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Circulating Adiponectin Levels Are Paradoxically Associated With Mortality Rate: A Systematic Review and Meta-Analysis

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Context: Some studies have surprisingly indicated that serum adiponectin level is positively related to mortality rate, thus casting doubts on its role as a therapeutic target for cardiovascular disease.

Objective: To summarize evidence about direction, strength, and modulators of this controversial association.

Methods: MEDLINE, Web of Science, CINHAL, Cochrane Library, and Scopus databases were searched from their inception dates through June 2018 for English-language prospective studies reporting the association between adiponectin and all-cause or cardiovascular mortality. Two investigators independently extracted data and assessed study quality using standard criteria following the Preferred Reporting Items for Systematic Reviews and Meta-analyses and The Newcastle-Ottawa Scale. Pooled hazard ratios (HRs) and 95% CIs were derived using fixed- or random-effects models when appropriate, and results were expressed to a 1-SD increment of adiponectin.

Results: We identified 55 studies (n = 61,676 subjects) with all-cause mortality data and 28 (n = 43,979 subjects) studies with cardiovascular mortality data. Pooled HRs, were 1.24 (1.17-1.31) and 1.28 (1.19-1.37) for all-cause and cardiovascular mortality, respectively. Similar results were obtained for high-molecular-weight adiponectin. When meta-analyses were restricted to studies reporting data on natriuretic peptides, reductions of 43% and 28% on a log scale of these respective associations were observed after adjusting for natriuretic peptides.

Conclusions: Our results point strongly to a paradoxical association between high adiponectin levels and increased mortality rate, which is partly modulated by natriuretic peptides. (***J Clin Endocrinol Metab*** **104: 1–12, 2019)**

Adiponectin is an adipokine reported to exert beneficial effects on chronic low-grade inflammation, oxidative stress, and atherosclerotic processes (1). This belief, mainly based on basic science and *in vivo* pathophysiological evidence, has made adiponectin a promising therapeutic target for tackling cardiovascular disease (CVD) (2), the worldwide leading cause of death (3). It was, therefore, highly surprising that some studies reported circulating adiponectin to be positively related to the rate of mortality of different origins (4–11). As a

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Abbreviations: BMI, body mass index; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; GP, general population; HMW, high molecular weight; log HR, natural/base 10/base 2 logarithm hazard ratio; NP, natriuretic peptide; T2D, type 2 diabetes.

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matter of fact, the number of studies that explored this association is extremely vast (12), so a comprehensive examination of all available data is needed before drawing firm conclusions.

In an attempt to unveil some of the uncertainties surrounding the relationship between adiponectin and mortality risk, we carried out a systematic and meticulous review of the available literature and then conducted an in-depth meta-analysis. Our aim was not only to clarify the controversial association between adiponectin and the risk of death but also to address the role that many variables may play on the biology underlying it. Among several possible confounding factors and/or effect modifiers, we focused on natriuretic peptides (NPs), which have been reported to increase adiponectin expression (13) and mortality rate (14).

Materials and Methods

Search strategy and selection criteria

The study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline (15, 16). MEDLINE, Web of Science, CINHAL, Cochrane Library, and Scopus databases were systematically searched for prospective studies published in English up to 30 June 2018, with no start-date restriction, with adiponectin [both total and high molecular weight (HMW)] as exposure and all-cause and cardiovascular (CV) mortality as outcome. Search terms used were "Adiponectin" or "ADIPOQ" for the exposure and "mortality" or "death" or "survival" for the outcome. Searching was limited to studies of humans and to longitudinal studies published as original (*i.e.*, abstracts, letters, reviews, and meta-analyses were excluded). Exclusion criteria were cross-sectional studies, papers in which mortality data were presented as part of a composite end point, or those reporting no quantitative data on adiponectin circulating levels and/or no hazard ratios (HRs) or relative risks. For studies published in more than one report (duplicates), the most comprehensive updated report, in terms of largest sample size and/or longer follow-up, was considered. Two investigators (M.G.S. and C.M.) independently screened titles and abstracts of all articles retrieved from the literature search; full texts of potentially eligible articles were further assessed for final inclusion. Disagreements were resolved through discussions between investigators until a consensus was reached.

Data extraction and quality assessment

Relevant data from each single study, using a standardized data extraction form, were obtained. Information extracted included first author; publication year; study name; type of outcome (*i.e.*, all-cause and/or CV mortality); adiponectin isoform (total and/or HMW); number of participants; number of events; duration of follow-up (years); clinical setting [*i.e.*, general population (GP), type 2 diabetes (T2D), CVD, end-stage renal disease]; geographical region (*i.e.*, Europe, North America, East Asia; note: data from Israel and Egypt were not investigated in this context because only one study from each country, and only for all-cause mortality, were available); sex (specifically, percentage of men); age at enrollment (years); body mass index (BMI; calculated as kilograms divided by meters squared), adiponectin levels (in micrograms per milliliter), estimated glomerular filtration rate (eGFR; calculated as milliliters per minute per 1.73m^2), NPs [*i.e.*, *N*-terminal pro brain natriuretic peptide-NT-proBNP, atrial natriuretic peptide, and brain natriuretic peptide (measured in nanograms per liter)]; and type of model adjustment. For each article, HRs or the natural/base 10/base 2 logarithm of the HRs (log HRs), expressing the association between adiponectin levels and the outcome were recorded, along with their 95% CIs.

Quality assessment was performed using the nine-item Newcastle-Ottawa Scale:, representativeness and selection of the exposed cohort, validity of exposure and outcome assessment, exclusion of outcome at baseline, selection of nonexposure group, adequacy of follow-up, proportion of those lost to follow-up and confounding adjustment (17). Overall, the scale awards a maximum of nine points for study quality (the higher score, the better the quality of the study).

Data synthesis and analysis

Data from each original study were collected, extracted, and preanalyzed to estimate a single HR within each study for all-cause and CV mortality. Because circulating adiponectin levels were often reported as the minimum-maximum range for each class of study-specific distribution, the representative dose value for each group was obtained by fitting a gamma function to total and HMW adiponectin distribution over the range class. To overcome the open-ended risk classes (*e.g.*, <4 μg/mL or >7 μg/mL), the minimum and maximum range of these classes was estimated (18, 19). To estimate gamma parameters, study-specific mean and SD of adiponectin levels were used (20).

For those studies reporting HRs for each adiponectin class or category (5, 10, 11, 21–33), a dose-response model was used within each study to provide an HR estimate expressed in terms of continuous adiponectin levels. Only studies in which HRs were given with respect to a study-specific categorical reference dose of total and/or HMW adiponectin (*i.e.*, median, tertiles, quartiles, or prespecified dose categories of adiponectin) were considered. Then, for each study, the specific slope (*i.e.*, log HR) across dose categories was estimated by weighted log-linear models. This was done by using study-specific rescaled doses (with respect to the reference representative dose category) as the main covariate and the variances of log HRs for nonreference doses (derived from the 95% CIs reported, along with each estimate) as weights. To account for the covariance between log HRs of nonreference doses, estimates of the total number of events and the number of subjects exposed to each dose were derived by using an iterative fitting algorithm (34). No intercept term was included in the model, because, by definition, when the rescaled dose is zero, the linear function would start from log HR = 0.

For studies reporting adiponectin levels expressed in at least three classes, weighted regression analyses were performed assuming either a linear or a quadratic model, with the best being defined as the one minimizing Akaike Information Criteria (35). In studies with HRs expressed in terms of continuous adiponectin levels, estimates were taken as reported. If more than one HR was reported, the "best adjusted" one was chosen. Adjustments mostly included age, sex, BMI, and smoking habits, along with other confounders specifically related to each

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clinical setting. When no HRs were available, the reported relative risks were used. Such estimates were then expressed for 1 SD increment of adiponectin level. When the mean and SD of adiponectin levels were unavailable, they were estimated following the algorithms suggested by Hozo *et al*. (18) and Wan *et al*. (19). For studies in which HRs were available only in patient subgroups (31, 36–38), a fixed-effect meta-analysis was performed to obtain a single HR estimate and its 95% CI.

Study-specific estimates were pooled using either fixed- or random-effects (in case of heterogeneity) models when appropriate (39). Statistical heterogeneity among studies was assessed by Cochran Q test and heterogeneity was defined as $P < 0.10$ (40). To explore heterogeneity, meta-regressions and subgroup analyses were evaluated using the following study-level covariates: percentage of men, mean age, mean BMI, mean eGFR, mean follow-up, different geographical regions and clinical settings (*i.e.*, GP, T2D, CVD, end-stage renal disease). Such meta-regressions and subgroup analyses were carried out only if there were at least 10 studies (41). Random-effects meta-regressions were performed for all study-level covariates, with the exception of clinical setting and geographical region (for which subgroup analyses were done). In the second case, pairwise comparisons of summarized HRs, estimated within each geographical region and within each clinical setting group, were assessed from least squares mean differences, derived by a mixed-effects linear model, including different geographical regions and clinical settings as fixed terms and three and four between-studies variances parameters as random terms.

Forest plots were created for each meta-analysis, with squares being plotted as center projections on the underlying scale corresponding to the study-specific HR. Square areas are proportional to the inverse of the variance (*i.e.*, precision) of the log HR and thus give a measure of the amount of statistical information available from that particular estimate. A diamond was used to plot the summary HRs; extremes of the summary HRs show the 95% CI.

Publication bias was assessed by Egger's test and symmetry and asymmetry were shown by funnel plot (42). In presence of publication bias, the trim-and-fill method was used to estimate the unbiased HR (43). Two-sided P values < 0.05 were considered statistically significant. Statistical analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC) and R, version 3.3.3 (package: metafor) (44).

Results

A total of 129 publications were retrieved. After excluding all articles that did not meet inclusion criteria, 55 studies [from 52 papers (4–8, 10, 11, 21–26, 29–32, 36–38, 45–76)] and 28 studies [from 24 papers (4, 5, 7, 8, 11, 23–28, 30, 36, 38, 46–48, 53, 59, 64, 66, 72, 76, 77)] reporting the association between total adiponectin and either all-cause or CV mortality, were eligible for the final meta-analysis. Seven studies [from five papers (8, 9, 29, 33, 75)] and five studies [from three papers (8, 33, 64)] reporting the association between HMW adiponectin level and either all-cause or CV mortality also were included in our meta-analysis (Fig. 1).

The sample size refers to the number of subjects actually analyzed. Quality assessment of the included studies was good for most of them; only four had a score of 6. The main features of studies included in the meta-analyses are presented in an online repository (16).

A linear relationship between adiponectin and mortality rate was assumed on the basis of the following considerations: (1) For studies reporting adiponectin expressed in classes (tertiles or quartiles) (5, 10, 21, 23, 25, 29, 31, 33), the best fitting model, defined as the one minimizing Akaike Information Criteria (35) between linear or quadratic model, was the linear model; (2) for studies reporting adiponectin level as a continuous variable (4, 6–9, 36–38, 45–77), testing for linearity of association with mortality was, unfortunately, not possible (an intrinsic limitation of any meta-analysis framework in the absence of individual patient data); notably, among all these studies (4, 6–9, 37, 38, 45–77), the nature of the association was reported as properly tested only in four (7, 8, 37, 51), with two of them reporting linearity (7, 37) and two reporting a quadratic association (8, 51).

The number of subjects for the association between total adiponectin and all-cause mortality was 61,676, with an overall event rate of 25% when excluding studies with an unknown number of events (11, 26, 70). This meta-analysis was powered at 90% (assuming a type I error of 0.05) to detect an HR $\leq$1.03 (SD 1). Mean follow-up ranged from 28 days (*i.e.*, in a study of patients admitted to an intensive care unit) (75) to 20 years. The Cochran Q test P value for total adiponectin effect heterogeneity across studies was $<$0.0001. The estimated pooled HR for all-cause mortality was 1.24 (SD 1 95% CI, 1.17 to 1.31; $P < 0.0001$; Fig. 2).

The number of subjects for the association between total adiponectin and CV mortality was 43,979, with an overall event rate of 11% when excluding studies with an unknown number of events (7, 26). This meta-analysis was powered at 90% (assuming a type I error of 0.05) to detect an HR $\leq$1.05 (SD 1). Mean follow-up ranged from 1 to 20 years. The Cochran Q test P value for total adiponectin effect heterogeneity across studies was $<$0.0001. The estimated pooled HR for CV mortality was 1.28 (SD 1; 95% CI, 1.19 to 1.37; $P < 0.0001$; Fig. 3).

The number of subjects for the association between HMW adiponectin and all-cause mortality was 8366, with an overall event rate of 46%. This meta-analysis was powered at 90% (assuming a type I error of 0.05) to detect an HR $\leq$1.05 (SD 1). Mean follow-up ranged from 28 days (*i.e.*, in a study of patients in an intensive care unit) (75) to 12 years. The Cochran Q test P value for HMW adiponectin effect heterogeneity across studies

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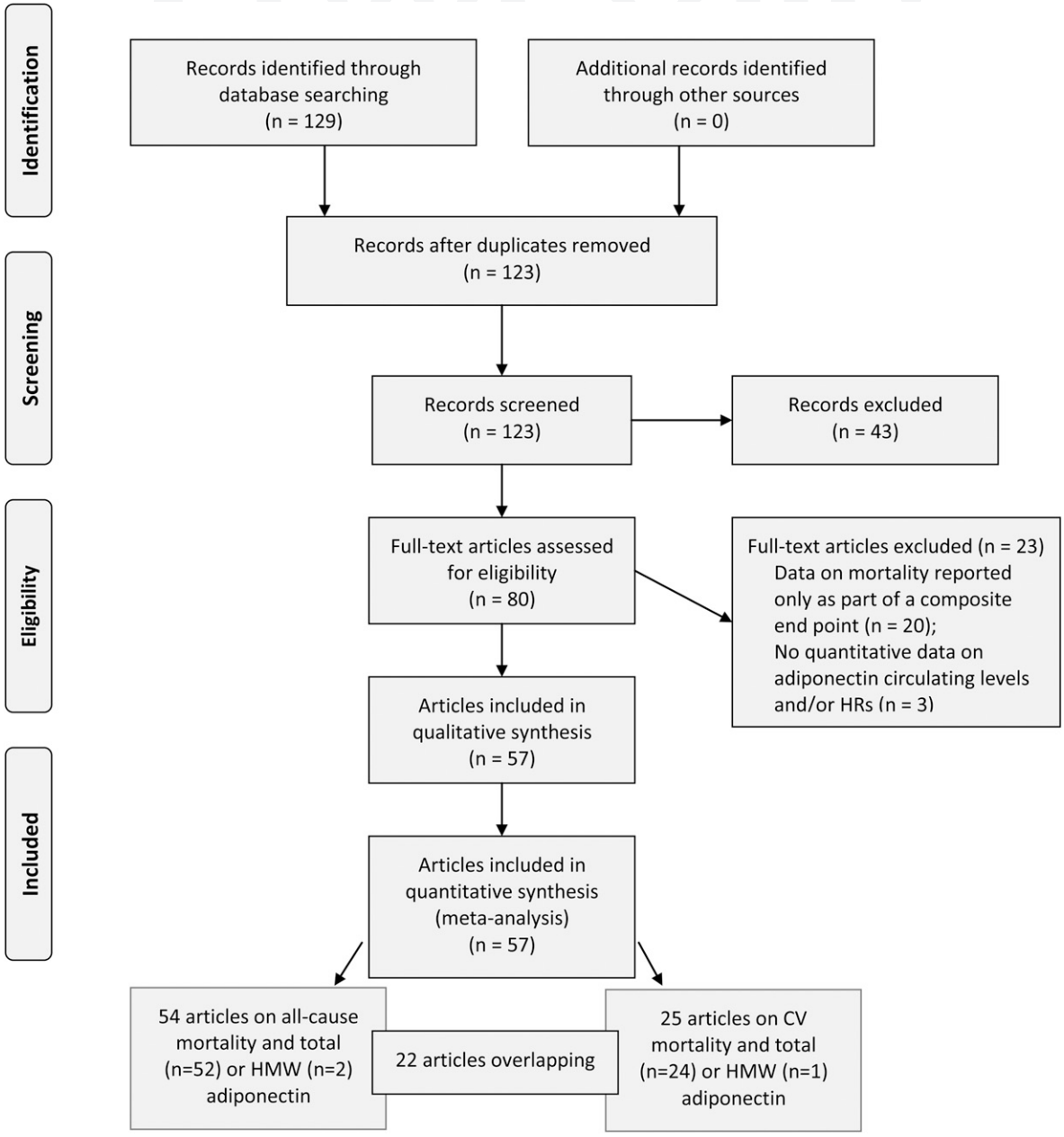

Q:11 **Figure 1.** Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of literature search and study selection.

was 0.154. The estimated pooled HR for all-cause mortality was 1.20 (SD 1; 95% CI, 1.13 to 1.28; $P < 0.0001$) (16).

The number of subjects for the association between HMW adiponectin and CV mortality was 5994, with an overall event rate of 24%. This meta-analysis was powered at 90% (assuming a type I error of 0.05) to detect an HR $\leq$ 1.09 (SD 1) for one SD increment of HMW adiponectin. Mean follow-up ranged from 5 to 22 years. The Cochran Q test *P* value for HMW adiponectin effect heterogeneity across studies was 0.141. The estimated pooled HR for CV mortality was 1.24 (SD 1; 95% CI, 1.14 to 1.35; $P < 0.0001$) (16).

Funnel plot symmetry results for studies with total Q:6 adiponectin and all-cause mortality suggested potential publication bias (Egger test $P = 0.087$) (16). Publication bias, instead, was clearly detected for studies with total adiponectin and CV mortality (Egger test $P = 0.0002$) (16). After performing the trim-and-fill method, HRs became 1.20 (95% CI, 1.12 to 1.28; $P < 0.0001$) and 1.23 (95% CI, 1.14 to 1.32; $P < 0.0001$) for all-cause and CV mortality, respectively (16). Publication bias for studies with HMW adiponectin and both outcomes was not investigated, owing to the small number of studies included (fewer than 10), following the recommendations of Sterne *et al.* (78) and Ioannidis *et al.* (79).

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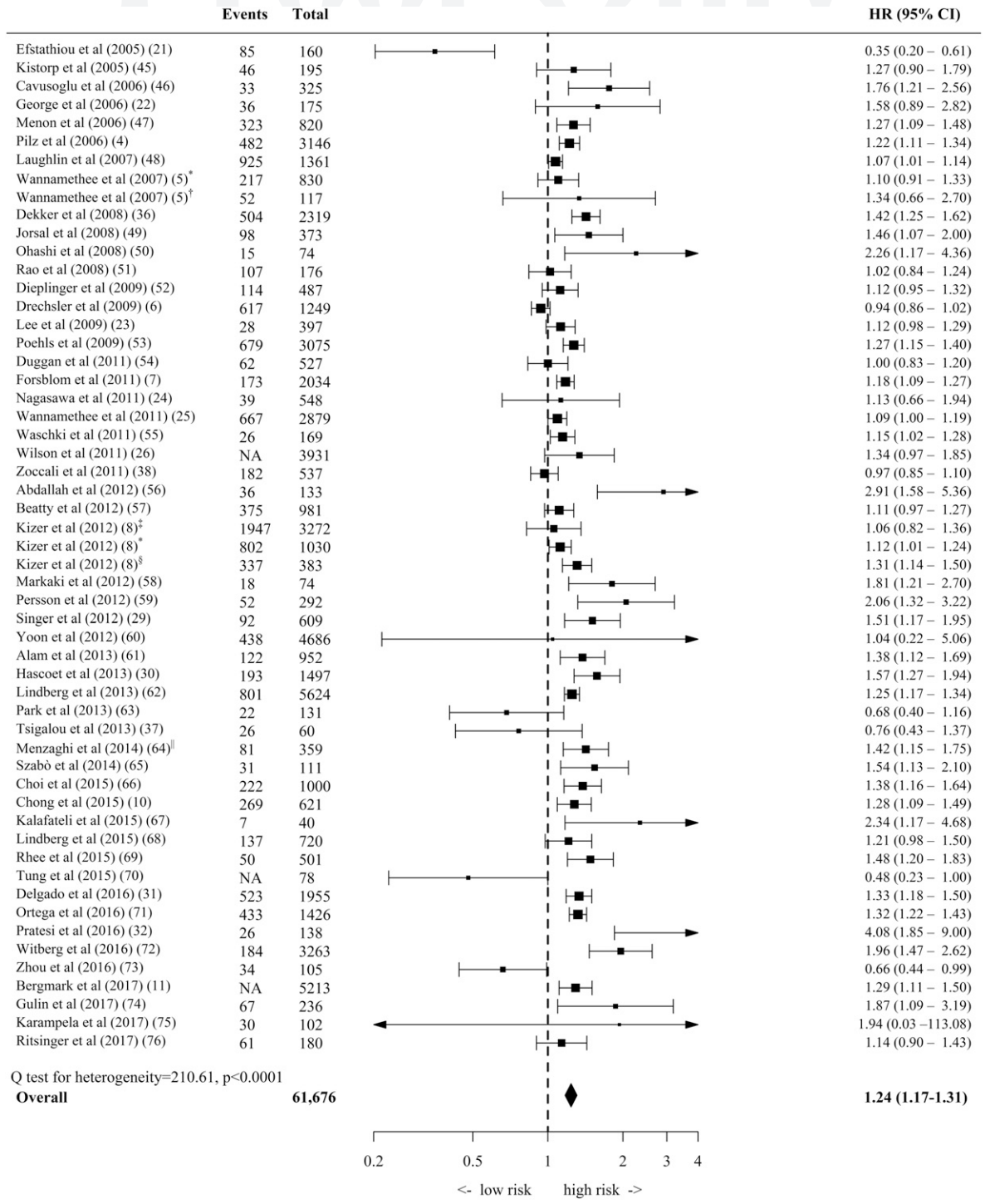

Figure 2. Forest plot for random-effects meta-analysis on the association between total adiponectin levels and all-cause mortality. Central squares of each horizontal line represent the HR for each study. Horizontal lines indicate the range of the 95% CIs and the vertical line indicates HR = 1.0 (which indicate no risk or benefit). *CVD; †chronic heart failure group; ‡GP; §chronic heart failure or atrial fibrillation group; ‖Gargano Heart Study.

Several study-level covariates, including sex, age, BMI, eGFR, and geographical region, did not significantly explain between-study heterogeneity in the association between total adiponectin and each of the two outcomes (*P* values ranged from 0.054 to 0.898). When meta-regression analyses on BMI were restricted to subjects of European ancestry (4–7, 21, 25, 27, 30–32, 36–38, 45, 48, 49, 52, 55, 58, 59, 61, 62, 64, 65, 67, 71, 74–76), results were totally superimposable on those obtained in the whole study (*P* = 0.701 and 0.230 for all-cause and CV mortality, respectively).

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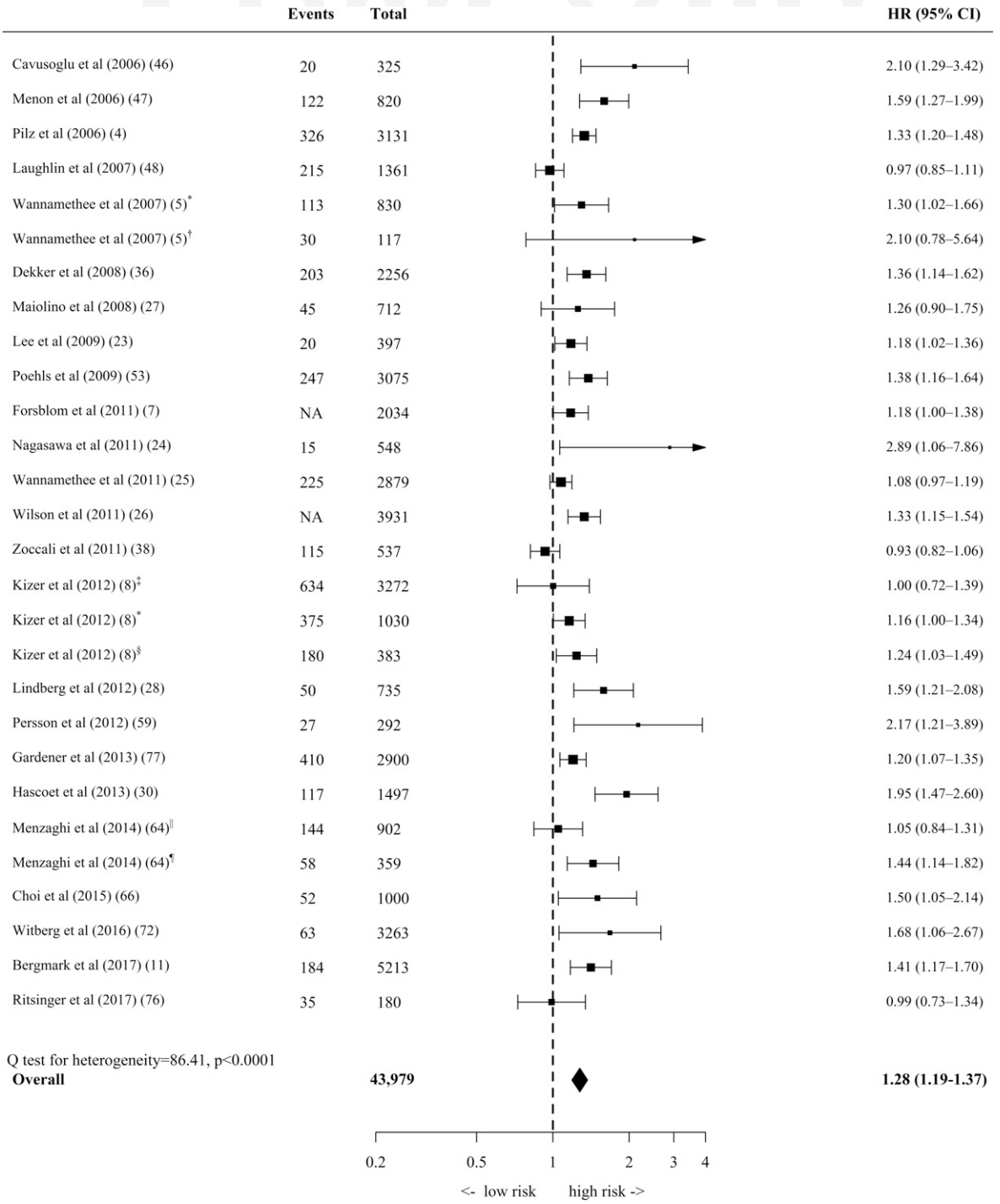

Figure 3. Forest plot for random-effects meta-analysis on the association between total adiponectin levels and CV mortality. Central squares of each horizontal line represent the HR for each study. Horizontal lines indicate the range of the 95% CIs and the vertical line indicates HR = 1.0 (which indicates no risk or benefit). *CVD group; †chronic heart failure group; ‡GP; §chronic heart failure or atrial fibrillation group; ‖Gargano Heart Study; ¶Nurses' Health Study.

Duration of follow-up explained some between-study heterogeneity for the association of total adiponectin with CV mortality (10% heterogeneity, $P = 0.038$; with studies with longer follow-up showing a weaker association), but not with all-cause mortality ($P = 0.453$).

Clinical setting explained 7% ($P = 0.037$) of between-study heterogeneity for the association of total adiponectin with all-cause mortality but not with CV mortality ($P = 0.945$) (16). When a subgroup pairwise analysis was conducted that was aimed at better addressing the role of the different clinical settings on the former association, the association in the T2D group was stronger than that observed in patients with CVD and

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was similar to that observed in the GP group ($P = 0.007$ and 0.562, respectively) (16).

In the 12 studies reporting NP values, HRs for all-cause mortality changed from 1.24 (95% CI, 1.16 to 1.34; $P < 0.0001$) to 1.13 (95% CI, 1.06 to 1.21; $P = 0.0003$; Fig. 4) after adjusting for NPs (4, 6, 8, 11, 25, 45, 52, 57, 65, 68). This 43% reduction on a log scale became significant ($P < 0.05$) when the assumed correlation between the HRs before and after adjusting for NPs (necessary because HRs came from two nested models) was >0.1 (16).

In the six studies reporting NP values, HRs for CV mortality changed from 1.21 (95% CI, 1.10 to 1.33; $P = 0.0001$) to 1.15 (95% CI, 1.06 to 1.24; $P = 0.001$) after adjusting for NPs (Fig. 4) (4, 8, 11, 25). The 28% reduction on a log scale became significant ($P < 0.05$) only when the assumed correlation between HRs derived from the two nested models was >0.8 (16). Meta-regression, subgroup analyses, and the analysis on the role of NPs for the association between HMW adiponectin and mortality rate were not performed, because <10 studies were available (41).

Discussion

The meta-analyses we here report clearly show robust evidence of a positive association between circulating adiponectin levels and both all-cause and CV mortality rates. In addition, they provide accurate and comprehensive estimates of these associations, thus expanding and updating those obtained by two previous meta-analyses dating back to 2014 and including only a few studies that addressed a specific subset of individuals (80, 81). Although they were derived from much less evidence, very similar results were obtained with HMW adiponectin, the biologically active form of circulating adiponectin (1), thus reinforcing data obtained by measuring only total adiponectin levels. Considering the existing strong correlation between total and HMW adiponectin (82), our finding is not unexpected and makes using total adiponectin reasonable as a biomarker to be tested in additional studies on mortality rate. Overall, our study establishes adiponectin as a predictor of increased mortality and suggests, therefore, caution should be taken when considering it as a pharmacological target for treating cardiometabolic abnormalities (83).

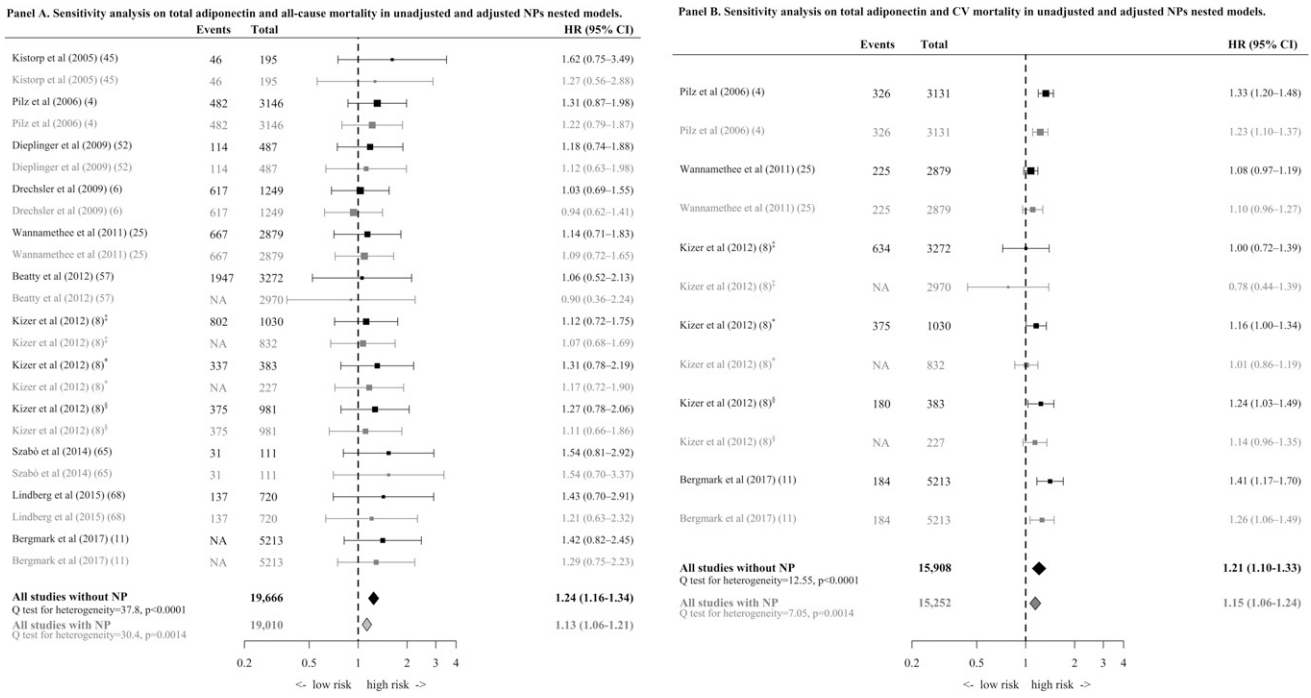

Figure 4. Sensitivity analysis on total adiponectin levels and all-cause mortality and CV mortality in nested models unadjusted and adjusted for NPs. (A) Forest plot for random-effects meta-analysis on the association between total adiponectin levels and all-cause mortality before and after adjustment for NPs. Central squares of each horizontal line represent the HR for each study. Horizontal lines indicate the range of the 95% CIs and the vertical line indicates HR = 1.0 (which indicates no risk or benefit). Analysis before and after NP adjustment is indicated in black and gray, respectively. ‡GP; *CVD group; §chronic heart failure or atrial fibrillation group. (B) Forest plot for random-effects meta-analysis on the association between total adiponectin levels and CV mortality before and after adjustment for NPs. Central squares of each horizontal line represent the HR for each study. Horizontal lines indicate the range of the 95% CIs and the vertical line indicates HR = 1.0 (which indicates no risk or benefit). Analysis before and after NP adjustment is indicated in black and gray, respectively. ‡GP; *CVD group; §chronic heart failure or atrial fibrillation group.

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It is noteworthy that among the 57 studies included in our analyses, a significantly negative association between total adiponectin and the risk of death was reported by only two studies for all-cause mortality (21, 73) and by no study for death of CV origin. Based on the results obtained with the trim-and fill method, the directional consistency of the observed association, therefore, does not seem to depend on publication biases affecting our analyses.

In subgroup analyses, the counterintuitive association between adiponectin and all-cause mortality was consistent across all clinical settings, though some differences between point estimates were detectable, with patients with T2D showing a significantly increased association than those with CVD. This might suggest that some of the association between adiponectin and all-cause mortality is either exacerbated in patients with hyperglycemia and/or attenuated in patients with a very high mortality risk, as those with preexisting CVD certainly are.

Some proportion of the heterogeneity affecting the association between adiponectin and CV mortality was explained by follow-up duration, with studies with longer follow-up showing a weaker association. Whether this phenomenon indicates that part of the deleterious effect of adiponectin on CV mortality is lost over the years is an intriguing possibility that cannot be further addressed by our analyses.

The biology underlying the paradoxical association between adiponectin and mortality rate is unclear. Because NPs, markers of vascular remodeling after atrial or ventricular wall stretch (84), are independent predictors of increased mortality rate (13) and increased adiponectin expression via a cyclic guanosine monophosphate-dependent pathway (14), they have been proposed as possible confounders of this counterintuitive relationship (25). To address this issue, we conducted a meta-analysis of studies reporting this association before and after adjusting for NPs. Indeed, in a total of 12 studies (4, 6, 8, 11, 25, 45, 52, 57, 65, 68), the association with all-cause mortality was almost halved, though still present, after considering NPs. Some risk reduction was also observed for CV mortality. Taken together, these sensitivity analyses clearly reinforce the belief that association between adiponectin and mortality rate is partially mediated by NPs (25). The intimate mechanism of NPs' effect is unknown and hopefully will be unraveled by specifically designed studies. Additional studies are also needed to address whether considering NPs and adiponectin levels in combination may help improve mortality risk stratification.

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Limitations

There are several limitations to our study. First, we performed our analyses assuming a linear association between adiponectin and mortality. However, such an assumption was based on incomplete data availability and cannot be considered as proved. Thus, we could not exclude that a different relationship between adiponectin and mortality does exist, and caution should be used in interpreting our findings. In particular, in some studies (8, 51), subjects with both low and high adiponectin levels were at higher mortality risk as compared with those with intermediate levels, leaving open the question of whether adiponectin replacement may be useful in individuals with severe hypoadiponectinemia.

Second, for some studies, the regression slope of adiponectin (*i.e.*, HR for an increment of 1 SD) was not reported and, therefore, was estimated by a linear weighted model. This is to say that the final obtained estimates could be affected by small approximation errors.

Third, we chose to perform a meta-analysis of the more complete adjusted models; however, the set of variables accounted for was not identical across studies, especially for those related to different clinical setting. This could have affected the size of risk estimates.

Fourth, using BMI as a proxy of adiposity measure could not be fully appropriate because it does not take into account difference in fat stores across diverse ethnicities (85). However, our sensitivity analysis conducted only in subjects of European ancestry yielded results completely superimposable on those obtained in the whole meta-regression, making it unlikely that this phenomenon played a role in biasing our results.

Fifth, the role of NPs in reducing the association between adiponectin and CV mortality has to be interpreted with great caution because it holds only when a high correlation between the two estimates was observed.

Finally, our meta-analysis could not address whether adiponectin has a direct deleterious role on increased mortality risk, as our previous preliminary data seem to indicate (86) or, in contrast, it is a mere marker of it.

In conclusion, to our knowledge, this is the first meta- Q:7
analysis of the association between circulating adiponectin levels and mortality rate. The results obtained by addressing different causes of death and by performing analyses of different subgroups are strongly consistent and clearly show that a paradox of adiponectin on the risk of mortality does exist; NPs are likely to explain a nontrivial proportion of it, especially when referring to all-cause mortality. Until a better understanding of this counterintuitive phenomenon is achieved, present data cast doubts on adiponectin as a new target for the treatment of metabolic and CV abnormalities (2). To go a

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step further and unveil all the uncertainties surrounding the relationship between adiponectin and the risk of death, the time has come for a large, collaborative, prospective study that includes genetic information, so Mendelian randomization analyses can be applied (87), and that provides individual data to be analyzed. This will make it possible to investigate whether adiponectin has a direct deleterious role on the risk of death (86) and to definitively address the role of NPs as confounders of the adiponectin paradox (13, 14, 88). Finally, a broad collaborative effort will also provide information on whether the addition of circulating adiponectin levels on top of established risk factors improves the predictability of mortality risk—an urgent need especially in high-risk patients such as those with T2D and CVD.

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Author Contributions: V.T. and C.M. conceived the study. M.G.S. and C.M. performed the literature search, selected the studies, and extracted the relevant information. M.G.S. synthesized the data and wrote the paper. A.F. and M.C. checked the final database. M.G.S., A.F., and M.C. performed statistical analyses. All authors designed the study protocol and critically revised the paper and approved the final version.

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