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## ORIGINAL ARTICLE

# Higher circulating adiponectin levels are associated with increased risk of atrial fibrillation in older adults

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**ABSTRACT**

**Background** Adiponectin has cardioprotective properties, suggesting that lower levels seen in obesity and diabetes could heighten risk of atrial fibrillation (AF). Among older adults, however, higher adiponectin has been linked to greater incidence of adverse outcomes associated with AF, although recent reports have shown this association to be U-shaped. We postulated that higher adiponectin would be linked to increased risk for AF in older adults in a U-shaped manner.

**Methods** We examined the associations of total and high-molecular-weight (HMW) adiponectin with incident AF among individuals free of prevalent cardiovascular disease (CVD) participating in a population-based cohort study of older adults (n=3190; age=74±5 years).

**Results** During median follow-up of 11.4 years, there were 886 incident AF events. Adjusted cubic splines showed a positive and linear association between adiponectin and incident AF. After adjusting for potential confounders, including amino-terminal pro-B-type natriuretic peptide 1–76, the HR (95% CI) for AF per SD increase in total adiponectin was 1.14 (1.05 to 1.24), while that for HMW adiponectin was 1.17 (1.08 to 1.27). Additional adjustment for putative mediators, including subclinical CVD, diabetes, lipids and inflammation, did not significantly affect these estimates.

**Conclusions** The present findings demonstrate that higher, not lower, levels of adiponectin are independently associated with increased risk of AF in older adults despite its documented cardiometabolic benefits. Additional work is necessary to determine if adiponectin is a marker of failed counter-regulatory pathways or whether this hormone is directly harmful in the setting of or as a result of advanced age.

adiponectin, whose levels decrease with higher adiposity and adipose-tissue inflammation, has demonstrated insulin-sensitising, anti-inflammatory and cardioprotective properties in experimental studies.<sup>6</sup> This raises the possibility that decreased circulating levels of adiponectin could help precipitate changes to the myocardial substrate necessary for the development of AF.

Population-based studies have reported, however, that among older adults, the demographic group most susceptible to AF, higher adiponectin levels are associated with increased risk of AF-related outcomes, including cardiovascular disease (CVD) and mortality. More recently, our group has shown the relationship between adiponectin and mortality<sup>7</sup> and CVD<sup>8</sup> in elders to be U-shaped, while that for incident HF was positive,<sup>9</sup> although with a threshold effect. With regard to AF in particular, two moderately powered longitudinal studies have examined this question to date in cohorts of varied age ranges.<sup>10–11</sup> The first study failed to demonstrate a significant relationship between total adiponectin and incident AF,<sup>10</sup> whereas the second study reported a positive association, but adjustment for AF risk factors was limited and did not include prevalent CVD.<sup>11</sup> Hence, the nature of the adiponectin-AF association, and whether it is independent of key potential confounders, remains uncertain.

We tested the hypothesis in a community-based cohort of older adults that circulating levels of total adiponectin and its high-molecular-weight (HMW) fraction bear a U-shaped relationship with incident AF. In particular, we took advantage of the detailed characterisation of this cohort to account for potential confounding, including levels of amino-terminal pro-B-type natriuretic peptide 1–76 (NT-proBNP<sub>1–76</sub>), and putative downstream intermediates, in defining the manner and extent to which adiponectin measures represent an independent risk factor for this arrhythmia.

**METHODS****Study cohort**

The Cardiovascular Health Study (CHS) is a prospective survey of risk factors for CVD in older adults.<sup>12–13</sup> Briefly, participants ≥65 years of age were identified from Medicare eligibility lists and recruited from four field centres in the USA. An original cohort of 5201 subjects was enrolled in 1989–1990, followed by a supplementary

Atrial fibrillation (AF) ranks as the most common chronic dysrhythmia and is associated with increased risks of stroke, heart failure (HF) and mortality.<sup>1</sup> Identification of novel factors influencing the development of AF is critical to the understanding and future prevention of the disease. Population-based studies have described risk factors for AF, including age, diabetes and hypertension, but more recently, body mass index (BMI), natriuretic peptides, and markers of inflammation have emerged as independent determinants.<sup>2–4</sup> Indeed, in the setting of the contemporary obesity epidemic, metabolic risk factors loom as increasingly prominent contributors to this cardiac dysrhythmia.<sup>5</sup> In particular, the adipocyte-derived hormone

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African-American cohort in 1992–1993. Participants had standardised assessments for medical history, anthropometry, blood pressure, electrocardiography and laboratory testing.<sup>12–14</sup>

There were 5265 individuals who took part in the 1992–1993 examination, of whom 4715 had specimens available for adiponectin measurement. Among these individuals, we excluded participants with prevalent AF or atrial flutter ( $n=301$ ). Because the association between adiponectin and outcomes is influenced by prevalent CVD,<sup>7</sup> which can obscure an otherwise protective relationship, we excluded participants with prevalent atherosclerotic CVD (coronary heart disease (CHD), stroke, transient ischaemic attack, peripheral arterial disease) and/or HF ( $n=1184$ ). Such prevalent CVD was ascertained via questionnaires, review of previous medical records or adjudication of new events between the 1989–1990 and 1992–1993 examinations. Another 40 individuals were excluded because of missing data on covariates, resulting in a study sample of 3190 participants.

### Ascertainment of AF

Surveillance for potential clinical events entailed semi-annual contacts alternating between clinic visits and telephone interviews until 1999, and telephone interviews only thereafter. Annual resting ECGs were performed during the period of yearly visits, and discharge diagnoses collected for all hospitalisations. The endpoint of interest comprised AF and atrial flutter. Case identification was based on: (i) interpretation of annual ECGs by the EPICARE Reading Center; (ii) the presence of diagnostic codes for AF or atrial flutter on hospital discharges from CHS files and Medicare inpatient claims, except when these accompanied hospitalisation for coronary bypass or valve replacement surgery; and (iii) diagnosis of AF or atrial flutter from two outpatient visits or physician carrier claims from Medicare data. Event ascertainment was complete through June 2009.

### Measurement of adiponectin

Laboratory measurements of total and HMW adiponectin were performed by ELISA (Millipore, Billerica, Massachusetts, USA) in EDTA-plasma stored at  $-70^{\circ}\text{C}$ ; inter-assay analytical coefficients of variation were 6.9% and 11.1%, respectively.

### Definition of covariates

Diabetes was defined by fasting glucose  $\geq 126$  mg/dL, non-fasting glucose  $\geq 200$  mg/dL, or glucose-lowering therapy. Homeostasis model assessment of insulin resistance (HOMA-IR) and estimated glomerular filtration rate (eGFR), based on cystatin C, were calculated using standard methods.<sup>15 16</sup> Subclinical CVD was based on carotid ultrasound, ankle-brachial index, electrocardiography and Rose angina questionnaire findings, as detailed previously.<sup>12</sup> Echocardiography was performed in returning participants in 1994–1995, with parameters of cardiac structure and function determined as described previously.<sup>9</sup>

### Statistical analysis

Standard descriptive statistics were used to present levels of covariates both overall and across quartiles of total or HMW adiponectin. The shapes of the relationships between adiponectin levels and incident AF were evaluated using Cox models, with adiponectin measures fit using penalised cubic splines. Multivariable models were adjusted sequentially for potential confounders from candidate variables previously documented to have associations with adiponectin and/or AF. The first model included adjustment for age, sex and race; followed by a model

with additional adjustment for education, weight, height, systolic blood pressure, antihypertensive medications, smoking, alcohol use, self-reported health status and eGFR. The final confounder model was further adjusted for NT-proBNP<sub>1–76</sub>, which was available for 88% of participants. Total and HMW adiponectin were highly correlated ( $r=0.94$ ), which precluded their inclusion in a single model. The proportional hazards assumption was verified using Schoenfeld residuals.

To assess the impact of putative mediators, we next entered covariates that experimental data suggest may be on the causal pathway between adiponectin and AF. Specifically, we included subclinical CVD, followed by diabetes or HOMA-IR, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides and high-sensitivity C-reactive protein (hsCRP). In separate exploratory models, we examined the impact of adjusting instead for echocardiographic parameters obtained 2 years later after excluding participants with interval development of AF. Echocardiographic measures included left atrial diameter index, LVEF and transmitral E/A ratio. The start of follow-up for these analyses was the 1994–1995 examination. Of the 3190 individuals included in the primary analyses, 219 did not participate in the 1994–1995 examination, an additional 72 were excluded for interim AF, and another 523 were missing at least one of the three echocardiographic measures, leaving 2376 participants available for these exploratory analyses.

In addition, we tested for first-order interactions between adiponectin and age, sex, race, diabetes, BMI and elevated NT-proBNP<sub>1–76</sub> ( $\geq 190$  ng/mL, previously determined as the HF risk threshold in this population<sup>17</sup>). In view of multiple testing, we applied a Bonferroni correction to the interaction analysis ( $n=2 \times 6$  tests;  $p=0.05/12=0.004$ ) in order to minimise false-positive findings. We also performed sensitivity analyses to assess the impact of early AF events or of specific comorbidities on the association of interest. Further analyses adjusted for CHD and HF as time-varying covariates. Last, an additional sensitivity analysis was undertaken to compare the associations when participants with and without prevalent CVD were combined.

All analyses were performed with STATA, V.12 (College Station, Texas, USA).

## RESULTS

### Baseline characteristics and outcomes

Table 1 presents the baseline characteristics of the study population, both overall and across quartiles of total adiponectin, along with crude numbers of events during 11.4 years of median follow-up. Age, alcohol use, oestrogen use, HDL level, concentration of NT-proBNP<sub>1–76</sub> and elevated left atrial diameter index increased with each quartile of total adiponectin. Similarly, unintentional weight loss was greatest in the highest adiponectin quartile. By contrast, men, African-Americans and lower educational attainment; anthropometric measures, diastolic blood pressure, hyperglycaemia, triglycerides; antihypertensive medications; and subclinical CVD decreased across increasing adiponectin quartiles. The same decrease across quartiles was observed for crude numbers of incident HF and CHD. Findings were similar for HMW adiponectin (see online supplementary table S1).

### Adiponectin levels and risk of AF

Adjusted cubic splines confirmed that the association of total and HMW adiponectin levels were directly and linearly related to AF risk (figure 1). Thus, subsequent analyses evaluated total and HMW adiponectin as continuous variables (table 2). After

**Table 1** Characteristics of the study population by quartiles of total adiponectin\*

Quartile (n)	Total	Q1 (798)	Q2 (797)	Q3 (798)	Q4 (797)
Adiponectin (mg/L)	0.8–55	≤8.7	>8.7–12.4	12.4–17.6	>17.6
Age, years	74±5	73±5	74±5	74±5	76±6
Men, n (%)	1159 (36.3)	463 (58.0)	329 (41.3)	231 (28.9)	136 (17.1)
African-American, n (%)	524 (16.4)	234 (29.3)	142 (17.8)	87 (10.9)	61 (7.7)
Education<high school, n (%)	807 (25.3)	235 (29.4)	209 (26.2)	177 (22.2)	186 (23.3)
BMI, kg/m <sup>2</sup>	26.8±4.8	28.6±4.7	27.6±4.4	26.5±4.7	24.6±4.2
Height, cm	164±9	167±9	165±9	163±9	160±8
Weight, kg	159±32	80.2±13.9	75.0±13.4	70.3±13.4	63.0±12.2
Systolic blood pressure, mm Hg	136±21	136±21	136±21	136±21	135±20
Diastolic blood pressure, mm Hg	72±11	73±11	73±11	71±11	71±11
Hypertensive medication, n (%)	1277 (40.0)	360 (45.1)	361 (45.3)	296 (37.1)	260 (32.6)
Diabetes, n (%)	385 (12.3)	211 (26.9)	78 (9.9)	65 (8.3)	31 (4.0)
HOMA-IR	3.7±7.3	6.3±11.6	3.6±6.1	2.9±5.2	2.2±2.5
LDL, mg/dL	128±33	126±34	129±34	129±33	126±34
HDL, mg/dL	55±14	47±11	51±12	57±12	65±15
Triglyceride, mg/dL	121 (87, 168)	145 (106, 208)	129 (95, 179)	116 (86, 154)	99 (74, 133)
Lipid medication, n (%)	198 (6.2)	55 (6.9)	62 (7.8)	46 (5.8)	35 (4.4)
Current smoker, n (%)	334 (10.5)	93 (11.7)	81 (10.2)	87 (10.9)	73 (9.2)
Alcohol use ≥7 drinks/week	421 (13.2)	92 (11.5)	94 (11.8)	113 (14.2)	122 (15.3)
Oestrogen replacement (women)	293 (9.2)	32 (4.0)	74 (9.3)	87 (10.9)	100 (12.5)
ACE inhibitor medication	267 (8.4)	91 (11.4)	68 (8.5)	62 (7.8)	46 (5.8)
Beta-blocker medication	265 (8.3)	93 (11.7)	86 (10.8)	47 (5.9)	39 (4.9)
Self-reported fair/poor health	479 (15.0)	133 (16.7)	111 (13.9)	109 (13.7)	126 (15.8)
Unintentional wt loss >10 lbs	136 (4.7)	33 (4.5)	26 (3.6)	32 (4.4%)	45 (6.3)
eGFR, mL/min/m <sup>1.73</sup>	75±18	75±19	75±18	75±17	76±19
hsCRP, mg/L	2.4 (1.1, 5.5)	3.7 (1.8, 6.7)	2.8 (1.2, 5.9)	2.1 (1.0, 5.1)	1.6 (0.8, 3.3)
NT-proBNP <sub>1–76</sub> , ng/L	114 (61, 212)	72 (40, 137)	101 (59, 177)	130 (74, 224)	170 (98, 289)
Subclinical CVD, n (%)	1958 (63.0)	529 (67.9)	487 (62.7)	482 (62.0)	460 (59.5)
High LA diameter index‡, n (%)	177 (6.8)	35 (5.2)	36 (5.5)	40 (6.0)	66 (10.7)
Low LVEF (<55%)†, n (%)	150 (5.9)	42 (6.5)	35 (5.6)	38 (5.9)	35 (5.7)
Transmitral E/A ratio†, n (%)					
<0.7	611 (23.7)	159 (23.7)	173 (26.7)	152 (23.3)	127 (20.8)
0.7–1.5	1908 (73.9)	501 (74.8)	454 (70.1)	488 (74.7)	465 (76.2)
>1.5	62 (2.4)	10 (1.5)	21 (3.2)	13 (2.0)	18 (3.0)
Incident AF, n (%)	886 (27.8)	211 (26.4)	219 (27.5)	239 (29.9)	217 (27.2)
Incident HF before AF, n (%)	619 (19.4)	163 (20.4)	163 (20.5)	152 (19.0)	141 (17.7)
Incident CHD before AF	822 (25.8)	240 (30.1)	222 (27.9)	193 (24.2)	167 (21.0)

\*Continuous values are presented as means±SD or as medians (IQR).

†Obtained 2 years after the 1992–1993 baseline (ie, at the 1994–1995 examination)

AF, atrial fibrillation; BMI, body mass index; CHD, coronary heart disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HF, heart failure; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment-insulin resistance; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; LA, left atrial; NT-proBNP<sub>1–76</sub>, amino-terminal pro-B-type natriuretic peptide 1–76; wt, weight.

adjustment for potential confounders, including NT-proBNP<sub>1–76</sub> (model 3), each SD higher in total (SD=7.9 mg/L) and HMW adiponectin (SD=5.9 mg/L) was associated with a 14% (5%–24%) and 17% (8%–27%) higher relative risk of AF, respectively (table 2). Additional adjustment for putative causal intermediates did not substantively alter the associations.

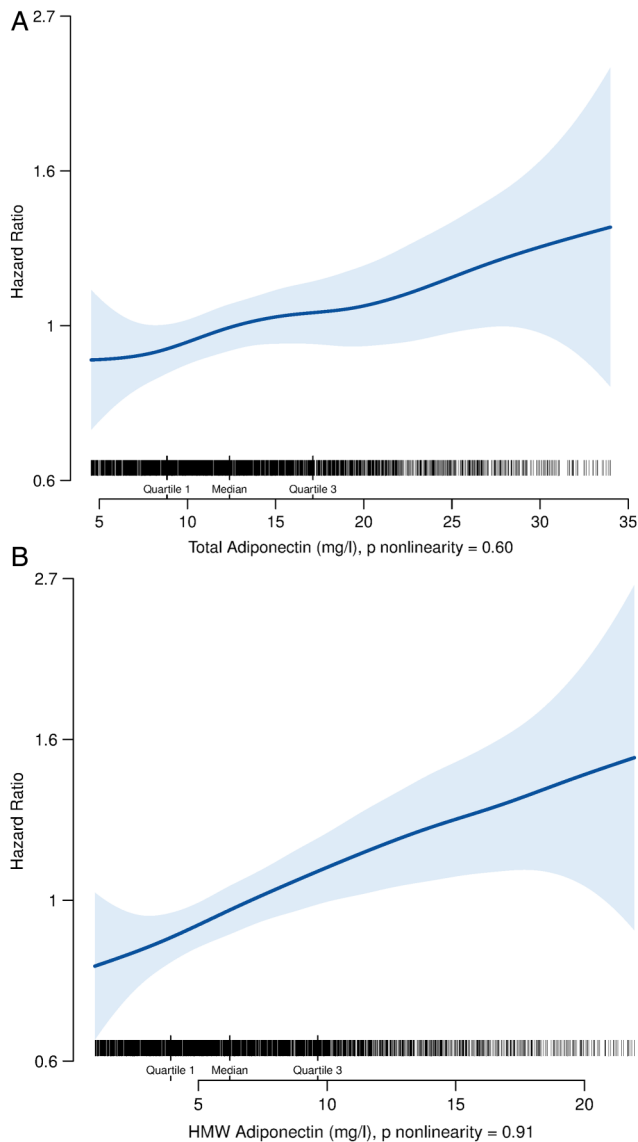
In exploratory analyses among the subset of participants free of prevalent AF at the 1994–1995 examination who had available echocardiographic measures, additional adjustment for left atrial diameter index, LVEF, and transmitral E/A ratio, individually or collectively, did not materially affect the risk estimates. There was no evidence of significant interaction by age, sex, race, diabetes, BMI or NT-proBNP<sub>1–76</sub>. Furthermore, estimates were not materially affected by excluding participants with diabetes, fair or poor health status, high NT-proBNP<sub>1–76</sub> and unintentional weight loss >10 lbs in the previous year; restricting the analysis to events that occurred after 5 years of follow-up;

or including adjustment for incident HF and CHD as time-varying covariates. In an additional sensitivity analysis that included the 1172 participants with prevalent CVD and non-missing covariates (n=961 with atherosclerotic CVD and 353 incident AF events; n=211 with HF and 94 incident AF events), the associations of total and HMW adiponectin with AF were mildly attenuated, but remained significant (HR 1.09 (95% CI 1.02 to 1.17) and HR 1.12 (95% CI 1.05 to 1.19) after adjustment for model 3 covariates, respectively). No evidence of significant effect modification by prevalent CVD status was detected.

**DISCUSSION**

**Main findings and previous studies**

The present study shows that among community-dwelling older persons free of clinically overt CVD, levels of total adiponectin were related to incident AF in a positive and linear fashion. The



**Figure 1** Adjusted cubic spline graphs depicting the associations of continuous levels of total (left panel) and high-molecular-weight (right panel) adiponectin with atrial fibrillation. Models are adjusted for age, sex, race, educational status, height, weight, systolic blood pressure, use of antihypertensive medication, smoking, alcohol, self-reported health status and estimated glomerular filtration rate (eGFR). The horizontal band above the X-axis represents individual participants (vertical lines) with corresponding values for adiponectin level (mg/L). Values at the extreme 2.5th percentiles have been removed from the plots.

current investigation also examined the HMW fraction of this multimeric hormone, which has been reported to have stronger insulin-sensitising properties, but findings were similar as for total adiponectin. To our knowledge, this study is the largest to investigate the adiponectin-AF relationship to date, with 886 incident AF events, as compared with 206 and 343 in the two previous cohort studies<sup>10 11</sup> to have addressed this question. Unlike earlier work, we accounted for an extensive set of potential confounders that included NT-proBNP<sub>1-76</sub>, and examined the impact of key putative mediators in evaluating the associations of interest. As such, the present analyses provide robust evidence that higher adiponectin concentrations are independently associated with greater risk of AF, specifically among older individuals without clinical CVD at baseline.

**Table 2** Cox proportional hazards models for risk of atrial fibrillation

Model	HR per 1-SD* increase (95% CI)	
	Total adiponectin	HMW adiponectin
1	1.12 (1.04 to 1.20) p=0.003	1.14 (1.06 to 1.22) p<0.001
2	1.17 (1.08 to 1.26) p<0.001	1.20 (1.12 to 1.29) p<0.001
3	1.14 (1.05 to 1.24) p=0.002	1.17 (1.08 to 1.27) p<0.001
4	1.20 (1.11 to 1.29) p<0.001	1.23 (1.14 to 1.32) p<0.001
5	1.23 (1.13 to 1.35) p<0.001	1.26 (1.16 to 1.37) p<0.001

Model 1. Adjusted for age, sex and race.

Model 2. Adjusted for age, sex, race, educational status, height, weight, systolic BP, use of antihypertensive medication, smoking, alcohol, self-reported health status and estimated GFR.

Model 3. Adjusted for covariates in Model 2 plus NT-proBNP<sub>1-76</sub>.

Model 4. Adjusted for covariates in Model 2 plus any subclinical cardiovascular disease.

Model 5. Adjusted for covariates in Model 4 plus diabetes, LDL, HDL, triglycerides and hsCRP. Replacement of diabetes by HOMA-IR in participants not receiving glucose-lowering therapy did not materially alter the effect estimates.

\*SD=7.9 mg/L for total adiponectin and 5.9 mg/L for HMW adiponectin.

BP, blood pressure; GFR, glomerular filtration rate; HDL, high-density lipoprotein; HMW, high molecular weight; HOMA-IR, homeostasis model assessment-insulin resistance; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein.

### Paradoxical association

The finding of a direct association between adiponectin and incident AF is counterintuitive because the adipokine has insulin-sensitising, anti-inflammatory and anti-atherogenic properties,<sup>6</sup> and would therefore be expected to offset pathways implicated in the pathogenesis of AF.<sup>4 18</sup> Additionally, laboratory studies have highlighted adiponectin's in vitro ability to protect cardiomyocytes against various types of injury.<sup>19</sup> These experimental observations would support an association wherein lower, not higher, adiponectin levels lead to an increased risk of AF. Our work adds to the conflicting associations between adiponectin and adverse outcomes observed in different clinical settings.<sup>20</sup>

### Potential confounding

Several factors associated with chronic disease or older age that can raise adiponectin levels, and are therefore apt to confound an otherwise protective association between adiponectin and adverse cardiovascular events, have been cited as potential contributors to the paradox. These factors include the weight loss and sarcopenia particularly associated with HF and ageing-related decline, as well as renal insufficiency itself. In the present analyses, however, we controlled for height, weight, and eGFR and also excluded those with antecedent weight loss; none of these meaningfully attenuated the observed association between adiponectin and AF.

Another crucial potential confounder is natriuretic peptides, which signal cardiomyocyte stretch and heighten risk for AF,<sup>3 21</sup> while simultaneously stimulating adiponectin production by adipose tissue.<sup>22</sup> Adjustment for NT-proBNP<sub>1-76</sub>, however, did not materially influence the risk estimates. Nor did adjustment for left atrial diameter index, a time-averaged measure of impaired LV filling that is a strong determinant of AF incidence, is closely related to NT-proBNP<sub>1-76</sub>, and was associated with adiponectin levels here, meaningfully affect the observed

relationship. Hence, although the possibility of residual confounding by natriuretic peptides or other aforementioned factors cannot be excluded, these factors do not appear to account for the entirety of the positive association uncovered between adiponectin and AF.

We also excluded participants with prevalent CVD because previous work in this cohort and elsewhere shows that the relationship between adiponectin and adverse events differs between those with and without prevalent CVD. Nevertheless, a sensitivity analysis demonstrated similar, if modestly attenuated, findings when participants with and without prevalent CVD were combined.

### Possible mechanisms

One potential explanation for the adiponectin paradox draws on adiponectin's high circulating concentrations, and the adipokine's ability to promote opsonisation of apoptotic bodies.<sup>23</sup> These observations suggest that adiponectin serves a mass action function, distinct from its endocrine signalling properties, to effect clearance of dying cells and reduce the inflammation that would otherwise result from their accumulation. That higher adiponectin concentrations carry an adverse prognosis late in life<sup>24</sup> could therefore reflect an insufficient or ineffective counter-regulatory response to underlying disease processes.

Another possible explanation for pathologically increased levels of adiponectin is overproduction by muscle tissue. Previous work has demonstrated that, in the setting of mild-moderate HF, skeletal muscle exhibits increased expression of adiponectin with concomitant adiponectin resistance.<sup>25</sup> Human cardiomyocytes can also produce adiponectin, and heart-derived adiponectin secretion contributes modestly to circulating concentrations in older adults.<sup>26</sup> Human and rodent experiments likewise support the presence of a local cardiac adiponectin system regulated independently of systemic adiponectin,<sup>27</sup> although results on cardiac adiponectin resistance have been mixed.<sup>27–28</sup>

The mechanisms underlying the direct association between adiponectin levels and adverse outcomes, and as specifically documented here, AF, are ill defined. We have previously shown in the same cohort that the associations between total and HMW adiponectin and incident CVD or mortality are not monotonic, but U-shaped,<sup>7</sup> such that high or low levels are associated with heightened risk. Moreover, adjustment for putative intermediates of the adipokine's proposed cardiometabolic benefits abolished the associations in the lower range of adiponectin concentrations but had no effect upon or strengthened the associations in the upper range. These findings support the view of offsetting influences on adiponectin's relationships with these outcomes, wherein the favourable associations with metabolic factors, particularly at lower concentrations, determine the lower risk associated with rising adiponectin levels, whereas at higher concentrations, other deleterious and yet to be described influences predominate. Interestingly, the absence of an inverse association at the lower range of concentrations was also seen in relation to incident HF,<sup>9</sup> but there was evidence of a threshold effect that disappeared after consideration of putative metabolic and inflammatory intermediates. The basis for the lack of a similarly dampened or, in the case of CVD and mortality, inverse association in the lower range of adiponectin concentrations with regard to AF is unclear, but larger studies or meta-analytic approaches are required to more precisely define the relationships at this lower end of the adiponectin distribution. Still, taken together these observations suggest that adverse, but still incompletely characterised, influences on or of adiponectin

levels, such as interaction with T-cadherin or direct activation of complement,<sup>20</sup> prevail in determining their association with AF and, to a lesser extent, HF.

### Strengths and limitations

CHS is a well-characterised population-based study with long-term follow-up. Although the present epidemiological study cannot demonstrate causality, the prospective association proved robust in its independence from an extensive set of potential confounders, both through adjustment and restriction to participants without prevalent CVD. Mendelian randomisation analysis can allow assessment of the potential causal basis of such associations, but this approach is unsuitable in the present instance. This is because genetic variants known to influence adiponectin levels (*CDH13*, the T-cadherin gene, among others)<sup>29</sup> can also promote adverse cardiovascular outcomes, including AF, through adiponectin-independent mechanisms. Moreover, such genetic variants may also come under the influence of confounders (*AdipoQ* may be under transcriptional regulation by insulin).<sup>30</sup> Hence, we did not undertake Mendelian randomisation analyses here, since the requisite assumptions do not hold for the association in question.

Among other study limitations, we were unable to probe the contributions of distinct tissue sources of adiponectin to the observed association. Advances on the local cardiac adiponectin system will require further experimental work. We also did not have direct imaging measures of skeletal muscle mass or adipose-tissue distribution, which might have provided better characterisation of ageing-related determinants of adiponectin levels and disease outcomes. Moreover, we lacked concurrent echocardiography parameters, assessment for sleep apnoea, or measures of sex hormones, and future studies will need to investigate further how these factors relate to the association in question. Furthermore, the numbers of participants with prevalent atherosclerotic CVD and, particularly, HF, and corresponding incident AF events were modest, which limits power to detect effect modification by such conditions or appropriately characterise corresponding adiponectin-AF relationships. Focused study in larger cohorts will be necessary to address the nature of the association in the setting of pre-existing atherosclerotic CVD and HF, and whether the same interaction documented for mortality<sup>7</sup> applies for AF.

In addition, because our ascertainment of AF depended on annual ECGs and diagnostic codes from hospitalisation reviews or Centers for Medicare and Medicaid Services claims data, it may have failed to capture incident cases, particularly cases of paroxysmal AF. A Holter substudy in CHS, however, showed that annual ECGs and hospital diagnostic codes failed to capture only 1 of 819 (0.1%) episodes of AF. Last, the present findings will require independent replication in separate cohorts, and particularly in different race-ethnic groups.

### Study implications

The importance of controlling risk factors for AF was recently underscored by a report of the National Heart, Lung, and Blood Institute,<sup>18</sup> which stated that preventing inflammation could reduce cardiac fibrosis and remodelling. While the positive association between adiponectin and AF uncovered here is of moderate strength, which limits the adipokine's value for risk prediction, it is nonetheless of potential relevance for prevention because the high incidence of events in this age group<sup>1</sup> would translate into important absolute reductions. Notably, the association documented was independent of a wide array of potential confounders and mediators. This suggests that

additional pathways could be involved and that understanding their mechanistic basis could potentially open new approaches to therapeutic intervention for this most frequent of sustained cardiac dysrhythmias and its associated comorbidities.

### Key messages

#### What is already known on this subject?

Adiponectin has shown adverse associations with cardiovascular outcomes in older adults, which are paradoxical given its atheroprotective effects in the laboratory. Of two moderately powered population-based studies that have examined the link between total adiponectin and incident atrial fibrillation (AF), only one detected a significant association, which was positive, but adjustment for potential confounders was limited. The nature of the relationship when factors known to influence both adiponectin levels and AF are well accounted for remains uncertain.

#### What might this study add?

This investigation demonstrates a positive, rather than inverse or U-shaped, association between circulating adiponectin levels (both total and high-molecular-weight fraction) and incident AF in a large cohort of community-dwelling older adults. The study shows that this association is independent of an extensive array of potential confounders—including measures of adiposity, antecedent weight loss and, importantly, amino-terminal pro-B-type natriuretic peptide 1–76—and putative mediators.

#### How might this impact on clinical practice?

This robust positive association of moderate strength suggests that improved understanding of factors influencing or influenced by adiponectin could potentially expose new therapeutic targets for prevention of this most common dysrhythmia in older adults. Given the limited preventive options for AF, and the dysrhythmia's rising prevalence with the increase of life expectancy around the world, this association points up an important area of investigation.

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