Effect modification by NT-proBNP on the association between adiponectin and total mortality in EPIC–Heidelberg: A case-cohort study

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Abstract

Background

NT-proBNP has been hypothesized as a possible explanation for the paradoxical association between adiponectin and cardiovascular and all-cause mortality. We examined the heterogeneities by NT-proBNP, sex, BMI, smoking status, hypertension and diabetes status in the association between adiponectin and cardiovascular disease risk and mortality.

Methods

We used a case-cohort design nested within the EPIC-Heidelberg cohort, including 1,387 incident cases of myocardial infarction or stroke, 582 deaths from cardiovascular causes and 2,352 total deaths. We estimated hazard ratios for the association between 1SD increase in log-transformed adiponectin levels and cardiovascular disease risk, cardiovascular mortality and total mortality using Prentice-weighted Cox-proportional hazard models and assessed heterogeneity of the associations across strata of covariates.

Results

Overall, adiponectin was significantly associated with all-cause mortality [HR = 1.09, 95%CI: 1.03-1.16, p = 0.004], the association with cardiovascular mortality did not reach statistical significance [1.10 (0.99-1.37), p = 0.073] whereas there was no association with cardiovascular disease risk. There was significant heterogeneity by NT-proBNP in the association between adiponectin and all-cause mortality (p_{het} = 0.019) such that significant increase in hazards of mortality were restricted to participants in the highest tertile of NT-proBNP. Among participants in the highest tertile NT-proBNP, adiponectin showed a dose-response relationship with total mortality such that; compared to participants in the lowest quintile, those in the third, fourth and fifth were at 1.22 (0.87-1.70), 1.50 (1.07-2.11), and 1.59 (1.15-2.21) higher hazards of mortality respectively.

Conclusions

Significant association between adiponectin and mortality was only observed in the context of high NT-proBNP. Our findings provide further support for hypothesis that NT-proBNP may explain the adiponectin paradox.

Background

Adiponectin is an adipocytokine mainly secreted by adipocytes in the visceral and subcutaneous adipose tissues.[1] The cytokine has been shown to have anti-inflammatory [2], insulin-sensitising [3] and cardiovascular protective properties.[4] Circulating levels of adiponectin are generally higher in healthy normal weight individuals and reduced with accumulation of adipose tissue. Thus, circulating adiponectin levels show an inverse correlation with obesity and central fat accumulation [5], and are lower in patients with diabetes.[6] However, because aging is associated with accumulation of fat particularly in the intra-abdominal depot, a negative correlation of adiponectin with age would be expected. Instead, adiponectin shows a positive association with age.[6, 7] A similar contradiction has also been reported for smoking, which is often associated with low body mass index (BMI) but levels of adiponectin tend to be lower in smokers than non-smokers.[8] Serum levels of adiponectin are also higher in women than men [6, 7], despite women having a higher percentage fat at any given BMI.[9] Adiponectin thus appears to have a complex relationship with adiposity and factors that influence adiposity.

Due to the insulin-sensitising, anti-inflammatory and cardio-protective effects exerted by adiponectin, having elevated circulating levels of the adipokine was believed to be beneficial to health. Indeed, several studies showed that low levels of circulating adiponectin (hypo-adiponectinemia) were associated with increased risk of insulin resistance and type-2 diabetes mellitus [10], metabolic syndrome, hypertension and cardiovascular diseases.[11] However, several and more recent epidemiologic studies and meta-analyses reported increased risk of cardiovascular and all-cause mortality among individuals and patients with high circulating levels of adiponectin.[12-16] The counterintuitive association of adiponectin with mortality despite its established protective effects is often referred to as the ‘adiponectin paradox’.[17, 18]

The mechanisms underlying the adiponectin paradox are of scientific and clinical interest but remain poorly understood. Possible interaction with natriuretic peptides in the relationship between adiponectin and mortality has been suggested as one potential

explanation for the adiponectin paradox.[19] Natriuretic peptides, particularly the N-terminal pro-brain natriuretic peptide (NT-proBNP), a protein secreted by ventricular myocytes to decrease vascular resistance has an established association with cardiovascular disease risk and mortality.[20-22] Natriuretic peptides are positively correlated with circulating levels of adiponectin and increasing levels of natriuretic peptides may stimulate production of adiponectin.[23-25] It has therefore been hypothesized that the increased risk of mortality associated with elevated levels of adiponectin could be attributed, at least in part, to the concomitantly increased levels of NT-proBNP.

Some studies assessing the association between adiponectin and mortality have also investigated the influence of natriuretic peptides on the relationship but produced conflicting findings.[26] In some studies evaluating the associations between adiponectin and mortality, adjusting for NT-proBNP resulted in attenuation of effects [16, 27, 28], while in others the associations lost statistical significance [25, 29, 30], suggesting that NT-proBNP may be a confounder in the relationship. Although studies did not formally evaluate effect modification by NT-proBNP, some studies reported substantial changes in the association between adiponectin and mortality following adjustment for NT-proBNP. [27, 31] Of note, most of the studies investigating the adiponectin-mortality relationship were conducted in clinical settings, including patients of symptomatic peripheral arterial disease [29], chronic heart failure [25], ischemic heart disease [28], diabetes [13] and other conditions or in elderly populations with high baseline risk of mortality and also included few outcome events. Fewer studies have so far been conducted in the general population context.[26] In light of the inconsistent findings on the role of NT-proBNP in the relationship between adiponectin and mortality, we conducted a population-based prospective case-cohort study within the European Prospective Investigation into Cancer and Nutrition (EPIC) – Heidelberg to investigate the heterogeneity in the adiponectin-cardiovascular disease risk and mortality associations by NT-proBNP. In addition, we examine other heterogeneities in the relationship between adiponectin and cardiovascular disease risk and mortality by sex, smoking, BMI, prevalent diabetes and hypertension, all of which have been previously reported in the literature.[32-35]

Methods

We used a case-cohort study design nested within the EPIC-Heidelberg study. EPIC-Heidelberg is one of the study centres for the European Prospective Investigation into Cancer and Nutrition (EPIC) study, which recruited more than half-million (510,000) participants across 10 European countries who have been followed up for more than 15 years to investigate the associations between diet, metabolic and lifestyle factors with risk of cancer and other chronic conditions. At the EPIC-Heidelberg study center, between 1994 and 1998, 25,540 participants were recruited from the local population in Heidelberg and surrounding municipalities and baseline information about participants' health, and social and economic status was collected, including anthropometric measurements (weight, height, waist and hip circumferences). A blood sample was also drawn from the participants on the day of recruitment, regardless of fasting status, and kept for a maximum of 24h at 4 to 10 ˚C until centrifugation, and further processing. Blood samples were aliquoted into fractions of plasma, serum, erythrocytes and buffy coat and stored under liquid nitrogen at −196 °C. Informed consent was obtained from all participants at baseline. Participants also provided self-reports about their hypertension and diabetes status. For diabetes status, heamoglobin A1c (HbA1c) levels were also measured from the blood samples collected at recruitment.

Prospective outcome ascertainment

Cases of chronic diseases among EPIC-Heidelberg participants were prospectively ascertained through active follow up of the study participants directly or through their next-of-kin, as well as through linkages to hospitalisation records and cancer and pathology registries. Mortality outcomes were ascertained from death certificates which were collected from mortality registries. For the cardiovascular disease incidence outcome, all verified incident cases of myocardial infarction (MI) (International Classification of Diseases (ICD)-10: I21) and stroke (ICD-10: I60, I61, I63, I64), diagnosed up to the end of December 2014 were included. All cases were validated and coded by a study physician based on medical records and only verified cases are included in this study.

Case-cohort sampling

We used the case-cohort design because it allows investigation of several different outcomes while sparing the excessive use of biological samples.[36] The detailed sampling process of the case-cohort has been previously described elsewhere.[20] Briefly, the sub-cohort was selected using a 2-step age-stratified sampling from the EPIC-Heidelberg cohort. The first step of the sampling process consisted of selection of a random 10% of all EPIC-Heidelberg cohort and included all incident cases of chronic diseases

diagnosed until December 2009. A second sampling consisted of additional 10% random sampling of the participants who were older than 50 years at baseline and were not part of the initial sample and included all cases of chronic diseases and deaths occurring until December 2014. The 2 samples were then merged to obtain the final sub-cohort, with a total of 3794 randomly selected study participants of whom 3,591 had their adiponectin levels measured. The case-cohort included a total of 1,387 verified cases of cardiovascular disease (MI and stroke), 582 deaths from cardiovascular causes and 2,352 total deaths that occurred until the end of December 2014. There were 253 cases of MI and stroke (18.2% of all cases of MI and stoke), 130 (22.4%) deaths from cardiovascular and 459 (19.5%) deaths from all causes in the subcohort.

Laboratory measurement of Adiponectin and NT-proBNP

Serum and erythrocyte samples from cases and controls were retrieved from long term liquid nitrogen storage (cryo-straws), placed in temporary -80°C storage and sorted into batches on dry ice. Adiponectin and NT-proBNP were measured on the Meso Scale Discovery (Maryland, USA) electrochemiluminescence Quickplex SQ120 platform. All assays were carried out according to the manufacture's protocols. Briefly, small spot streptavidin plates were coated with a biotin coupled capture antibody for two hours followed by washing. Wells were then coated with assay buffer followed by the addition of standards, QCs and samples with an incubation of one hour with shaking. Wells were washed and detection antibody added for an hour with shaking. Wells were then washed a final time, read buffer added and the plate read within five minutes. HbAc1 was measured using the Variant II Turbo HPLC system (Bio-Rad-Laboratories, Inc., Hercules, California, USA) according to the manufactures protocols. The inter- and intra-batch coefficients of variation (CV) for quality controls were 3.2% and 18.7% for adiponectin, 3.9% and 18.8% for NT-proBNP and 2.0% and 3.9% for HbA1c. All samples were blinded to laboratory personnel and went through only one freeze thaw cycle before measurement.

Statistical analyses

The characteristics of participants at baseline are described separately for the sub-cohort and for cases of each of the outcomes namely; cardiovascular disease incidence, cardiovascular mortality and all-cause mortality. We conducted analysis of variance to compute marginal means and tests for differences in the mean concentrations of adiponectin by strata of categorical covariates. For continuous covariates, we calculated partial correlations with adiponectin using Pearson's coefficients. Marginal means and partial correlations were adjusted for sex, BMI (continuous), smoking (never, long time quitters, short time quitters, current light, and current heavy smokers).

Relative hazards for cardiovascular disease risk and mortality were estimated for the associations between log-transformed and standardised adiponectin levels and CVD risk and mortality using Prentice-weighted Cox proportional hazards models. We used inverse sub-cohort sampling probability to account for case-cohort sampling design and the oversampling of older participants.[36] Participants who were 50 years or younger were assigned a probability of 10%. Those who were older than 50 years were assigned a probability of 19% (10% given they were not drawn in the first selection step (a 90% probability): 10% + (10% × 90%)). The standardisation of adiponectin was sex specific and based on the distribution of the adipokine in the subcohort. The hazards ratios were thus estimated per 1-standard deviation (SD) in the log-transformed adiponectin levels. In all models, age was the underlying timescale, and all models were additionally stratified by age at recruitment (5-year category). All models were adjusted for sex, BMI (continuous), and smoking (never, long time quitters, short time quitters, current light, and current heavy smokers). For cardiovascular disease incidence, the hazard ratios (HR) and their 95% confidence intervals (CI) were computed for any first occurrence of incident cardiovascular event (where stroke and MI were considered as mutually competing events). Proportional hazards assumption was tested and was not violated in any of the models according to an extended version of the Schoenfeld residuals test.[37]

First, we examined heterogeneity in the association between adiponectin and three endpoints; cardiovascular disease incidence, cardiovascular mortality and all-cause mortality within sub-groups according to: NT-proBNP, sex, BMI, smoking status, waist circumference, diabetes, and hypertension status. NT-proBNP was binned into tertiles. For diabetes, we had both information on both laboratory measured HbA1c and self-reported diabetes status. HbA1c was categorised using cut-offs; ≥42 mmol/mol as normal, 42 - <48 mmol/mol as prediabetes and ≥48 as diabetes.[38] Non-smokers and quitters were merged together because our earlier analyses showed similar incidence and mortality trends for the two groups. Heterogeneity was examined by including

interaction terms between adiponectin and covariates of interest and p-values for interaction/heterogeneity (p_{het}) were based on the Wald test.

For NT-proBNP which showed significant associations with outcomes and significant heterogeneity, we conducted further analyses to examine the shape of the association between adiponectin and incidence and mortality within tertiles of NT-proBNP. For these analyses, adiponectin concentrations were binned into quintiles in a sex-specific manner. Within each tertile of NT-proBNP, hazards ratios were estimated for increasing levels of adiponectin with the lowest quintile (Q1) as the reference. Visualisation of the dose-response association between adiponectin and mortality by strata of NT-proBNP were performed using natural cubic spline plots, specifying 3 knots evenly placed across the range of the data and with median adiponectin levels (19.5 mg/ml) as the reference value. All analyses were performed using SAS v.9.4 (SAS Institute).

Results

The median age of participants at blood collection in the sub-cohort was 54.1 years (min = 35.2 years, max = 66 years). The median follow-up was 15.6 years. Baseline mean adiponectin concentrations within participants in the sub-cohort was 27.5 mg/ml (standard deviation, SD = 26.9) and appeared to be lower for participants who experienced outcomes; 24.5 mg/ml for cardiovascular disease cases and 25.8 mg/ml for participants who died from cardiovascular causes (**Table 1**). The sub-cohort comprised of similar proportions of men (49.3) and women (50.7). The prevalence of self-reported hypertension was 31.9%, 4% for self-reported diabetes and 16.9% for obesity (BMI $\geq$ 30 kg/m^2). Participants who experienced outcomes were older (average age was 55.4 years, 57.7 and 56.5), heavier (average BMI was 27.6 kg/m², 28.4 kg/m² and 27.6 kg/m²) had higher prevalence of self-reported hypertension (prevalence was 45.8, 54.6 and 44.5) for participants had a myocardial infarction or stroke, those who died from cardiovascular causes and those who died from any causes respectively, than participants in the sub-cohort, at baseline. (**Table 1**).

Mean circulating adiponectin concentrations were 12.1 mg/ml (95% CI: 10.3-13.9, p <0.001) higher in women than in men (**Table 2**). Participants with self-reported diabetes had, on average, lower levels of adiponectin than their counterparts without the disease. Partial correlation between HbA1c was negative and very weak (r = -0.04, p = 0.008). There was no statistically significant differences in mean concentrations of adiponectin between current smoker and never/former smokers. NT-proBNP showed a weak but statistically significant partial correlation with adiponectin levels (r = 0.07, p <0.001). The correlation was slightly stronger when restricted to participants within the top tertile of NT-proBNP concentrations (r = 0.11, p <0.001) as compared to 0.01 and 0.06 for the first and second tertiles respectively. Both BMI and waist circumference also showed weak but statistically significant negative partial correlations with adiponectin concentrations with Pearson's coefficients, r of -0.13 and -0.14 respectively. Adiponectin level was positively correlated with age at blood draw, r = 0.10, p<0.001 (**Table 2**).

There was significant interaction by levels of NT-proBNP on the association between adiponectin and all-cause mortality (p_{het} > 0.019). There was no significant association between adiponectin and mortality for participants with lower NT-proBNP concentrations (first and second tertiles). However, for participants in the highest tertiles of NT-proBNP, a 1SD increase in adiponectin concentrations was associated with 20% higher hazards of mortality [1.20 (1.07-1.35), p = 0.002] (**Table 3**). There was significant heterogeneity by hypertension status in the association between adiponectin and cardiovascular disease incidence (p_{het} = 0.017), although the associations did not reach statistical significance in both participants with and without hypertension. Although there was no statistically significant heterogeneity, adiponectin showed a statistically significant association with cardiovascular mortality among participants without self-reported diabetes [HR = 1.13, 95% CI: 1.01-1.26), p = 0.030], or who had normal (<42 mmol/mol) HbA1c levels [1.13 (1.01-1.27), p = 0.034], and among participants with self-reported hypertension [1.16 (1.01-1.33) p = 0.041] and participants who quit smoking or had never smoked [1.16 (1.03-1.30), p = 0.012] (**Table 3**).

In further sub-group analysis by tertiles of NT-proBNP, for participants with high NT-proBNP levels (third tertile), adiponectin showed a dose response relationship with cardiovascular (p_{trend} = 0.009) and all-cause mortality (p_{trend} = 0.002). For instance, compared to participants in the lowest quintile of adiponectin, a 1SD increase in levels of the adipokine was associated with a 22% [1.22 (0.87-1.7)], 50% [1.50 (1.07-2.11)], and 59% [1.59 (1.15-2.21)] increase in hazards of all-cause mortality for participants in third, fourth and fifth quintiles of adiponectin respectively (**Table 4** and **Figure 1**). Figures 1 shows the shape of the relation between adiponectin and cardiovascular mortality and all-cause mortality by tertiles of NT-proBNP.

Discussion

In this prospective study among middle aged healthy population in Germany, we explored a number of possible effect modifiers reported in previous studies including sex, BMI, diabetes and hypertension status, smoking status, waist-circumference and NT-proBNP [32-35], for the association between adiponectin and cardiovascular disease risk, cardiovascular mortality and all-cause mortality. We found that, overall adiponectin was associated with all-cause mortality but not cardiovascular risk or mortality, although the p-value for cardiovascular mortality neared statistical significance. We further found a statistically significant effect modification by NT-proBNP for the association between adiponectin and all-cause mortality such that higher hazards of mortality were observed for participants with high levels of adiponectin only among participants with high levels of NT-proBNP. Among individuals with high NT-proBNP levels, adiponectin showed a significant dose-response relationship with cardiovascular and all-cause mortality. We also found that although there was no significant statistical heterogeneity, hazard ratios for the association between adiponectin and cardiovascular and total mortality were more pronounced among participants did not have diabetes, were obese, were non-smokers or had hypertension.

Our findings provide further support for the hypothesis that NT-proBNP may explain the adiponectin paradox. It has been suggested that adiponectin may simply be a marker of elevated NT-proBNP levels and that natriuretic peptides may be responsible for the increased risk of mortality attributed to adiponectin.[26] We did not find an association between adiponectin and cardiovascular disease risk, which was in line with findings of a systematic review.[39] An earlier large Mendelian randomisation study involving more than 85,000 cases of coronary heart disease and more than 19,500 controls also found no association between alleles increasing adiponectin and risk of cardiovascular disease [40]. Taken together, these studies suggest that adiponectin may simply be a marker and not a pathogenic factor of metabolic dysfunction. In individuals with underlying heart disease, NT-proBNP levels rise due to myocardial stretch and resistance.[41] The concomitant increase in levels of adiponectin may be a compensatory mechanism in response to adiponectin resistance resulting from downregulation of AdipoR1 that has been reported in cardiovascular disease cases.[42] Increasing levels of NT-proBNP may also stimulate an increase in circulating adiponectin levels. Infusion of NT-proBNP stimulated adiponectin production [23] and in a recent Mendelian randomisation study reported a causal relationship between NT-proBNP and adiponectin.[43] Thus, adiponectin may play a downstream role in the natriuretic peptides-mediated responses of the heart to improve vascular compliance.[43]

Our results further highlight the need for cautious clinical interpretation of adiponectin levels, which should take into account levels of NT-proBNP.[44] Adiponectin is considered as a biomarker for cardiovascular risk with higher levels indicating a favourable risk profile. However, our findings suggest that in the context of low NT-proBNP, elevated adiponectin levels may not be indicative of increased risk of mortality from cardiovascular disease and other causes. Instead, adiponectin may be a proxy marker of increased risk of mortality in the context of elevated NT-proBNP. Relatedly, we did not observe a protective or deleterious effect of increased adiponectin levels on cardiovascular disease risk (myocardial infarction and stroke). There have been studies that have identified some drugs (such as statins, thiazolidinediones) and dietary supplements (such as vitamin E, omega-3, and fish oils) as upward regulators of adiponectin expression.[45] The lack of protective effect against adverse cardiovascular events and the possible side effects of adiponectin inducing drugs suggest the need to exercise caution in using pharmacological interventions to increase adiponectin levels.

Our study was well powered and one of the largest to investigate the association between adiponectin and cardiovascular disease risk and mortality in healthy participants (without major cardiovascular conditions and cancer at baseline) selected from the general population. The relatively long follow-up (median follow-up ~ 16 years) allowed for investigation of log-term endpoints such as mortality. Our analyses focused on investigating heterogeneities that have been previously reported in the literature, reducing the chances of false-positive discoveries. Our study also had some limitations. We had samples from participants at a single time point (at recruitment) and were only able to have single measurements of both adiponectin and NT-proBNP. The use of single measurement for assessing long-term outcomes means that we cannot rule-out the possibility of a dilution effect. It is however unlikely that such a dilution effect would be differential with respect to case-control status. Nonetheless, it could have led to an underestimation of associations. Secondly, despite the overall large sample size of our study, there were few clinically verified cardiovascular deaths which might have reduced the power of the study particularly for sub-group analyses.

Conclusion

In this large population based study, the association between adiponectin and cardiovascular and total mortality varied according to levels of NT-proBNP. Our findings provide further support for hypothesis that NT-proBNP may explain the adiponectin paradox and highlight the need for cautious clinical interpretation of adiponectin levels.

Abbreviations

BMI body mass index

CI confidence intervals

EPIC European Prospective Investigation into Cancer and Nutrition

HbA1c heamoglobin A1c

HR hazard ratios

ICD International Classification of Diseases

NT-proBNP N-terminal pro-brain natriuretic peptide

MI myocardial infarction

Declarations

Ethics approval and consent to participate:

This project is covered by the ethical approval for the EPIC–Heidelberg cohort (Ethical Committee of the Medical Faculty Heidelberg, reference number 13/94).

Consent for publication:

Not applicable

Availability of data and materials:

EPIC–Heidelberg was launched in the 1990s. Unlike in new studies run today, public access to data from the EPIC population was not part of the study protocol at that time. Thus, the data protection statement and informed consent of the EPIC participants do not cover the provision of data in public repositories. Nevertheless, we are open to providing our dataset upon request for (a) statistical validation by reviewers and (b) pooling projects under clearly defined and secure conditions and based on valid data transfer agreements.

Competing interest:

The authors declare that they have no competing interests

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Author contributions:

RK, VK and TM contributed to the conception of the study. TJ organised the sample handling and laboratory analyses. TM performed statistical analyses. TM drafted the manuscript, which all authors reviewed and revised. All authors reviewed and approved the final manuscript.

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Tables

Table 1

Socio-demographic characteristics of the EPIC-Heidelberg case-cohort study participants

	Sub-cohort (n = 3,591)		CVD cases[1] (n = 1,387)		CVD deaths[2] (n = 582)		All-cause deaths [3] (n = 2,352)	
Characteristic	**N**	**Mean ± SD/ Percent**	**N**	**Mean ± SD/ Percent**	**N**	**Mean ± SD/ Percent**	**N**	**Mean ± SD/ Percent**
Adiponectin	3,591	27.5 ± 26.9	1,387	24.5 ± 24.8	582	25.8 ± 26	2,352	27.3 ± 31.1
Age at blood draw (years)	3,591	52.8 ± 7.7	1,386	55.4 ± 6.9	582	57.7 ± 6	2,352	56.5 ± 6.7
Sex								
Men	1,772	49.3	994	71.7	429	73.7	1,568	66.7
Women	1,819	50.7	393	28.3	153	26.3	784	33.3
BMI (kg/m^2)								
Continuous	3,591	26.3 ± 4.2	1,387	27.6 ± 4.1	582	28.4 ± 4.5	2,352	27.6 ± 4.6
<25	1,498	41.7	357	25.7	134	23	667	28.4
≥25 - <30	1,486	41.4	677	48.8	271	46.6	1,064	45.2
≥30	607	16.9	353	25.5	177	30.4	621	26.4
Waist circumference (cm)	3,591	89.1 ± 13.2	1,387	94.9 ± 11.9	582	97.9 ± 12.9	2,352	95.3 ± 13.5
Self-reported diabetes								
No	3,447	96	1,251	90.2	498	85.6	2,114	89.9
Yes	144	4	136	9.8	84	14.4	238	10.1
HbA1c (mmol/mol**)**								
Continuous	3,516	36 ± 8	1,331	38.6 ± 10.6	567	40.5 ± 13.6	2,281	39.1 ± 11.6
Normal (<42)	3,195	90.9	1,092	82	433	76.5	1,816	79.6
Prediabetes (42 - <48)	169	4.8	105	7.9	56	9.9	230	10.1
Diabetes (≥48)	152	4.3	134	10.1	77	13.6	234	10.3
Self-reported hypertension								
No	2,447	68.1	752	54.2	264	45.4	1,306	55.5
Yes	1,144	31.9	635	45.8	318	54.6	1,046	44.5
Smoking								
Pack-years	3,591	8.9 ± 13.9	1,387	14.1 ± 17.5	582	17.9 ± 21.5	2,352	16.6 ± 19.6
Former & never smokers	2,819	78.7	938	67.9	381	65.7	1,558	66.4
Current smokers	763	21.3	444	32.1	199	34.3	789	33.6
Lifetime alcohol	3,590	17.6 ±	1,387	21.8 ±	582	27.1 ±	2,350	28.9 ±

consumption (g/day)		26.2		26.4		33.8		44
NT-proBNP (pg/ml)	3,562	216.7 ± 298.4	1,379	270.9 ± 383.8	574	477.3 ± 784.4	2,325	322.2 ± 564.5
Lipid lowering medications								
No	925	25.8	441	31.8	166	28.5	620	26.4
Yes	356	9.9	186	13.4	101	17.4	318	13.5
Treatment for hypertension								
No	2,774	77.2	914	65.9	329	56.5	1,531	65.1
Yes	756	21.1	442	31.9	235	40.4	711	30.2

[]cardiovascular disease cases include only clinically verified incident cases of myocardial infarction (ICD-10: I21) and stroke (ICD-10: I60, I61, I63, I64). The number of cases also includes 253 (18.2%) cases in the subcohort.

[][]cardiovascular disease deaths included all deaths from cardiovascular events as coded according to ICD-10. Number of deaths also includes 130 (22.4%) deaths that occurred among participants selected in the subcohort.

[][][]Number of all-cause deaths also includes 459 (19.5%) deaths which occurred in participants selected in the subcohort.

Table 2

Differences in mean concentrations and correlations with adiponectin by strata of covariates

Category	N	Mean (95%CI) / correlation coefficient*	Difference in means of adiponectin (mg/ml)	p-value for difference in means /correlation
Sex				
Male	1,772	21.3 (19.9-22.6)	-12.1 (-13.9–10.3)	**<0.001**
Female	1,819	33.4 (32-34.8)		
Age				
<50	1,168	0.01		0.733
≥50	2,423	0.01		0.631
All	3,591	0.10		**<0.001**
Diabetes				
No	3,447	27.3 (26.3-28.4)	5.9 (1.4-10.4)	**0.010**
Yes	144	21.4 (17-25.8)		
Treatment for hyperlipidemia				
No	925	24.9 (23.1-26.7)	1.5 (-1.3-4.3)	0.294
Yes	356	23.4 (20.9-25.9)		
Hypertension				
No	2,447	27.6 (26.4-28.8)	1.6 (-0.4-3.6)	0.110
Yes	1,144	26 (24.3-27.7)		
Treatment for hypertension				
No	327	26.2 (23.1-29.3)	1.4 (-2.1-4.8)	0.430
Yes	756	24.8 (22.6-27)		
BMI (kg/m²)				
≥18.5 - <25	1,498	-0.08		**0.001**
≥25 - <30	1,486	-0.05		0.055
≥30	607	-0.01		0.755
All	3,591	-0.13		**<0.001**
HbA1c (mmol/mol)				
<42	3,195	-0.03		0.051
≥42 - <48	169	0.01		0.909
≥48	152	0.03		0.752
All	3,516	-0.04		**0.008**
NT-proBNP				
Tertile 1	1,238	-0.01		0.676
Tertile 2	1,181	0.06		0.054
Tertile 3	1,143	0.11		**<0.001**
All	3,562	0.07		**<0.001**

Smoking				
Former & never smokers	2,819	28.5 (26.2-30.9)	3.6 (-1.6-8.9)	0.175
Current smokers	763	24.9 (21.5-28.3)		
Waist circumference (cm)				
<94 in men|<80 in women	1,633	28 (26.3-29.7)	1.7 (-0.6-4)	0.150
≥94 in men|≥80 in women	1,957	26.3 (24.8-27.8)		
Waist circumference (cm)				
<94 in men|<80 in women	1,633	-0.06		**0.016**
≥94 in men|≥80 in women	1,957	-0.09		**<0.001**
All	3,590	-0.14		**<0.001**

*Marginal means and partial Pearson's correlation coefficients were adjusted for; sex, age, BMI (continuous) and smoking

Table 3

Sub-group analysis of the association between adiponectin and cardiovascular disease incidence, cardiovascular disease mortality and all-cause mortality

	CVD incidence (cases = 1,387)				CVD mortality (deaths = 582)				Total mortality (deaths = 2,352)			
Covariates	**N**	**HR (95% CI)**	**p**	**p_{het}**	**N**	**HR (95% CI)**	**p**	**p_{het}**	**N**	**HR (95% CI)**	**p**	**p_{het}**
BMI (kg/m²)												
<25	357	0.97 (0.88-1.07)	0.572	0.294	134	1.14 (0.95-1.37)	0.158	0.903	667	1.15 (1.03-1.27)	**0.011**	0.466
≥25 - <30	677	0.95 (0.85-1.06)	0.331		271	1.03 (0.89-1.19)	0.698		1,064	0.99 (0.91-1.08)	0.853	
≥30	353	1.11 (0.96-1.28)	0.177		177	1.16 (0.92-1.45)	0.201		621	1.23 (1.07-1.43)	**0.004**	
Diabetes												
No	1,251	0.98 (0.91-1.04)	0.489	0.081	498	1.13 (1.01-1.26)	**0.030**	0.775	2,114	1.11 (1.04-1.18)	**0.002**	0.811
Yes	136	1.24 (0.94-1.63)	0.132		84	0.98 (0.72-1.35)	0.910		238	1.05 (0.82-1.33)	0.716	
HbA1c												
Normal (<42)	1,092	0.99 (0.92-1.07)	0.860	0.500	433	1.13 (1.01-1.27)	**0.034**	0.524	1,816	1.10 (1.03-1.17)	**0.007**	0.911
Prediabetes (42 - <48)	105	0.75 (0.53-1.06)	0.104		56	1.07 (0.66-1.74)	0.785		230	1.06 (0.81-1.38)	0.675	
Diabetes (≥48)	134	1.16 (0.9-1.5)	0.258		77	0.97 (0.71-1.32)	0.852		234	1.11 (0.88-1.39)	0.393	
Hypertension												
No	752	0.93 (0.86-1.01)	0.077	**0.017**	264	1.07 (0.92-1.24)	0.392	0.454	1,306	1.09 (1.01-1.18)	**0.029**	0.892
Yes	635	1.09 (0.98-1.21)	0.110		318	1.16 (1.01-1.33)	**0.041**		1,046	1.12 (1.01-1.24)	**0.025**	
NT-proBNP												
Tertile 1	415	0.97 (0.87-1.08)	0.556	0.103	137	0.96 (0.81-1.15)	0.661	0.055	714	1.03 (0.93-1.14)	0.587	**0.019**
Tertile 2	458	0.90 (0.81-1.00)	**0.046**		155	1.02 (0.85-1.21)	0.850		729	1.01 (0.92-1.1)	0.874	
Tertile 3	506	1.08 (0.96-1.21)	0.213		282	1.16 (0.99-1.37)	0.073		882	1.20 (1.07-1.35)	**0.002**	
Sex												
Men	994	0.96 (0.88-1.05)	0.365	0.071	429	1.11 (0.98-1.25)	0.110	0.582	1,568	1.1 (1.01-1.19)	0.021	0.687

Women	393	1.07 (0.95-1.19)	0.260		153	1.12 (0.94-1.33)	0.190		784	1.09 (0.99-1.2)	0.071	
Smoking												
Former/Never	938	1.02 (0.94-1.1)	0.696	0.141	381	1.16 (1.03-1.3)	**0.012**	0.135	1,558	1.12 (1.04-1.2)	**0.002**	0.396
Current	444	0.94 (0.84-1.05)	0.260		199	0.97 (0.81-1.17)	0.754		789	1.04 (0.92-1.16)	0.548	
Waist circumference (cm)												
<94 in men | <80 in women	474	0.95 (0.86-1.04)	0.226	0.557	151	1.03 (0.88-1.21)	0.689	0.773	750	1.11 (1.01-1.23)	**0.034**	0.527
≥94 in men | ≥80 in women	913	0.99 (0.9-1.08)	0.759		430	1.07 (0.95-1.21)	0.281		1,599	1.05 (0.98-1.13)	0.195	

p_{het} = p-value for interaction; Cox models were stratified for age-group at baseline

Models are adjusted for; Age at blood draw, sex, smoking status and BMI

HRs represent the change in hazards of incidence/mortality per 1sd increase in log-transformed adiponectin concentrations

Table 4

Association between adiponectin (1SD increase) and CVD incidence and mortality and total mortality by strata of hypertension status and NT-proBNP tertiles across quintiles of adiponectin concertation

				Quintiles of adiponectin concentration*					
		All		Q1	Q2	Q3	Q4	Q5	
Strata	**N**	**HR (95% CI)**	**p-value**		**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**p-trend**
CVD incidence									
Overall	1,387	0.99 (0.93-1.06)	0.782	1.00 (Ref)	0.99 (0.81-1.22)	0.97 (0.79-1.19)	0.97 (0.79-1.2)	0.98 (0.8-1.21)	0.839
Self-reported hypertension status									
No hypertension	752	0.93 (0.86-1.01)	0.077	1.00 (Ref)	1.02 (0.78-1.35)	0.94 (0.71-1.24)	0.88 (0.67-1.17)	0.84 (0.63-1.11)	0.115
Hypertension	635	1.09 (0.98-1.21)	0.110	1.00 (Ref)	0.96 (0.7-1.32)	1.01 (0.74-1.38)	1.14 (0.83-1.57)	1.24 (0.91-1.7)	0.096
CVD mortality									
Overall	574	1.1 (0.99-1.21)	0.071	1.00 (Ref)	1.16 (0.86-1.56)	1.05 (0.77-1.43)	1.17 (0.86-1.58)	1.34 (0.99-1.81)	0.081
NT-proBNP (pg/ml)									
Tertile 1	137	0.96 (0.81-1.15)	0.661	1.00 (Ref)	1.29 (0.74-2.25)	1.09 (0.63-1.89)	0.96 (0.52-1.75)	0.81 (0.43-1.53)	0.316
Tertile 2	155	1.02 (0.85-1.21)	0.850	1.00 (Ref)	0.83 (0.47-1.44)	0.66 (0.36-1.21)	0.62 (0.35-1.13)	1 (0.57-1.75)	0.671
Tertile 3	282	1.16 (0.99-1.37)	0.073	1.00 (Ref)	1.18 (0.72-1.95)	1.26 (0.76-2.1)	1.76 (1.07-2.91)	1.68 (1.03-2.74)	**0.009**
Total mortality									
Overall	2,325	1.09 (1.03-1.16)	**0.004**	1.00 (Ref)	1.16 (0.97-1.4)	1.11 (0.92-1.34)	1.2 (1-1.45)	1.27 (1.06-1.53)	**0.015**
NT-proBNP (pg/ml)									
Tertile 1	714	1.03 (0.93-1.14)	0.587	1.00 (Ref)	1.07 (0.79-1.45)	1.17 (0.87-1.58)	1.12 (0.82-1.53)	1.09 (0.79-1.50)	0.550
Tertile 2	729	1.01 (0.92-1.1)	0.874	1.00 (Ref)	1.19 (0.86-1.65)	0.92 (0.66-1.28)	1.03 (0.75-1.41)	1.01 (0.72-1.42)	0.746
Tertile 3	882	1.20 (1.07-1.35)	**0.002**	1.00 (Ref)	1.18 (0.85-1.64)	1.22 (0.87-1.7)	1.50 (1.07-2.11)	1.59 (1.15-2.21)	**0.002**

*Adiponectin binning into quintiles was sex-specific

Cox models were stratified for age-group and adjusted for; sex, age at blood draw, smoking status and BMI

HRs represent the change in hazards of incidence/mortality per 1sd increase in log-transformed adiponectin concentrations

Figures

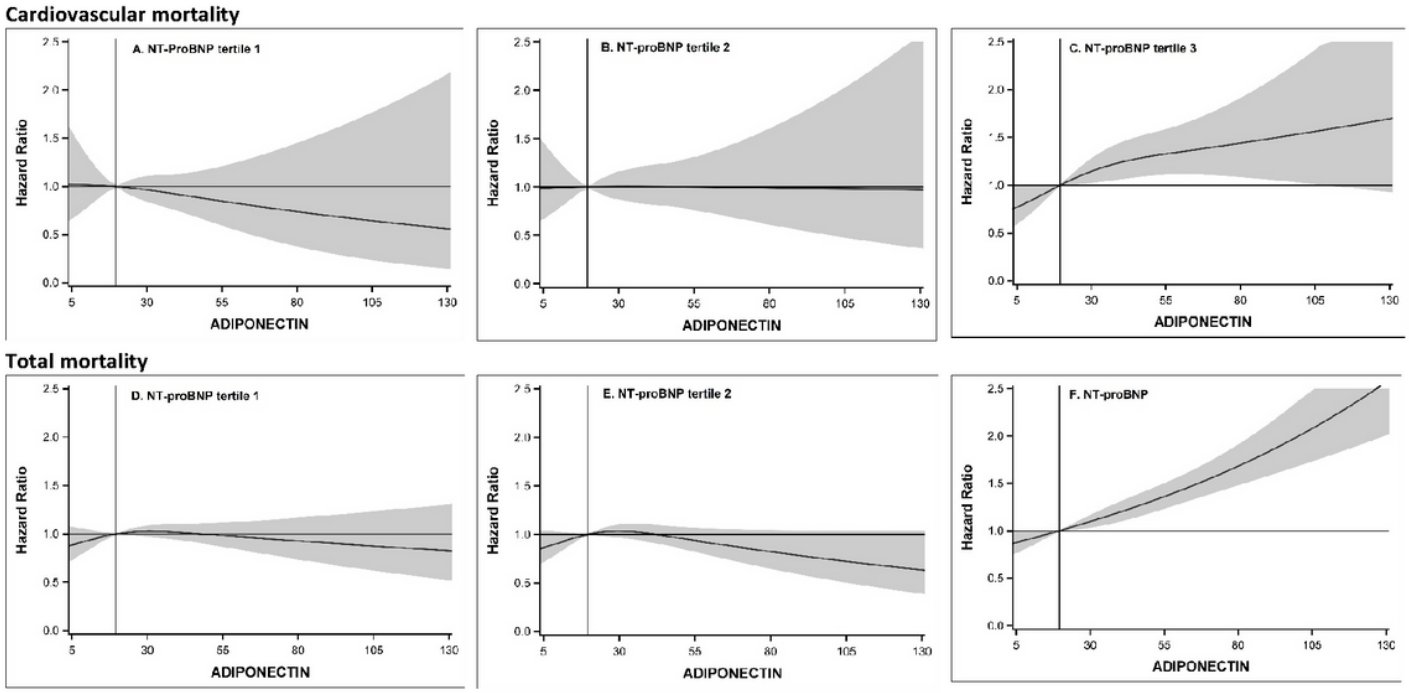

Figure 1

Restricted cubic spline graphs showing the associations of continuous levels of adiponectin with cardiovascular mortality (panels A to C) and all-cause mortality (panels D to F) for tertiles of NT-proBNP. The vertical reference line is drawn at median adiponectin level (27.5 mg/ml). Extreme values below the 1st and above the 99th percentiles have been removed from the plots. All models were adjusted for age at blood draw, sex, smoking, and BMI at baseline.