risk factors, as well as prevalent subclinical CVD, which are favorably influenced by adiponectin in laboratory studies, and could confer a protective association with CVD outcomes. Although adjustment for causal intermediates can introduce bias, we decided to proceed with such adjustment not to formally quantitate direct, as distinct from indirect, effects, but to gain a general insight into the impact of these intermediate factors on the observed confounder-adjusted associations. These analyses were further justified by the complex, and still incompletely defined, biology of adiponectin, which leaves open the possibility that these proposed intermediates could also act as confounders.

To assess for interactions of adiponectin with key covariates, appropriate cross-product terms were assessed by the likelihood ratio test. We did not examine total and HMW adiponectin jointly in multivariable models, because the two measures were very highly correlated (r=0.94).

Last, we conducted sensitivity analyses restricting or stratifying the cohort by selected clinical features or length of follow-up.

All analyses were performed with STATA, version 11.0 (College Station, TX), or R version 2.13.0 (http://www.r-project.org).

Results

Baseline Characteristics and Cross-sectional Associations

Groups 1 (n=3,272), 2 (n=1,030) and 3 (n=383) had mean ages of 74.4±5.1, 75.6±5.3, and 77.0±6.1 years, respectively; they included 63%, 46%, and 47% women, and 16%, 18%, and 14% blacks, respectively. Participants in Group 1 had higher levels (geometric mean [95% CI]) of total and HMW adiponectin than individuals in Group 2 (12.4 mg/L [12.2-12.6] vs. 11.0
[10.6-11.4], p<0.001, and 5.8 mg/L [5.6-6.0] vs. 5.0 [4.7-5.2], p<0.001, respectively). In turn, participants in Group 3 had higher levels of both total (13.3 mg/L [12.6-14.1]) and HMW adiponectin (6.7 mg/L [6.2-7.3]) than those in Group 1 (p=0.007 and p=0.001, respectively). These intergroup differences in adiponectin levels changed minimally in analyses adjusting for age, sex, and race.

The relationships of total adiponectin with baseline covariates in each subgroup are presented in Table 1. Total adiponectin was positively correlated with age, HDL-cholesterol, and NT-proBNP, but negatively correlated with body mass index (BMI), waist-hip ratio, HOMA-IR, triglycerides, 3-year antecedent weight change, and high-sensitivity C-reactive protein (hsCRP) in all or most subgroups. All or most subgroups showed higher concentrations of total adiponectin in women, especially those taking estrogen replacement therapy, non-blacks, and California and Maryland, but exhibited lower concentrations in participants with diabetes, and those receiving antihypertensive treatment (particularly, beta-blockers) and lipid-lowering therapy. Higher concentrations of total adiponectin were also present among participants on aspirin in Group 3, and in those receiving angiotensin-converting-enzyme inhibitors or free of subclinical CVD in Group 1. The higher levels of total adiponectin in participants without subclinical CVD persisted after adjustment for age, sex, and race (12.8 [12.5-13.2] vs. 12.1 [11.9-12.4] mg/L, p=0.001). Associations were similar for HMW adiponectin (data not shown), which was highly correlated with total adiponectin in all 3 Groups (Table 1).

**Relationships with Mortality by Prevalent Cardiovascular Status**

During a median follow-up of 11.8 years, there were 1,947 deaths (634 cardiovascular) in Group 1; 802 deaths (375 cardiovascular) in Group 2; and 337 deaths (180 cardiovascular) in Group 3. We first tested whether the association of total adiponectin with mortality was similar across the
3 Groups (i.e., whether significant interaction existed by prevalent CVD and/or HF/AF). Such testing was significant for both all-cause and cardiovascular mortality (p=0.009 and p=0.034, respectively). This validated our decision to stratify by prevalent cardiovascular status in all analyses.

Figure 1A shows cubic spline plots depicting the relationship between total adiponectin and all-cause mortality after adjustment for potential confounders. The association of total adiponectin with fatal events was significantly non-linear in Group 1, where a roughly U-shaped relationship occurred. By contrast, there was no evidence of a significant non-linear relationship in Group 2 or 3. The same relationships, modeled using linear splines, are presented in Figure 1B. Findings were similar for HMW adiponectin, and for the endpoint of cardiovascular mortality (data not shown).

Group 1
The relationships in Group 1 were such that total adiponectin was inversely associated with all-cause and cardiovascular mortality up to approximately its median value, 12.4 mg/L; beyond this concentration, further increases were directly associated with either outcome.

Table 2 presents the associations of total adiponectin with fatal outcomes modeled as linear splines below and above the median adiponectin concentration. After adjustment for potential confounders (model 2), every 1-SD (7.9 mg/L) increase in total adiponectin at concentrations below its median was associated with 19% and 37% lower risks of all-cause and cardiovascular death, respectively. Above the median, there were instead 18% and 24% higher risks of all-cause and cardiovascular mortality, respectively, after adjustment for confounders (model 2). Additional adjustment for NT-proBNP (model 3) led to lower risk estimates below the median adiponectin concentration, but did not materially alter the risk estimates above it.
Further adjustment for putative mediators showed little effect for subclinical CVD at either end of adiponectin’s distribution. But inclusion of diabetes or HOMA-IR, either individually or in combination with lipid fractions and hsCRP, led to blunting of the inverse associations in the lower range of concentrations without meaningfully altering the direct associations in the higher range.

Table 3 further details the non-linear relationship in Group 1 by showing the risk estimates from the cubic-splines models corresponding to specific concentrations of adiponectin as compared with the median concentration (nadir of risk). To ensure comparability of estimates before and after adjustment for NT-proBNP, the results for the subset of participants with available NT-proBNP measurements are given. Risk estimates in the entire cohort for models not adjusting for NT-proBNP were similar.

Findings from the cubic splines were consistent with the linear-spline results. After adjustment for confounders (model 2), a concentration of total adiponectin at the 10th percentile was associated with a 13% greater risk of all-cause mortality relative to the median concentration, as was a concentration at the 90th percentile. These risk estimates were not meaningfully changed by adjustment for NT-proBNP or subclinical CVD, but adjustment for putative metabolic and inflammatory mediators, particularly diabetes and HOMA-IR, again attenuated the associations below the median.

The observed bidirectional association for total adiponectin tended to be more marked for cardiovascular than for all-cause mortality, with somewhat stronger risk estimates in both the linear-spline (Table 2) and cubic-spline (Table 3) models. Corresponding associations for HMW adiponectin were comparable, if generally weaker, than for total adiponectin, as shown in Supplemental Tables 1 and 2.
Groups 2 and 3

In Group 2, there were no significant associations for total adiponectin with all-cause and cardiovascular death after adjustment for potential confounders (Table 2). With additional adjustment for proposed metabolic and inflammatory mediators, and especially diabetes or HOMA-IR, there was a modest direct association with all-cause mortality, suggesting that the null association in Group 2 may represent an admixture of lower risk from such putative mediators and high risk related to other mechanisms.

Turning to Group 3, we found a significant direct association between total adiponectin and all-cause, but not cardiovascular, mortality after adjustment for confounders. There was, however, strengthening of the associations after additional adjustment for proposed metabolic/inflammatory mediators, which were comparable and significant for both outcomes. This suggests that such intermediates partly counter the adverse associations of total adiponectin with mortality from other causes. Findings were consistent for HMW adiponectin (Supplemental Table 1).

Assessment of Effect-Modification within Subgroups

We next tested whether the adiponectin-mortality associations in the 3 subgroups with distinct cardiovascular profiles differed according to levels of key covariates. We found effect modification by baseline BMI that was significant in Groups 1 and 2, but not Group 3. For Group 1, the interaction of total adiponectin with BMI was significant for all-cause (p=0.016), but not cardiovascular (p=0.17) mortality. As seen in Figure 2, this interaction was characterized by blunting of total adiponectin’s inverse association with fatal events at values below its median concentration for participants in the lowest tertile of BMI. In Group 2, formal tests of interaction with BMI were significant for all-cause mortality (p=0.028) and nearly so for cardiovascular...
mortality (p=0.054), but risk estimates were not discernibly different across increasing tertiles of BMI (data not shown). Findings were again similar for HMW adiponectin (data not shown).

There was no evidence of effect modification by age, sex, diabetes, or NT-proBNP for any subgroup. A nominally significant overall interaction with race, however, was detected in Group 1 for total adiponectin and all-cause mortality (p=0.031), though not cardiovascular mortality (p=0.80). The upslope in risk for levels above the median was stronger among non-blacks (HR=1.16 per 1-SD, 95% CI=1.09-1.23) than blacks (HR=1.05, 95% CI=0.80-1.37) above the median concentration. There was no corresponding evidence of interaction for HMW adiponectin and either endpoint.

Because weight change, poor health, and subclinical HF can influence adiponectin levels, we repeated our analyses after exclusion of participants with fair/poor health status, antecedent weight loss >10 lbs, or elevated NT-proBNP (≥190 pg/mL),20 with no change in our results. Likewise, results were not meaningfully altered when only incident events after 5 years of follow-up were considered to reduce the potential effect of unrecognized morbidity at baseline on adiponectin levels.

Discussion

Principal Findings

To our knowledge, the present study is the largest to date to assess the relationship of total adiponectin with fatal events in older men and women, and the first to do so concurrently for HMW adiponectin. The scale of the current investigation afforded the opportunity to characterize the associations of total and HMW adiponectin with mortality more precisely than has been possible previously, revealing that among community-dwelling elders such associations differ
significantly in nature depending on the presence of clinically overt CVD or HF/AF. In particular, we found that the associations of adiponectin with all-cause and cardiovascular mortality became progressively less favorable across subgroups with increasing baseline cardiovascular risk, shifting from a U-shaped relationship for participants free of prevalent clinical CVD, HF and AF after extensive adjustment for potential confounders, to a flat association for participants with prevalent CVD, and to a direct linear association for individuals with prevalent HF or AF. Additional inclusion of metabolic/inflammatory risk factors proposed to be favorably regulated by adiponectin, particularly diabetes and insulin resistance, rendered these associations across subgroups more adverse and similar in shape, eliminating the inverse association in the lower range observed in the first group, suggesting a direct association in the second, and strengthening the direct association in the third.

Previous Studies
Several population-based studies of older adults have found higher total adiponectin to be associated with an increased risk of fatal events. Such associations are at odds with favorable metabolic/vascular effects documented for total, and particularly HMW, adiponectin in experimental studies, and with significant inverse associations with incident CHD reported in healthy middle-aged adults. One potential explanation for the paradoxical associations would be a disjunction between levels of HMW and total adiponectin in older people. The current findings refute this premise, as does a previous study which failed to detect a significant association between HMW adiponectin and incident CHD in older women.

The direct relationship of total adiponectin with mortality in older adults has been similarly documented in younger cohorts with prevalent CHD or HF, suggesting that increases in adiponectin levels in response to underlying cardiac or vascular dysfunction serve as markers
of heightened risk in these settings. Indeed, in a middle-aged/older cohort, increased levels of total adiponectin were significantly associated with higher all-cause mortality in age- and sex-adjusted analyses among subjects with, but not without, prevalent CVD. By contrast, in a population of older men stratified by prevalent CVD and HF status, increasing tertiles of total adiponectin showed significant direct associations with fatal events after adjustment for potential confounders and intermediates in the subgroup without prevalent CVD/HF and the one with prevalent HF, but not in the subgroup with prevalent CVD and no HF.

Previous work in the long-lived CHS All Stars subset showed a non-linear association between total adiponectin (measured in 2005-06) and mortality that was characterized by significantly increased risk starting at levels ~20 mg/L. After additional adjustment for inflammatory markers, however, the relationship became U-shaped, with a significantly lower risk of death for increasing adiponectin levels up to 20 mg/L. The present findings now demonstrate that the association with mortality is in fact U-shaped for elders without clinically overt CVD or HF/AF, but not apparently so for those with prevalent CVD or HF/AF. Interestingly, a bidirectional association has also been reported between total adiponectin and left ventricular mass index among middle-aged African-Americans free of prevalent CHD.

It bears noting that the inflection point selected in CHS All Stars is higher than that of 12.4 mg/L chosen here. This may relate in part to the higher average adiponectin levels observed, consistent with the older age of CHS All-Stars participants, but the immunoassays used in the two studies are also different. Because adiponectin assays have not been standardized, the inflection points presented are not intended to serve as absolute cutpoints for determination of adiponectin-related risk, but instead as guides to the non-linear associations observed.

Potential Explanation for Findings
The relationship detailed here for participants without prevalent CVD/HF/AF is consistent with the U-shaped association documented in these subjects for total adiponectin and incident CHD and stroke, or with flattening of the inverse association between adiponectin and new-onset diabetes observed in the upper range of concentrations. Taken together, these findings refine understanding of the adiponectin paradox, indicating that within the lower range of the adipokine’s distribution in elders, higher levels do indeed confer a lower risk of all-cause, and particularly cardiovascular, mortality, much as they do for incident CHD in younger cohorts. That these lower mortality risks were attenuated substantially after adjustment for insulin resistance and diabetes accords with the proposition that adiponectin’s regulation of these factors largely mediates the adipokine’s favorable association with outcomes. At the upper range of concentrations, however, higher levels cease to lower, and instead heighten, the risk of death, an association that is not meaningfully altered by consideration of metabolic and inflammatory intermediates.

Such adverse prognostic implications for higher adiponectin concentrations in the upper range are consistent with the premise that they represent reactive increases to underlying disease processes. That adiponectin may play an important housekeeping function has gained support from findings that the adipokine promotes the phagocytic clearance of such cells by macrophages, forestalling the inflammation that would otherwise result from their unchecked accumulation. Indeed, the high concentrations of adiponectin found in the bloodstream are consistent with such a “mass action” role that goes beyond the adipokine’s receptor-mediated hormonal effects.

The hormonal and mass action properties of adiponectin are believed to be of particular importance to the vascular compartment, but the observation that adiponectin was inversely
associated with prevalent subclinical CVD in Group 1 does not support underlying vascular
disease as the basis for the heightened risk in the upper range. Nor did we find evidence that such
elevated risk reflected the influence of higher natriuretic peptide levels, which contrasts with
findings in an older male cohort.11 Still, the null association observed in Group 2, characterized
by clinically manifest CVD at baseline, could stem from offsetting favorable and unfavorable
vascular influences of, or upon, adiponectin in this setting. That adjustment for
metabolic/inflammatory factors presumed to be favorably influenced by the adipokine revealed a
nominally significant direct association lends support to offsetting links to other adverse
processes, vascular or otherwise.

Another important factor is the impact of aging-associated weight loss and sarcopenia,
which are major determinants of mortality in older adults and are associated with increased
adiponectin levels.17,37 We were therefore careful to adjust for BMI, and to take antecedent
weight loss into account, but these had minimal impact. There was, however, a suggestion of
effect-modification by baseline adiposity in Groups 1 and 2, though not in the smallest subgroup,
Group 3. For Group 1 in particular, this was marked by disappearance of the inverse associations
below the median among participants with BMI’s in the lowest tertile, much as occurred in this
group overall after adjustment for insulin resistance and diabetes. In the context of multiple
comparisons, the nominally significant p values for interaction and the modest effect-
modification noted (for BMI as for race-ethnicity) will require independent replication.
Nevertheless, the blunted inverse associations at lower BMI’s could reflect lower relevance of
the adipokine’s salutary metabolic effects in the absence of excess adiposity, and a predominance
of deleterious influences on adiponectin levels among older adults more afflicted by wasting and
sarcopenia.
The latter considerations also apply to Group 3, and likely explain the similarity of its cubic spline plot to that for the lowest BMI tertile of Group 1, since wasting and sarcopenia are as much hallmarks of the HF syndrome as of aging-associated decline. In fact, it has been documented that among patients with mild-moderate HF, skeletal-muscle wasting is associated with reduced expression of the AdipoR1 receptor and accompanying up-regulation of adiponectin production, attesting to the presence of adiponectin resistance. Whether elevated adiponectin levels in HF (or aging-related sarcopenia) reflect a sizable contribution from skeletal muscle production is uncertain. But in this subgroup with the worst overall prognosis, as in older adults with wasting and lower body weights, dysfunctional homeostatic processes are at their peak. In this context, a compensatory rise in adiponectin levels would be most expected, and its direct link to mortality more apparent after factoring in the adipokine’s favorable relationships with metabolic and inflammatory factors. It is also possible, however, that such adiponectin increases could themselves be harmful, either through undesirable catabolic effects in the setting of aging- or HF-associated sarcopenia, or other actions. Further research is necessary to define the underlying mechanisms.

Limitations
Because adiponectin measurements were available only for a healthier subset of CHS participants, the current findings do not necessarily apply to higher-risk older cohorts. Despite counting on a larger number of endpoints than prior investigations, the power to define the shape of adiponectin’s relationship with mortality was limited in the subgroups with prevalent CVD and prevalent HF/AF. Further detailing of these associations among elders with clinically overt cardiovascular disorders will require larger samples. In addition, the lack of skeletal muscle mass determinations precluded direct assessment of sarcopenia, whose role in adiponectin-associated
adverse risks warrants further study. Last, our analyses adjusting for metabolic and inflammatory factors must be interpreted with caution owing to the potential for bias in assessing the impact of causal intermediates. The results of such analyses are nonetheless consistent with – but cannot prove – the proposed role of insulin resistance and dysglycemia as key mediators of adiponectin’s beneficial association with outcomes.

In conclusion, in this large cohort of community-dwelling older adults, the nature of total and HMW adiponectin’s associations with all-cause and cardiovascular mortality differed similarly according to baseline cardiovascular status. Our findings shed light on the adiponectin paradox by documenting a bidirectional, rather than a monotonic, association with mortality among older adults free of clinical cardiovascular disorders; and by highlighting the mixture of favorable and unfavorable influences governing the prognostic associations of adiponectin in elders, and how progressively more advanced cardiac disease tilts the balance toward an adverse relationship with survival. The adipokine’s distinct associations with mortality suggest that further work to disentangle the underlying pathophysiological mechanisms could prove fruitful in the search for novel therapeutic targets in aging and related disorders.

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**Conflict of Interest Disclosures:** None.
References:


Table 1. Relationship of Total Adiponectin with Baseline Covariates

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<td>&lt;0.001</td>
<td>-0.01</td>
<td>0.81</td>
<td>-0.05</td>
<td>0.32</td>
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<tr>
<td>Antihypertensive medication</td>
<td>9.3(8.9-9.8)</td>
<td>&lt;0.001</td>
<td>8.6(8.0-9.3)</td>
<td>&lt;0.001</td>
<td>10.8(9.0-13.0)</td>
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<td>Yes</td>
<td>13.1(12.8-13.3)</td>
<td>&lt;0.001</td>
<td>11.6(11.2-12.0)</td>
<td>&lt;0.001</td>
<td>13.8(13.0-14.6)</td>
<td>0.145</td>
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<td>No</td>
<td>12.0(11.6-12.4)</td>
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<td>10.8(10.1-11.6)</td>
<td>&lt;0.001</td>
<td>11.5(10.2-13.0)</td>
<td>0.001</td>
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<td>Diabetes</td>
<td>11.8(11.4-12.3)</td>
<td>&lt;0.001</td>
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<td>&lt;0.001</td>
<td>12.3(10.9-13.9)</td>
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<td>11.8(11.3-12.3)</td>
<td>&lt;0.001</td>
<td>13.9(12.8-15.0)</td>
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<td>HOMA-IR</td>
<td>-0.17</td>
<td>&lt;0.001</td>
<td>-0.13</td>
<td>&lt;0.001</td>
<td>-0.13</td>
<td>0.014</td>
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<td>LDL-C</td>
<td>-0.04</td>
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<td>0.01</td>
<td>0.68</td>
<td>0.00</td>
<td>0.99</td>
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<td>HDL-C</td>
<td>0.48</td>
<td>&lt;0.001</td>
<td>0.49</td>
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<td>0.50</td>
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<td>Triglycerides</td>
<td>-0.27</td>
<td>&lt;0.001</td>
<td>-0.26</td>
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<td>-0.27</td>
<td>&lt;0.001</td>
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<td>Lipid-lowering medication</td>
<td>-0.27</td>
<td>&lt;0.001</td>
<td>-0.26</td>
<td>&lt;0.001</td>
<td>-0.27</td>
<td>&lt;0.001</td>
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<td>9.3(8.5-10.2)</td>
<td>&lt;0.001</td>
<td>10.9(9.5-12.5)</td>
<td>&lt;0.001</td>
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<td>&lt;0.001</td>
<td>12.3(11.8-12.8)</td>
<td>&lt;0.001</td>
<td>15.4(14.4-16.5)</td>
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<td>Albumin</td>
<td>-0.03</td>
<td>0.064</td>
<td>-0.05</td>
<td>0.098</td>
<td>-0.11</td>
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<td>Smoking status</td>
<td>0.004</td>
<td>0.171</td>
<td>0.653</td>
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<td>Current</td>
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<td>Never/Ever</td>
<td>12.5(12.2-12.7)</td>
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<td>13.4(12.6-14.2)</td>
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<td>Alcohol use</td>
<td>0.067</td>
<td>0.254</td>
<td>0.57</td>
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<td>≥7 drinks/wk</td>
<td>11.8(11.1-12.5)</td>
<td>10.4(9.4-11.5)</td>
<td>12.5(9.7-16.0)</td>
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<td>&lt;7 drinks/wk</td>
<td>12.4(12.2-12.7)</td>
<td>11.1(10.7-11.5)</td>
<td>13.4(12.6-14.2)</td>
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<td>Estrogen replacement (women)</td>
<td>&lt;0.001</td>
<td>0.197</td>
<td>0.036</td>
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<td>15.6(13.3-18.3)</td>
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<td>12.2(12.0-12.5)</td>
<td>10.9(10.5-11.3)</td>
<td>13.1(12.3-13.9)</td>
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<td>Self-reported health status</td>
<td>0.928</td>
<td>0.169</td>
<td>0.64</td>
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<td>Fair/poor</td>
<td>12.3(11.7-13.0)</td>
<td>10.6(10.0-11.3)</td>
<td>13.1(11.9-14.4)</td>
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<tr>
<td>Excellent/Very good/good</td>
<td>12.4(12.1-12.6)</td>
<td>11.2(10.8-11.6)</td>
<td>13.5(12.5-14.5)</td>
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<tr>
<td>Unintentional weight loss&gt;10 lbs</td>
<td>0.072</td>
<td>0.073</td>
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<td>Yes</td>
<td>13.4(12.2-14.8)</td>
<td>12.2(10.8-13.8)</td>
<td>15.1(13.0-17.6)</td>
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<td>No</td>
<td>12.3(12.0-12.5)</td>
<td>10.9(10.5-11.2)</td>
<td>13.0(12.2-13.9)</td>
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<td>Weight change (1992-93–1989-90)</td>
<td>-0.12</td>
<td>&lt;0.001</td>
<td>0.083</td>
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<td>Estimated GFR</td>
<td>0.01</td>
<td>0.58</td>
<td>0.25</td>
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<td>hsCRP</td>
<td>-0.08</td>
<td>&lt;0.001</td>
<td>0.11</td>
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<td>NT-proBNP</td>
<td>0.17</td>
<td>&lt;0.001</td>
<td>0.25</td>
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<td>Aspirin therapy</td>
<td>0.488</td>
<td>0.415</td>
<td>0.01</td>
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<td>12.3(11.9-12.6)</td>
<td>10.9(10.4-11.4)</td>
<td>12.4(11.4-13.4)</td>
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<tr>
<td>No</td>
<td>12.4(12.1-12.7)</td>
<td>11.2(10.6-11.8)</td>
<td>14.4(13.3-15.6)</td>
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<td>Warfarin therapy</td>
<td>0.058</td>
<td>0.313</td>
<td>0.114</td>
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<td>Yes</td>
<td>14.7(12.1-17.8)</td>
<td>10.1(8.5-12.0)</td>
<td>14.7(12.8-16.9)</td>
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<tr>
<td>No</td>
<td>12.4(12.1-12.6)</td>
<td>11.0(10.7-11.4)</td>
<td>13.1(12.3-13.9)</td>
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<td>Beta-blockers</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.002</td>
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<td>Yes</td>
<td>10.3(9.7-10.9)</td>
<td>9.3(8.7-10.0)</td>
<td>10.2(8.5-12.2)</td>
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<tr>
<td>No</td>
<td>12.6(12.4-12.8)</td>
<td>11.6(11.2-12.0)</td>
<td>13.7(12.9-14.6)</td>
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<td>ACE inhibitors</td>
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<td>0.222</td>
<td>0.949</td>
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<td>Yes</td>
<td>10.8(10.2-11.5)</td>
<td>10.4(9.5-11.5)</td>
<td>13.4(12.1-14.7)</td>
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</tr>
<tr>
<td>No</td>
<td>12.5(12.3-12.8)</td>
<td>11.1(10.7-11.5)</td>
<td>13.3(12.4-14.3)</td>
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<tr>
<td>Subclinical CVD†</td>
<td>0.001</td>
<td>Not applicable</td>
<td>Not applicable</td>
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<tr>
<td>Yes</td>
<td>12.1(11.8-12.4)</td>
<td>Not applicable</td>
<td>--</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>12.9(12.5-13.2)</td>
<td>Not applicable</td>
<td>--</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>HMW adiponectin</td>
<td>0.94</td>
<td>&lt;0.001</td>
<td>0.95</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Group 1, No prevalent CVD or HF/AF; Group 2, Prevalent CVD but no HF/AF; Group 3, Prevalent HF or AF.

*Geometric mean in mg/L; †Examined as a covariate only in participants without clinical CVD or HF/AF (Group 1)
Table 2. Associations of Total Adiponectin with All-Cause and Cardiovascular Mortality

<table>
<thead>
<tr>
<th>Group</th>
<th>Deaths</th>
<th>Mortality rate*</th>
<th>Cardiovascular Deaths</th>
<th>Cardiovascular mortality rate*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1,947</td>
<td>5.13</td>
<td>634</td>
<td>1.67</td>
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<tr>
<td></td>
<td>Total Adiponectin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;12.4 mg/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥12.4 mg/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>HR per 1-SD† (95% CI)</td>
<td>p</td>
<td>HR per 1-SD† (95% CI)</td>
<td>p</td>
</tr>
<tr>
<td>Model 1</td>
<td>0.84(0.71-0.98)</td>
<td>0.031</td>
<td>1.19(1.13-1.26)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 2</td>
<td>0.81(0.68-0.95)</td>
<td>0.011</td>
<td>1.18(1.12-1.26)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 3</td>
<td>0.71(0.58-0.85)</td>
<td>&lt;0.001</td>
<td>1.15(1.07-1.23)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 4a</td>
<td>0.81(0.69-0.95)</td>
<td>0.012</td>
<td>1.19(1.12-1.27)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 4b</td>
<td>0.90(0.76-1.07)</td>
<td>0.23</td>
<td>1.19(1.12-1.26)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 4c</td>
<td>0.93(0.78-1.11)</td>
<td>0.40</td>
<td>1.20(1.13-1.28)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 4d</td>
<td>0.91(0.75-1.10)</td>
<td>0.32</td>
<td>1.20(1.13-1.28)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Group 2 (n=1,030)</td>
<td>802</td>
<td>8.24</td>
<td>575</td>
<td>5.85</td>
</tr>
<tr>
<td></td>
<td>Total Adiponectin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>HR per 1-SD† (95% CI)</td>
<td>p</td>
<td>HR per 1-SD† (95% CI)</td>
<td>p</td>
</tr>
<tr>
<td>Model 1</td>
<td>1.02(0.94-1.10)</td>
<td>0.68</td>
<td>0.98(0.88-1.11)</td>
<td>0.80</td>
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<tr>
<td>Model 2</td>
<td>1.03(0.95-1.13)</td>
<td>0.47</td>
<td>1.00(0.88-1.14)</td>
<td>0.98</td>
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<td>Model 3</td>
<td>1.07(0.96-1.19)</td>
<td>0.21</td>
<td>1.01(0.86-1.19)</td>
<td>0.88</td>
</tr>
<tr>
<td>Model 4b</td>
<td>1.09(1.00-1.19)</td>
<td>0.049</td>
<td>1.06(0.93-1.21)</td>
<td>0.38</td>
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<tr>
<td>Model 4c</td>
<td>1.12(1.01-1.24)</td>
<td>0.026</td>
<td>1.16(1.00-1.34)</td>
<td>0.054</td>
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<tr>
<td>Model 4d</td>
<td>1.08(0.97-1.21)</td>
<td>0.144</td>
<td>1.12(0.95-1.32)</td>
<td>0.169</td>
</tr>
<tr>
<td>Group 3 (n=383)</td>
<td>557</td>
<td>11.54</td>
<td>180</td>
<td>6.17</td>
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<td>Total Adiponectin</td>
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<tr>
<td></td>
<td>HR per 1-SD† (95% CI)</td>
<td>p</td>
<td>HR per 1-SD† (95% CI)</td>
<td>p</td>
</tr>
<tr>
<td>Model 1</td>
<td>1.18(1.07-1.31)</td>
<td>0.001</td>
<td>1.13(0.98-1.30)</td>
<td>0.086</td>
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<tr>
<td>Model 2</td>
<td>1.16(1.04-1.30)</td>
<td>0.007</td>
<td>1.11(0.95-1.30)</td>
<td>0.170</td>
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<td>Model 3</td>
<td>1.17(1.03-1.32)</td>
<td>0.013</td>
<td>1.14(0.97-1.35)</td>
<td>0.121</td>
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<tr>
<td>Model 4b</td>
<td>1.20(1.07-1.35)</td>
<td>0.002</td>
<td>1.19(1.02-1.40)</td>
<td>0.030</td>
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<tr>
<td>Model 4c</td>
<td>1.31(1.15-1.50)</td>
<td>&lt;0.001</td>
<td>1.24(1.03-1.49)</td>
<td>0.023</td>
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<tr>
<td>Model 4d</td>
<td>1.33(1.16-1.53)</td>
<td>&lt;0.001</td>
<td>1.22(1.01-1.48)</td>
<td>0.041</td>
</tr>
</tbody>
</table>

*per 100 person-years; †1-SD =7.9 mg/L; Model 1. Adjusted for age, sex, and race.
Model 2. Adjusted for age, sex, race, center, BMI, smoking status, alcohol consumption, systolic blood pressure, beta-blockers, angiotensin-converting-enzyme inhibitors, self-reported health status, estimated GFR. (Replacement of BMI by waist-hip ratio did not meaningfully alter the findings.)
Model 3. Adjusted for covariates in Model 2 and NT-proBNP (n=2,970, 832, and 227 in Groups 1, 2, and 3, respectively).
Model 4a. Adjusted for covariates in Model 2 and subclinical CVD.
Model 4b. Adjusted for covariates in Model 2 and diabetes. (Adjustment for covariates in Model 2 and HOMA-IR in the subset of participants not receiving diabetes medication [n=3,506, 937, and 239 in Groups 1, 2, and 3, respectively] led to similar risk estimates.)
Model 4c. Adjusted for covariates in Model 2 and diabetes, LDL-C, HDL-C, log(triglycerides), and log( hsCRP).
Model 4d. Adjusted for covariates in Model 2 and HOMA-IR, LDL-C, HDL-C, log(triglycerides), log( hsCRP) in subjects not receiving diabetes medication (n=3,506, 937, and 239, respectively).
Table 3. Associations of Specific Concentrations of Total Adiponectin with All-Cause and Cardiovascular Mortality in Group 1*

<table>
<thead>
<tr>
<th>Total Adiponectin</th>
<th>10&lt;sup&gt;th&lt;/sup&gt; Percentile</th>
<th>25&lt;sup&gt;th&lt;/sup&gt; Percentile</th>
<th>50&lt;sup&gt;th&lt;/sup&gt; Percentile</th>
<th>75&lt;sup&gt;th&lt;/sup&gt; Percentile</th>
<th>90&lt;sup&gt;th&lt;/sup&gt; Percentile</th>
<th>p†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6.1 mg/L</td>
<td>8.4 mg/L</td>
<td>12.1 mg/L</td>
<td>17.4 mg/L</td>
<td>24.5 mg/L</td>
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<td>All-cause Mortality</td>
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<tr>
<td>Model 1</td>
<td>1.09(0.97-1.21)</td>
<td>1.04(0.98-1.11)</td>
<td>1(ref)</td>
<td>1.02(0.96-1.09)</td>
<td>1.16(1.02-1.32)</td>
<td>0.001</td>
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<td>Model 2</td>
<td>1.13(1.01-1.26)</td>
<td>1.06(1.00-1.13)</td>
<td>1(ref)</td>
<td>1.01(0.94-1.08)</td>
<td>1.13(0.99-1.30)</td>
<td>0.001</td>
</tr>
<tr>
<td>Model 3</td>
<td>1.16(1.04-1.29)</td>
<td>1.08(1.01-1.15)</td>
<td>1(ref)</td>
<td>0.99(0.92-1.06)</td>
<td>1.10(0.95-1.26)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 4a</td>
<td>1.12(1.00-1.25)</td>
<td>1.06(0.99-1.12)</td>
<td>1(ref)</td>
<td>1.01(0.95-1.09)</td>
<td>1.14(1.00-1.31)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 4b</td>
<td>1.06(0.94-1.18)</td>
<td>1.03(0.96-1.09)</td>
<td>1(ref)</td>
<td>1.03(0.97-1.11)</td>
<td>1.17(1.02-1.35)</td>
<td>0.002</td>
</tr>
<tr>
<td>Model 4c</td>
<td>1.04(0.93-1.17)</td>
<td>1.02(0.95-1.09)</td>
<td>1(ref)</td>
<td>1.04(0.97-1.12)</td>
<td>1.18(1.02-1.37)</td>
<td>0.003</td>
</tr>
<tr>
<td>Cardiovascular Mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>1.30(1.08-1.57)</td>
<td>1.16(1.04-1.29)</td>
<td>1(ref)</td>
<td>0.96(0.86-1.08)</td>
<td>1.17(0.93-1.47)</td>
<td>0.002</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.32(1.09-1.60)</td>
<td>1.16(1.04-1.30)</td>
<td>1(ref)</td>
<td>0.99(0.87-1.11)</td>
<td>1.26(0.99-1.60)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 3</td>
<td>1.37(1.13-1.67)</td>
<td>1.19(1.07-1.33)</td>
<td>1(ref)</td>
<td>0.96(0.85-1.08)</td>
<td>1.19(0.94-1.52)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 4a</td>
<td>1.29(1.06-1.57)</td>
<td>1.15(1.03-1.28)</td>
<td>1(ref)</td>
<td>1.00(0.89-1.13)</td>
<td>1.28(1.00-1.63)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 4b</td>
<td>1.20(0.98-1.46)</td>
<td>1.10(0.98-1.23)</td>
<td>1(ref)</td>
<td>1.03(0.91-1.16)</td>
<td>1.33(1.04-1.69)</td>
<td>0.002</td>
</tr>
<tr>
<td>Model 4c</td>
<td>1.16(0.94-1.42)</td>
<td>1.08(0.96-1.21)</td>
<td>1(ref)</td>
<td>1.05(0.92-1.19)</td>
<td>1.36(1.05-1.77)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

*All risk estimates are for subset with available NT-proBNP measurements (n=2,970).†p for partial likelihood test comparing the model with and without inclusion of total adiponectin.

Models are as in Table 2. Findings for model 2 were similar when waist-hip ratio replaced BMI, as were findings for model 4b when HOMA-IR was used in the subset not on diabetes medications.
Figure Legends:

**Figure 1.** Cubic (panel A) and linear (panel B) spline graphs depicting the associations of continuous levels of total adiponectin with all-cause mortality. The horizontal band above the x-axis represents individual participants (vertical lines) with corresponding values for total adiponectin. Values at the extreme 2.5th percentiles have been removed from the plots. All models are adjusted for age, sex, race, BMI, systolic blood pressure, beta-blockers, angiotensin-converting-enzyme inhibitors, smoking, alcohol use, health status, and eGFR.

**Figure 2.** Cubic spline graphs depicting the associations of continuous levels of total adiponectin with all-cause mortality in Group 1, stratified by tertiles of BMI. Description of plots, and adjustment for covariates are as in Figure 1.
Associations of Total and High-Molecular-Weight Adiponectin with All-Cause and Cardiovascular Mortality in Older Persons: The Cardiovascular Health Study
Jorge R. Kizer, David Benkeser, Alice M. Arnold, Kenneth J. Mukamal, Joachim H. Ix, Susan J. Zieman, David S. Siscovick, Russell P. Tracy, Christos S. Mantzoros, Christopher R. deFilippi, Anne B. Newman and Luc Djousse

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Data Supplement (unedited) at:
http://circ.ahajournals.org/content/suppl/2012/11/16/CIRCULATIONAHA.112.135202.DC1

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### Supplemental Table 1. Associations of HMW Adiponectin with All-Cause and Cardiovascular Mortality

<table>
<thead>
<tr>
<th>Group 1 (n=3,272)</th>
<th>All-cause Mortality</th>
<th>Cardiovascular Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMW Adiponectin</td>
<td>&lt;6.2 mg/L</td>
<td>≥6.2 mg/L</td>
</tr>
<tr>
<td></td>
<td>HR per 1-SD* (95% CI)</td>
<td>p</td>
</tr>
<tr>
<td>Model 1</td>
<td>0.95 (0.79-1.14)</td>
<td>0.59</td>
</tr>
<tr>
<td>Model 2</td>
<td>0.92 (0.77-1.11)</td>
<td>0.38</td>
</tr>
<tr>
<td>Model 3</td>
<td>0.77 (0.62-0.94)</td>
<td>0.012</td>
</tr>
<tr>
<td>Model 4a</td>
<td>0.93 (0.77-1.11)</td>
<td>0.42</td>
</tr>
<tr>
<td>Model 4b</td>
<td>1.04 (0.86-1.25)</td>
<td>0.71</td>
</tr>
<tr>
<td>Model 4c</td>
<td>1.06 (0.87-1.28)</td>
<td>0.59</td>
</tr>
<tr>
<td>Model 4d</td>
<td>1.03 (0.83-1.26)</td>
<td>0.81</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group 2 (n=1,030)</th>
<th>All-cause Mortality</th>
<th>Cardiovascular Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMW Adiponectin</td>
<td>Entire Range</td>
<td>Entire Range</td>
</tr>
<tr>
<td></td>
<td>HR per 1-SD* (95% CI)</td>
<td>p</td>
</tr>
<tr>
<td>Model 1</td>
<td>1.01 (0.93-1.09)</td>
<td>0.81</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.02 (0.94-1.11)</td>
<td>0.59</td>
</tr>
<tr>
<td>Model 3</td>
<td>1.08 (0.97-1.20)</td>
<td>0.174</td>
</tr>
<tr>
<td>Model 4b</td>
<td>1.08 (0.99-1.17)</td>
<td>0.081</td>
</tr>
<tr>
<td>Model 4c</td>
<td>1.09 (1.00-1.20)</td>
<td>0.058</td>
</tr>
<tr>
<td>Model 4d</td>
<td>1.07 (0.97-1.18)</td>
<td>0.175</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group 3 (n=383)</th>
<th>All-cause Mortality</th>
<th>Cardiovascular Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMW Adiponectin</td>
<td>Entire Range</td>
<td>Entire Range</td>
</tr>
<tr>
<td>HR per 1-SD* (95% CI)</td>
<td>p</td>
<td>HR per 1-SD* (95% CI)</td>
</tr>
<tr>
<td>Model 1</td>
<td>1.19 (1.09-1.31)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.18 (1.06-1.31)</td>
<td>0.002</td>
</tr>
<tr>
<td>Model</td>
<td>Hazard Ratio (95% CI)</td>
<td>P-Value</td>
</tr>
<tr>
<td>---------</td>
<td>----------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Model 3</td>
<td>1.16 (1.03-1.30)</td>
<td>0.011</td>
</tr>
<tr>
<td>Model 4b</td>
<td>1.22 (1.10-1.37)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 4c</td>
<td>1.36 (1.20-1.55)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 4d</td>
<td>1.36 (1.19-1.55)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*1-SD = 5.9 mg/L

Model 1. Adjusted for age, sex, and race.
Model 2. Adjusted for age, sex, race, center, BMI, smoking status, alcohol consumption, systolic blood pressure, beta-blockers, angiotensin-converting-enzyme inhibitors, self-reported health status, estimated glomerular filtration rate. (Replacement of BMI by waist-hip ratio did not meaningfully alter the findings.)
Model 3. Adjusted for covariates in Model 2 and NT-proBNP (n=2,970, 832, and 227 in Groups 1, 2, and 3, respectively).
Model 4a. Adjusted for covariates in Model 2 and subclinical cardiovascular disease.
Model 4b. Adjusted for covariates in Model 2 and diabetes. (Adjustment for covariates in Model 2 and HOMA-IR in the subset of participants not receiving diabetes medication [n=3,506, 937, and 239 in Groups 1, 2, and 3, respectively] led to similar risk estimates.)
Model 4c. Adjusted for covariates in Model 2 and diabetes, LDL-C, HDL-C, log(triglycerides), and log(hsCRP).
Model 4d. Adjusted for covariates in Model 2 and HOMA-IR, LDL-C, HDL-C, log(triglycerides), and log(hsCRP) in subjects not receiving diabetes medication (n=3,506, 937, and 239, respectively).
Supplemental Table 2. Associations of Specific Concentrations of HMW Adiponectin with All-Cause and Cardiovascular Mortality in Group 1*

<table>
<thead>
<tr>
<th>HMW Adiponectin</th>
<th>Hazard Ratio (95% Confidence Interval)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10th Percentile</td>
<td>25th Percentile</td>
</tr>
<tr>
<td>All-cause Mortality</td>
<td>2.1 mg/L</td>
<td>3.7 mg/L</td>
</tr>
<tr>
<td>Model 1</td>
<td>1.04 (0.94-1.15)</td>
<td>1.02 (0.96-1.07)</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.08 (0.97-1.19)</td>
<td>1.04 (0.98-1.09)</td>
</tr>
<tr>
<td>Model 3</td>
<td>1.10 (0.99-1.22)</td>
<td>1.05 (1.00-1.11)</td>
</tr>
<tr>
<td>Model 4a</td>
<td>1.07 (0.96-1.18)</td>
<td>1.03 (0.98-1.09)</td>
</tr>
<tr>
<td>Model 4b</td>
<td>1.02 (0.92-1.13)</td>
<td>1.01 (0.95-1.06)</td>
</tr>
<tr>
<td>Model 4c</td>
<td>1.02 (0.92-1.13)</td>
<td>1.01 (0.95-1.06)</td>
</tr>
</tbody>
</table>

Cardiovascular Mortality

| Model 1         | 1.17 (0.99-1.40)                      | 1.09 (0.99-1.19) | 1 (ref) | 0.96 (0.86-1.08) | 1.09 (0.88-1.35) | 0.022 |
| Model 2         | 1.18 (0.99-1.41)                      | 1.09 (0.99-1.20) | 1 (ref) | 0.98 (0.88-1.11) | 1.16 (0.92-1.46) | 0.007 |
| Model 3         | 1.23 (1.03-1.47)                      | 1.11 (1.01-1.22) | 1 (ref) | 0.96 (0.85-1.07) | 1.10 (0.87-1.38) | 0.005 |
| Model 4a        | 1.16 (0.97-1.38)                      | 1.08 (0.98-1.18) | 1 (ref) | 0.99 (0.88-1.12) | 1.18 (0.94-1.48) | 0.007 |
| Model 4b        | 1.08 (0.90-1.30)                      | 1.04 (0.94-1.15) | 1 (ref) | 1.02 (0.91-1.15) | 1.23 (0.98-1.55) | 0.008 |
| Model 4c        | 1.07 (0.89-1.29)                      | 1.03 (0.93-1.14) | 1 (ref) | 1.04 (0.92-1.17) | 1.26 (0.99-1.61) | 0.012 |

*All risk estimates are for subset with available NT-proBNP measurements (n=2,970).
†p for partial likelihood test comparing the model with and without inclusion of HMW adiponectin.
Models are as in Supplemental Table 1. Findings for model 2 were similar when waist-hip ratio replaced BMI, as were findings for model 4b when HOMA-IR was used in the subset not on diabetes medications.