CARDIOVASCULAR DISEASE

Association between adiponectin levels and coronary heart disease and mortality: a systematic review and meta-analysis

Eon Sook Lee,1 Sang-shin Park,2 Eugene Kim,3 Yeong Sook Yoon,1 Hong-Yup Ahn,4 Cheol-Young Park,5 Young Ho Yun6 and Sang Woo Oh3*

1Department of Family Medicine, Inje University Ilsan Paik Hospital, Gyeonggi-Do, South Korea, 2Department of Veterinary Integrative Biosciences, College of Veterinary Medicine and Biomedical Sciences, Texas A&M University, College Station, TX, USA, 3Center for Obesity, Nutrition, and Metabolism, Department of Family Medicine, Dongguk University Ilsan Hospital, Dongguk University College of Medicine, Gyeonggi-Do, South Korea, 4Department of Statistics, Dongguk University-Seoul, Seoul, South Korea, 5Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, South Korea and 6Seoul National University College of Medicine, Seoul, South Korea

*Corresponding author. Center for Obesity, Nutrition and Metabolism, Department of Family Medicine, Dongguk University Ilsan Hospital, Siksa-dong 814, Ilsandong-Gu, Goyang-Si, Gyeonggi-Do, 410-773, South Korea. E-mail address: osw6021@yahoo.co.kr

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Background Our aim was to systematically review prospective studies of the association of plasma adiponectin levels with the risk of coronary heart disease (CHD) events, cardiovascular mortality and all-cause mortality.

Methods We searched Medline, EMBASE, the Cochrane Library and CINAHL for reports published through October 2011. Search terms included ‘adiponectin’ AND ‘cardiovascular disease’ OR ‘mortality’. We included prospective studies lasting more than 1 year with plasma adiponectin levels at baseline and all-cause mortality and/or major cardiovascular morbidity and mortality as outcomes. We used a random-effects model to pool the data and conducted additional subgroup meta-analyses according to the pre-existence of CHD. Pooled relative risk (RR) was estimated by a 1-SD increase in the logarithmically transformed circulating adiponectin levels.

Results A total of 24 prospective studies were included in the meta-analysis. The pooled RR of adiponectin for CHD events (23 studies) was 1.03 [95% confidence interval (CI): 1.00, 1.06]. In subgroup analyses, the RR of adiponectin was 0.99 (95% CI: 0.94, 1.03) for new-onset CHD (17 studies), but there was an increased risk (RR = 1.12, 95% CI: 1.04, 1.22) for CHD recurrence (seven studies). A 10% increased risk (RR = 1.10, 95% CI: 1.04, 1.16) of all-cause mortality (six studies) and a 14% increased risk (RR = 1.14, 95% CI: 1.05, 1.23) of cardiovascular disease mortality (five studies) were observed.

Conclusions No association was observed between adiponectin levels and CHD events. Our results suggest that higher circulating adiponectin levels may be associated with an increased risk of CHD recurrence and all-cause/CVD mortality.

Keywords Adiponectin, all-cause mortality, cardiovascular mortality, coronary heart disease
Introduction

Adipose tissue is an active endocrine organ that secretes various bioactive molecules, collectively called ‘adipokines’. Many of these adipokines play potent roles in modulating energy balance, metabolic homeostasis and inflammatory processes. Among these, adiponectin draws special attention because its levels show an inverse association with adiposity. Additionally, adiponectin has insulin-sensitizing, anti-inflammatory and anti-atherogenic activities.5

Many laboratory and clinical studies have shown that adiponectin has a protective effect against type 2 diabetes. A recent systematic review and meta-analysis also confirmed an inverse relationship between adiponectin levels and the risk for type 2 diabetes.7 Growing evidence suggests a protective effect of adiponectin against dyslipidaemia, metabolic syndrome and some types of cancer (breast, colon, prostate, and others).8

However, the beneficial effects of adiponectin are unclear in the case of coronary heart disease (CHD). Many cellular and animal studies have suggested various signalling pathways and mechanisms supporting beneficial effects of adiponectin against atherosclerosis. However, the results of clinical studies on this issue are inconsistent, and a previous meta-analysis that included seven cohort studies failed to demonstrate this effect.4

There is increasing interest in the clinical application of adiponectin, and some trials are now being conducted or planned using drugs that enhance endogenous adiponectin production or using recombinant adiponectin.8 Before the realization of a clinical application, it is necessary to thoroughly assess the effects of adiponectin on CHD because its safety is unclear. For example, a recent meta-analysis reported a paradoxical increase in myocardial infarction and cardiovascular disease (CVD) mortality with rosiglitazone therapy,6 although other medications enhancing adiponectin production are supposed to be unrelated to or to decrease these risks.

We conducted this meta-analysis with currently available epidemiological data to determine the effect of adiponectin on CHD. Additionally, we explored the issue of CVD and all-cause mortality.

Methods

Search strategy and eligibility criteria

We searched Medline (PubMed and Ovid), EMBASE, the Cochrane Library and CINAHL for reports published through October 2011. We conducted searches using Medical Subject Heading terms including ‘adiponectin’ AND ‘(cardiovascular disease’ OR ‘mortality’). Search terms were explored and properly modified according to the databases. Searching was limited to humans, but no language restriction was applied. We conducted the systematic review according to the Centre for Reviews and Dissemination (CRD) and Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.7 All relevant studies identified were included. Bibliographies of relevant studies including recent reviews were hand-searched for additional publications. Some studies without sufficient data were included after contact with the author. Clinical trial data were not available on this issue. Cohort or case-control epidemiological studies were included if they fulfilled the following criteria: (i) accrued more than 1 year of follow-up; (ii) assessed adiponectin levels at baseline; and (iii) recorded all-cause mortality and/or major cardiovascular morbidity and mortality. We excluded cross-sectional studies, reviews, studies on animals or cell lines and studies of genetic variation in adiponectin-related genes. We also excluded studies that compared the degree of coronary artery stenosis and studies on subjects with type 1 diabetes or end-stage renal disease.

Data extraction

Data were extracted independently by two authors (E.S.L. and E.K.). Disagreements between authors were resolved by discussion with a third investigator (S.W.O.). We extracted information about the effect size [relative risk (RR) or odds ratio (OR)], circulating adiponectin levels, authors, name of the study, publication year, study design, duration of follow-up, type of outcome events, baseline comorbidity (diabetes, cerebrovascular disease and others), sample size, number of cases (CHD events and all-cause/CVD deaths), mean/range of age, proportion of men, country, race/ethnicity, assay method for measuring adiponectin levels and body mass index (BMI). Adiponectin levels were reported as continuous logarithmically transformed adiponectin levels or as tertiles or quartiles in original articles. We converted these scales to a logarithmic scale. CHD event, CVD mortality and all-cause mortality were endpoints in this analysis. In the studies included in the meta-analysis, CHD events included fatal and nonfatal myocardial infarction, angina, hospitalization for coronary heart disease and so on. CVD mortality was defined as death from cardiovascular disease. Usually, all data were based on the hospital record or death certificate.

Statistical analysis

Multivariable-adjusted hazard ratios or ORs reported in each study were used to estimate the summary statistics. Because the OR asymptotically approaches the RR when an event has a low rate, we assumed that ORs would be appropriate estimates of RR. Pooled RRs were estimated for a 1-SD increase in logarithmically transformed adiponectin levels. Random-effects models were applied to obtain pooled RR estimates across studies. In this model, between-study variances in effect sizes were estimated using the DerSimonian and Laird method and summed to within-study error for calculating
total variance in the studies. A test for the assumption of homogeneity was conducted using Cochrane Q statistics, and the ratio of heterogeneity to total variance was calculated as:

\[ I^2 = \frac{Q - df}{Q} \times 100\% \]

Random-effects meta-regression analyses were performed to search for potential effect modifiers that contributed to the heterogeneity between studies and for sub-group analyses. We considered the effect of race/ethnicity (Caucasian, African-American, American Indian, Asian and mixed ethnicity), gender (proportion of men), mean age (continuous and two categories: <65 or \( \geq 65\) years), BMI (continuous and three categories: <25, 25–30, \( \geq 30\) kg/m\(^2\)), follow-up period (continuous and two categories: <5 or \( \geq 5\) years), type 2 diabetes (yes or no), stroke (yes or no), assay method for measuring adiponectin [enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA) or others], study design (cohort or nested case-control study) and measures of effect size (RR or OR).

The influence of an individual study on the summary estimates was investigated by sensitivity analysis in which the meta-analysis estimates were computed omitting one study in turn. Publication bias was assessed by the rank correlation test proposed by Begg and Mazumdar\(^8\) and the linear regression test proposed by Egger \textit{et al}.\(^9\). Considering the low statistical power of these two tests, we additionally prepared a funnel plot for visual inspection when searching for publication bias. When asymmetry was suspected in funnel plots, we employed Duval and Tweedie’s nonparametric trim-and-fill method\(^10\) and tested how the effect size shifted to assess the validity of the summary RR.

Because discrimination between fatal and nonfatal CHD is obscure in most studies, we classified both events into the CHD category in the meta-analyses. Because five studies counted cerebrovascular events in their outcome, we conducted additional sensitivity meta-analyses estimating the influence of these studies on our pooled RR. Only cases reported as death from CVD were included in the CVD mortality analyses.

Of the studies, one study (British Regional Heart Study) published two articles: Sattar \textit{et al}.\(^4\) and Wannamethee \textit{et al}.\(^11\); hence, it is possible that some study subjects were double-counted in our analyses. However, these two nested case-control studies reported different outcome variables (one reported a CHD event with CHD mortality and the other reported all-cause and CVD mortality) and different follow-up periods. Therefore, when reasonable plausibility could be assumed, we included both studies simultaneously in the meta-analyses and conducted a sensitivity analysis for the influence of the studies on the estimation of the pooled effect size. All analyses were performed with Stata version 11.2 (StataCorp, College Station, TX, USA).

### Results

#### Search results

The literature searches yielded 3380 studies. Initial screening of abstracts and full reviews of original articles were performed; 161 studies were included after first screening. Of these, 137 were excluded because of cross-sectional data, insufficient data on baseline adiponectin or duplication. By our criteria, 24 studies were finally eligible for inclusion in the meta-analyses (Figure 1). Among the 24 studies, 13 (12–24) were cohort studies, and 11 (4, 11, 25–33) were nested case-control studies (Table 1). In total, 30,945 subjects were available for analysis. Among these, 22,635 had no history of myocardial infarction, angina or stroke at initial recruitment; 8193 had a history of coronary heart disease; and 117 were patients with heart failure. Six studies evaluated the association between adiponectin and all-cause mortality and/or cardiovascular mortality, and 22 studies had information about cardiovascular events such as myocardial infarction or angina.

#### Coronary heart disease

Twenty-three studies were used to estimate the summary effects of adiponectin on coronary events (Fig. 2). The pooled RR was 1.03 (95% confidence interval (CI): 1.00, 1.06, \( P = 0.089\)). High

![Figure 1 Selection of studies included in the meta-analysis.](http://example.com/fig1.png)
Table 1 Characteristics of the studies (n = 24) on adiponectin levels and the risk of cardiovascular events and mortality

<table>
<thead>
<tr>
<th>Source</th>
<th>Publication year</th>
<th>Study name</th>
<th>Mean duration of follow-up, years</th>
<th>Baseline status of subjects</th>
<th>Baseline adiponectin</th>
<th>No. of subject</th>
<th>No. of cases</th>
<th>Age range, years (mean at baseline)</th>
<th>Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cohort studies</strong></td>
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</tr>
<tr>
<td>Cavusoglu et al.</td>
<td>2006</td>
<td>CHD patients Q1: ≤4.431</td>
<td>2</td>
<td>CHD patients</td>
<td>Q1: ≤4.431</td>
<td>325</td>
<td>79</td>
<td>NA (63.4)</td>
<td>All-cause mortality, CVD mortality, Myocardial infarction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CHD patients Q2: ≥4.431≤8.008</td>
<td></td>
<td></td>
<td>Q2: ≥4.431≤8.008</td>
<td></td>
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<td></td>
<td></td>
<td>CHD patients Q3: &gt;8.008</td>
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<td></td>
<td>Q3: &gt;8.008</td>
<td></td>
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</tr>
<tr>
<td>Iwashima et al.</td>
<td>2006</td>
<td>CHD patients</td>
<td>2.7</td>
<td>CHD patients</td>
<td>4.8 (3.0–9.8)</td>
<td>150</td>
<td>31</td>
<td>NA (67.7)</td>
<td>Cardiovascular events</td>
</tr>
<tr>
<td>Koenig et al.</td>
<td>2006</td>
<td>MONICA project</td>
<td>18</td>
<td>Non CHD patients</td>
<td>6.3 (4.4–9.1)</td>
<td>937</td>
<td>126</td>
<td>45–64</td>
<td>Cardiovascular events</td>
</tr>
<tr>
<td>Pilz et al.</td>
<td>2006</td>
<td>LURIC study</td>
<td>5.5</td>
<td>Highly suspected CHD patients</td>
<td>9.9 (9.4–10.3)</td>
<td>3146</td>
<td>482</td>
<td>NA</td>
<td>All-cause mortality, CVD mortality</td>
</tr>
<tr>
<td>Frystyk et al.</td>
<td>2007</td>
<td>ULSAM study</td>
<td>10.4</td>
<td>Non CHD patients</td>
<td>10.4±4.3</td>
<td>832</td>
<td>116</td>
<td>NA (71)</td>
<td>Cardiovascular events</td>
</tr>
<tr>
<td>Laughlin et al.</td>
<td>2007</td>
<td>Rancho Bernardo study</td>
<td>20</td>
<td>Non CHD patients</td>
<td>11.9 (11.6–12.3)</td>
<td>1352</td>
<td>252</td>
<td>50–91</td>
<td>Cardiovascular events</td>
</tr>
<tr>
<td>Dekker et al.</td>
<td>2008</td>
<td>Hoorn Study</td>
<td>15</td>
<td>Non CHD patients</td>
<td>Q1,Q2,Q3,Q4</td>
<td>1886</td>
<td>340</td>
<td>50–75</td>
<td>All-cause mortality, CVD mortality</td>
</tr>
<tr>
<td>Schnabel et al.</td>
<td>2008</td>
<td>AtheroGene study</td>
<td>2.5</td>
<td>CHD patients</td>
<td>Q1,Q2,Q3,Q4</td>
<td>433</td>
<td>164</td>
<td>50–75</td>
<td>All-cause mortality, CVD mortality</td>
</tr>
<tr>
<td>von Eynatten et al.</td>
<td>2008</td>
<td>Health Care Professional Follow-up study</td>
<td>4.7</td>
<td>CHD patients</td>
<td>Q1,Q2,Q3,Q4</td>
<td>1890</td>
<td>116</td>
<td>NA (63)</td>
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</tr>
<tr>
<td>Dieplinger et al.</td>
<td>2009</td>
<td>Peripheral arterial disease patients</td>
<td>2.4</td>
<td>Peripheral arterial disease patients</td>
<td>9.1 (6.3–13.7)</td>
<td>487</td>
<td>114</td>
<td>59–80</td>
<td>All-cause mortality</td>
</tr>
<tr>
<td>Krzyzanowska et al.</td>
<td>2009</td>
<td>Type II DM patients</td>
<td>1.6</td>
<td>Type II DM patients</td>
<td>3.7 (2.4–5.7)</td>
<td>147</td>
<td>61</td>
<td>59–70</td>
<td>Cardiovascular events</td>
</tr>
<tr>
<td>Poehls et al.</td>
<td>2009</td>
<td>Health ABC study</td>
<td>6.6</td>
<td>Non CHD patients</td>
<td>Q1: ≤6.77</td>
<td>3075</td>
<td>679</td>
<td>69–79</td>
<td>All-cause mortality, CVD mortality</td>
</tr>
<tr>
<td>Urbonaviciene et al.</td>
<td>2010</td>
<td>Peripheral arterial disease patients</td>
<td>3.5</td>
<td>Peripheral arterial disease patients</td>
<td>Q1: ≤6.77</td>
<td>468</td>
<td>215</td>
<td>NA (65.7)</td>
<td>Non-fatal cardiovascular disease</td>
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<tr>
<td><strong>Nested cohort studies</strong></td>
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<tr>
<td>Pischon et al.</td>
<td>2004</td>
<td>Health Care Professional Follow-up study</td>
<td>6</td>
<td>Non CHD patients</td>
<td>15.6±8.5/17.9±8.8</td>
<td>798</td>
<td>266</td>
<td>40–75</td>
<td>Cardiovascular events</td>
</tr>
<tr>
<td>Lawlor et al.</td>
<td>2005</td>
<td>British Women’s Heart and Health study</td>
<td>4</td>
<td>Non CHD patients</td>
<td>14.5 (13.5–15.7)/15.1 (14.3–16.0)</td>
<td>499</td>
<td>167</td>
<td>60–75</td>
<td>Cardiovascular events</td>
</tr>
</tbody>
</table>

(continued)
<table>
<thead>
<tr>
<th>Source</th>
<th>Publication year</th>
<th>Study name</th>
<th>Mean duration of follow-up, years</th>
<th>Baseline status of subjects</th>
<th>Baseline adiponectin*</th>
<th>No. of subject</th>
<th>No. of cases</th>
<th>Age range, years (mean at baseline)</th>
<th>Endpoints</th>
</tr>
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<tbody>
<tr>
<td>Lindsay et al.</td>
<td>2005</td>
<td>Strong Heart Study</td>
<td>10</td>
<td>American Indians</td>
<td>9.6(6.8–13.3)/19.4</td>
<td>502</td>
<td>295</td>
<td>NA</td>
<td>Cardiovascular events</td>
</tr>
<tr>
<td>Sattar et al.</td>
<td>2006</td>
<td>British Regional Heart Study</td>
<td>16</td>
<td>Non CHD patients</td>
<td>10.2 (7.2–13.9)/10.8</td>
<td>1820</td>
<td>589</td>
<td>40–59</td>
<td>Cardiovascular events</td>
</tr>
<tr>
<td>Wannamethee et al.</td>
<td>2007</td>
<td>British Regional Heart Study</td>
<td>6</td>
<td>Non CHD patients</td>
<td>6.8(4.4–10.9)</td>
<td>3099</td>
<td>465</td>
<td>60–79</td>
<td>All-cause mortality, CVD mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CHD patients</td>
<td>6.6 (4.1–11.4)</td>
<td>830</td>
<td>217</td>
<td>60–79</td>
<td>All-cause mortality, CVD mortality</td>
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<tr>
<td></td>
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<td></td>
<td>CHF patients</td>
<td>9.2(6.0–15.2)</td>
<td>117</td>
<td>52</td>
<td>60–79</td>
<td>All-cause mortality, CVD mortality</td>
</tr>
<tr>
<td>Hajer et al.</td>
<td>2007</td>
<td>SMART study</td>
<td>2.3</td>
<td>Vascular disease patients</td>
<td>7.5 ± 5.1/5.4 ± 3.6</td>
<td>431</td>
<td>215</td>
<td>NA(59)</td>
<td>Cardiovascular events</td>
</tr>
<tr>
<td>Kizer et al.</td>
<td>2008</td>
<td>Cardiovascular Health Study</td>
<td>10</td>
<td>Non CHD patients</td>
<td>12.6 (11.5–13.8)/12.4</td>
<td>1386</td>
<td>604</td>
<td>65–100</td>
<td>Cardiovascular events</td>
</tr>
<tr>
<td>Hatano et al.</td>
<td>2009</td>
<td>JMS Cohort study</td>
<td>9.4</td>
<td>Non CHD patients</td>
<td>7.6(5.0–12.2)/7.4(5.4–11.0)</td>
<td>127</td>
<td>38</td>
<td>19–93</td>
<td>Cardiovascular events</td>
</tr>
<tr>
<td>Söderberg et al.</td>
<td>2009</td>
<td>LIPID study</td>
<td>4.4</td>
<td>CHD patients</td>
<td>8.3 (5.3–11.7)/7.1</td>
<td>368</td>
<td>184</td>
<td>31–75</td>
<td>Cardiovascular events</td>
</tr>
<tr>
<td>Luc et al.</td>
<td>2009</td>
<td>PRIME study</td>
<td>10</td>
<td>Non CHD patients</td>
<td>10.6 (5.4–20.6)/11.0</td>
<td>1832</td>
<td>617</td>
<td>50–59</td>
<td>Cardiovascular events</td>
</tr>
<tr>
<td>Cote et al.</td>
<td>2011</td>
<td></td>
<td>7.7</td>
<td>Non CHD patients</td>
<td>8.74 ± 4.50/9.13 ± 4.31</td>
<td>2955</td>
<td>1035</td>
<td>45–79</td>
<td>Cardiovascular events</td>
</tr>
</tbody>
</table>

CHD, coronary heart disease; CVD, cardiovascular disease; CHF, congestive heart failure; LURIC, Ludwigshafen Risk and Cardiovascular Health Study; MONICA, MONItoring of trends and determinants in Cardiovascular disease Augsburg project; ULSAM, Uppsala Longitudinal Study of Adult Men; Health ABC, the Health, Aging, and Body Composition study; SMART, Second Manifestations of ARTERial disease study; LIPID, Long-Term Intervention with Pravastatin in Ischaemic Disease study; JMS Cohort study, Jichi Medical School Cohort Study.

*Baseline level of adiponectin was presented as mean ± standard deviation or median (interquartile range).

†Baseline level of adiponectin of study by Dekker was follows as: Q1(8.10 ± 1.59), Q2(12.10 ± 1.07), Q3(16.01 ± 1.28)Q4(24.61 ± 5.87) for women; Q1(5.54 ± 0.95), Q2(7.85 ± 0.60), Q3(10.27 ± 0.83), Q4(15.58 ± 3.71) for men.

‡Baseline adiponectin levels among nested case–control studies were presented as mean ± standard deviation or median (interquartile range) in the case group and control group.

§Baseline adiponectin levels of study by Wannamethee were shown as median (interquartile range) among non CHD group, CHD patient group and CHF group.
heterogeneity was noted among the studies ($I^2 = 71.1\%$, $P < 0.0005$). Publication bias was not detected by the Begg’s ($P = 0.659$) and Egger’s tests ($P = 0.314$), and visual inspection of the funnel plot indicated that it was symmetric. No influential study was found in the sensitivity analyses, which omitted one study at a time and calculated a pooled RR for the remainder of the studies. The estimated RR in this sensitivity analysis ranged from 1.02 (95% CI: 0.99, 1.05) to 1.04 (95% CI: 1.00, 1.07). No influential changes were observed in the sensitivity analyses concerning the two articles from the same study mentioned above. In the meta-regression analyses, we considered the potential variables mentioned above but found no effect modifier. Meta-analyses were conducted excluding the five studies that used cerebrovascular disease events in outcome measures, and the pooled effect size did not appreciably change (RR = 1.03, 95% CI: 0.99, 1.08, $P = 0.089$).

Because new-onset and recurrent CHD must be considered separately, we applied stratified meta-analyses to these studies (Fig. 3). No increased risk was observed (pooled RR = 0.99, 95% CI: 0.94, 1.03, $P = 0.603$) for new-onset CHD events (17 articles) in which subjects had no CHD at recruitment. No publication bias or potential effect modifiers were detected. However, in the case of CHD recurrence, an increased risk (RR = 1.12, 95% CI: 1.04, 1.22, $P = 0.004$) was observed, indicating publication bias (Egger’s test, $P = 0.030$). A trim-and-fill analysis was conducted to identify the effect of publication bias. The resultant pooled RR was 1.09 (95% CI: 1.01, 1.18, $P = 0.028$), and the conclusion was unchanged.

**All-cause mortality**

Six articles reported all-cause mortality (Figure 4A). The pooled RR of all-cause mortality was 1.10 (95% CI: 0.99, 1.21, $P = 0.20$) with no evidence of publication bias ($P = 0.486$). In the meta-regression analyses, we considered the potential variables mentioned above but found no effect modifier. Meta-analyses were conducted excluding the five studies that used cerebrovascular disease events in outcome measures, and the pooled effect size did not appreciably change (RR = 1.10, 95% CI: 1.08, 1.12, $P = 0.001$).

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**Figure 2** Relative risks per one standard deviation increase in log-transformed adiponectin level for cardiovascular events. For the 23 studies, 26 data points are included because results for patients with cardiovascular disease and no cardiovascular disease at baseline were shown separately in the British Regional Heart Study and the Hoorn study. Size of squares corresponds to the weight of each study in the meta-analysis. CI, confidence interval; CVD, cardiovascular disease.
CI: 1.04, 1.16, \( P < 0.0005 \) per 1-SD increase in log-transformed adiponectin level. The \( I^2 \) was 77.6%, suggesting a high degree of heterogeneity between studies (Q statistic, \( P < 0.0005 \)). Sensitivity analyses showed that none of the individual studies dramatically influenced the pooled RR [RR range, 1.07 (95% CI: 1.02, 1.13) to 1.12 (95% CI: 1.05, 1.19)]. The tests for publication bias were not significant (Begg’s test = 0.348, Egger’s test = 0.056). However, visual inspection of the funnel plot suggested some asymmetry. A trim-and-fill analysis was performed to determine whether the results were biased. The estimated RR from this analysis was 1.08 (95% CI: 1.02, 1.14, \( P = 0.007 \)), indicating that the effect size shift was too small to suggest bias.

Four studies reported RR for all-cause mortality in patients with CHD (Figure 3). The pooled RR was 1.24 (95% CI: 1.06, 1.44, \( P = 0.006 \)). Because publication bias was also suspected from visual inspection of the funnel plot, a trim-and-fill analysis was conducted, resulting in an RR of 1.18 (95% CI: 1.01, 1.38, \( P = 0.037 \)). In the case of non-CHD subjects, four original studies reported RRs. The meta-analysis yielded an RR of 1.05 (95% CI: 1.01, 1.10, \( P = 0.023 \)). No publication bias was detected. We could not conduct meta-regression and/or stratified analyses on this question because of the limited number of recruited studies.

### Cardiovascular disease mortality

The association between adiponectin and cardiovascular mortality was explored by five studies (Figure 4B). Pooling of individual RRs from these studies showed a 14% increased risk of cardiovascular mortality with a 1-SD increase in the log-transformed adiponectin level (RR = 1.14; 95% CI: 1.05, 1.23, \( P = 0.001 \)). A moderate degree of heterogeneity (\( I^2 = 56.5\% \); Q statistic, \( P = 0.024 \)) was observed. No influential study was suggested by sensitivity analyses [range of the RR: 1.12 (95% CI: 1.02, 1.22) to 1.16 (95% CI: 1.04, 1.29)]. The funnel plot suggested asymmetry, so we conducted a trim-and-fill analysis. The resulting RR was 1.12 (95% CI: 1.03, 1.23, \( P = 0.012 \)), and the conclusion was unchanged.

The pooled RR in patients with CHD (four studies) was 1.26 (95% CI: 1.08, 1.46, \( P = 0.003 \)) and that in non-CHD subjects (three studies) was 1.08 (95% CI: 1.00, 1.16, \( P = 0.055 \)) (Figure 3). In patients with CHD, asymmetry was suggested by the funnel plot, but the results of the trim-and-fill analysis revealed no change in the RR estimate (RR = 1.20; 95% CI: 1.01, 1.44, \( P = 0.041 \)). Meta-regression and stratified analyses were not conducted because of the limited number of original studies.

### Discussion

Many cellular and animal studies have suggested a protective role for adiponectin on atherosclerosis and CHD. However, no protective association between adiponectin and CHD was found in our meta-analysis. Only one previous meta-analysis on this issue has been conducted, and the authors concluded that
Figure 4 Effects on all-cause mortality (A) and cardiovascular mortality (B) per one standard deviation increase in log-transformed adiponectin level. Nine data points are included for the six studies (A) and eight data points are included for the five studies (B), because results for patients with cardiovascular disease and no cardiovascular disease at baseline were shown separately in the British Regional Heart Study and the Hoorn study. Size of squares corresponds to the weight of each study in the meta-analysis. CI, confidence interval; CVD, cardiovascular disease
any association of adiponectin with CHD risk was comparatively moderate and required further investigation. That meta-analysis found no significant increase in risk and a relatively wide CI (OR = 0.84; 95% CI: 0.70, 1.01). Because that analysis was conducted with seven small-scale studies, the authors suspected that this finding resulted from insufficient statistical power for detecting real effects. Additionally, they reported a decreased OR of borderline significance (OR = 0.81; 95% CI: 0.67, 0.97) in the case of new-onset CHD (four studies). To resolve this uncertainty, we conducted meta-analyses with a larger number of studies including recently published articles, and we conclude that no association exists between adiponectin and CHD (pooled RR = 1.03, 95% CI: 1.00, 1.06, P = 0.089). Furthermore, contrary to the previous finding, no protective effect (pooled RR = 0.99, 95% CI: 0.94, 1.03, P = 0.603) was observed for new-onset CHD events (17 articles) in our meta-analysis. Of the seven studies included in the prior meta-analysis (two cohort studies and five nested case-control studies), three studies were excluded from our analyses because two had recruited patients with type 1 diabetes and end-stage renal disease and one did not report adiponectin data. Our conclusion was not changed after conducting additional analysis including the three study results reported in that meta-analysis.

We additionally conducted stratified meta-analyses according to the presence (seven studies) or absence (17 studies) of pre-existing CHD because new-onset and recurrent CHD are different clinical issues that should be considered separately. No association was found between circulating adiponectin levels and new-onset CHD (pooled RR = 0.99, 95% CI: 0.94, 1.03). However, an increased risk was observed in the case of recurrence (pooled RR = 1.12, 95% CI: 1.04, 1.22). When considering the findings from laboratory studies showing anti-atherogenic effects of adiponectin, this increased risk of recurrence was quite contrary to our expectation. To explain this phenomenon, the possibility of counter-regulatory upregulation of adiponectin has been suggested by some researchers because adiponectin is elevated in patients with renal dysfunction or heart failure. This concept seems plausible to explain our paradoxical result with respect to patients with recurrent CHD, but it does not explain the absence of a protective effect in non-CHD subjects because we excluded patients with renal dysfunction and heart failure in this meta-analysis. Furthermore, this explanation is more plausible if the original studies were conducted with a cross-sectional design. However, the original studies in this meta-analysis were prospective cohort or nested case-control studies showing a temporal causal relationship between circulating adiponectin and CHD events. In summary, there appears to be an association between higher circulating adiponectin and an increased risk of recurrence in patients with pre-existing CHD. However, this concept requires re-evaluation in further studies focusing on whether elevated adiponectin is only a surrogate marker for the underlying disease or whether it provokes recurrence of CHD.

This study is the first meta-analysis of the association between adiponectin and all-cause and CVD mortality ever conducted. Similarly to the CHD occurrence results, the mortality meta-analysis also failed to demonstrate a protective effect for adiponectin. Instead, we found a 10% increased risk (RR = 1.10, 95% CI: 1.04, 1.16) of all-cause mortality and a 14% increased risk (RR = 1.14, 95% CI: 1.05, 1.23) of CVD mortality per 1-SD elevation in log-transformed adiponectin level. Stratified analyses according to the pre-existence of CHD also showed increased risks for these mortalities, with one exception. In the case of CVD mortality in non-CHD subjects, pooled estimates showed only borderline significance (RR = 1.08, 95% CI: 1.00, 1.16, P = 0.055). Considering the small case numbers of the three original studies, we cannot exclude the possibility of a type 2 error due to low power. Therefore, additional data are needed for a clearer conclusion with respect to mortality in non-CHD subjects.

The underlying mechanisms for these paradoxical associations among adiponectin, CHD and mortality are unclear, and there is scarce evidence to explain these findings. It is also unclear whether direct effects of adiponectin mediate these results. Additionally, adiponectin resistance may intervene in these associations. Currently, we do not know why the various beneficial effects of adiponectin suggested by laboratory studies do not apply to these human data. Further studies are needed to elucidate these paradoxical findings.

Nevertheless, we found that higher circulating adiponectin levels are not associated with protection against CHD. Our finding suggests the possibility that interventions related to increased adiponectin may be associated with greater risk of CHD recurrence or all-cause/CVD mortality, though it is well demonstrated to be beneficial in the control of type 2 diabetes. This is an important issue that must be carefully evaluated, and our findings support this conclusion. Many clinical trials directly or indirectly related to an elevation in circulating adiponectin levels have been recently conducted or planned.

Our results suggest that the adverse effects of adiponectin need to be carefully monitored in these trials. Potential limitations of our study are as follows. Analyses were conducted using data from observational prospective studies. Meta-regressions were not conducted in some analyses due to the limited number of recruited studies. In these cases, we could not fully exclude potential effect modifiers. Although temporal and other causal relationships were demonstrated, some limitations on confirming the sole effect of adiponectin remain. Many factors could be involved in the regulation of circulating adiponectin and may have caused some heterogeneity in our meta-analyses. Although we considered these factors when conducting this meta-analysis, the possibility remains that we missed some covariates that
should have been evaluated, because of limited information from the original articles. Another limitation is that we could not conduct an additional analysis focusing on high-molecular-weight adiponectin, which seems to be a better predictor of insulin resistance than is total plasma adiponectin. Two original studies considered this issue, and both found no predictive ability on this issue. Furthermore, some publication biases were suspected in some of the meta-analyses. Although trim-and-fill analyses did not alter the results, which might change our conclusions, the possibility of this type of bias remains. We expect future studies will carefully evaluate the effect of such bias. Age could be an important factor to be considered in interpreting our results. Our meta-analyses were conducted with all age groups available but the effect of adiponectin may vary according to age group. Indeed, previous studies showed no association in middle-aged participants (aged 40–59 years) but a positive association at older ages (age 60–79 years). In considering this, we conducted a meta-analysis stratified by a mean age of 60 years (>60 vs. <60). The results showed no clear evidence supporting an age-dependent hypothesis. The pooled RRs were 0.99 (95% CI: 0.96, 1.02, \( P = 0.46 \)) for <60 years and 1.05 (95% CI: 1.00, 1.10, \( P = 0.05 \)) for \( \geq 60 \) years. However, regardless of these findings, our results did not show a protective effect of adiponectin against CHD and all-cause/CVD mortality. Further study is necessary to clarify whether age could affect the association between adiponectin and cardiovascular disease. This meta-analysis had several strengths. This analysis was conducted with large-scale data covering 30,945 subjects. Furthermore, the consistent finding of a non-protective effect of adiponectin against CHD and all-cause/CVD mortality strongly supports our conclusion. It is also notable that studies reporting distinctly higher or lower effect sizes had wider CIs than did others, and studies showing relatively lower variance were gathered around an RR of 1. This distribution suggests that larger-scale, more reliable studies tend to report trivial or no effects.

**Conclusion**

Our findings suggest that higher circulating adiponectin levels do not show a protective association with CHD events or all-cause/CVD mortality. Additionally, our results suggest that higher circulating adiponectin levels may be associated with increased risk of CHD recurrence and all-cause/CVD mortality.

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**Conflict of interest:** None declared.

**KEY MESSAGES**

- This meta-analysis indicates that current epidemiological data do not support the hypothesis regarding a protective role of adiponectin against CHD events and all-cause/CVD mortality.
- Instead, higher circulating adiponectin levels were associated with an increased risk of CHD recurrence and all-cause/CVD mortality.
- Adiponectin may be a more complex molecule than expected in the association with cardiovascular disease. Further research including clinical trials is needed to elucidate this association.

**References**

ADIPONECTIN, CORONARY HEART DISEASE AND MORTALITY

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