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Sleep Apnea is Associated with Subclinical Myocardial Injury in the Community: The ARIC-SHHS Study

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"At a Glance Commentary": Obstructive sleep apnea (OSA) is associated with cardiovascular morbidity and mortality, particularly heart failure. We found that after adjustment for potential confounders, OSA severity was significantly associated with higher levels of hs-TnT, but not NT-proBNP, suggesting that subclinical myocardial injury caused by OSA may play a role in the subsequent risk of heart failure. Our findings suggest that high sensitivity troponin T may be an early marker of the adverse myocardial impact of OSA.

"This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org"

Abstract

Aims: Obstructive sleep apnea (OSA) is associated with cardiovascular morbidity and mortality, although the underlying mechanisms are not well understood. We aimed to determine whether more severe OSA, measured by the respiratory disturbance index (RDI), is associated with subclinical myocardial injury and increased myocardial wall stress

Methods and Results: 1,645 participants (62.5 ± 5.5 years and 54% women) free of coronary heart disease and heart failure and participating in both the Atherosclerosis Risk in the Communities and the Sleep Heart Health Studies underwent overnight polysomnography and measurement of high sensitivity Troponin T (hs-TnT) and N terminal pro B-type natriuretic peptide (NT-proBNP). OSA severity was defined using conventional clinical categories: none (RDI≤5), mild (RDI 5-15), moderate (RDI 15-30) and severe (RDI>30). Hs-TnT, but not NT-proBNP, was associated with OSA after adjusting for 17 potential confounders (p=0.02). Over a median of 12.4 [IQR 11.6-13.1] years follow up, hs-TnT was related to risk of death or incident heart failure in all OSA categories (p≤0.05 in each category).

Conclusion: In middle aged to older individuals OSA severity is independently associated with higher levels of hs-TnT, suggesting that subclinical myocardial injury may play a role in the association between OSA and risk of heart failure. OSA was not associated with NT-proBNP levels after adjusting for multiple possible confounders.

Key Word List: Sleep disorders, Troponin T, NT-proBNP, Risk factors

Background

Obstructive sleep apnea (OSA) affects at least 2-6% of the U.S. population[1] and is associated with multiple cardiovascular (CV) co-morbidities.[2,3] Epidemiologic studies suggest an association between OSA and both coronary heart disease (CHD) and heart failure (HF).[4] Repetitive apneas leading to intermittent nocturnal hypoxemia and sympathetic hyperactivity are thought to result in systemic[2] and pulmonary hypertension,[5] with resulting increased myocardial load, wall stress, and injury. However, a causal relationship between OSA and cardiovascular outcomes has been difficult to establish due to the strong association of OSA with other CV risk factors.

Cardiac troponins reflect myocardial injury. Previous studies have not demonstrated a significant association between OSA severity and troponin levels.[6] High sensitivity troponin T (hs-TnT) levels, measured by newer assays with a 10-fold lower detection range than traditional assays, are predictive of both CHD and HF in the general population.[7] However, the relationship between OSA severity and hs-TnT levels has not been well described.[8] N-terminal pro B type natriuretic peptide (NT-proBNP) levels reflect ventricular wall stress and carry prognostic value across a spectrum of cardiovascular disease.[9] Previous studies of the relationship between natriuretic peptides and OSA have shown conflicting results.[10,11,12]

We hypothesized that more severe OSA would be significantly and independently associated with subclinical myocardial injury (elevated hs-TnT) and increased ventricular wall stress (elevated NT-proBNP). We also explored whether the relationship between OSA and these pathway biomarkers would explain the association between OSA and incident cardiovascular disease.

Methods

Population

The study population was comprised of 1,645 participants in both the Atherosclerosis Risk in Communities (ARIC) Study and the Sleep Heart Health Study (SHHS) who underwent overnight home polysomnography and measurement of hs-TnT and NT-proBNP, and were free of prevalent coronary heart disease (CHD) or heart failure (HF) at baseline assessment. ARIC is a prospective epidemiologic cohort study designed to investigate the etiology and natural history of clinical and subclinical atherosclerosis.[13] 15,792 middle-aged participants were enrolled between 1987 and 1989. Between 1996 and 1998, surviving participants underwent a fourth visit at which time blood samples were obtained from which soluble biomarker levels were measured.[7] The SHHS is a prospective cohort study that recruited participants older than 40 years from 9 cohorts, including 1,920 participants from ARIC (from Minnesota and Maryland's sites).[14] All underwent overnight home polysomnography and lung function tests between 1995-1998.[14] The SHHS visit and the fourth ARIC visit were performed independently of each other during the same three-year period. Therefore, assessments of OSA severity and clinical and laboratory values were not performed at the same time (median difference of ARIC visit relative to the SHHS visit 172 days [range -51 to 387 days]).

Demographics, clinical characteristics, and laboratory values were obtained from ARIC visit 4 data. Pulmonary function test results were obtained from the SHHS visit. Prevalent HF or CHD was defined as either prevalent HF or CHD at ARIC visit 1 or incident CHD or HF between ARIC visit 1 and the later of either ARIC visit 4 or the SHHS visit. Definitions of prevalent HF and CHD, and of incident events during follow-up, have been previously described.[15,16,17,18]

Of 1,892 participants who underwent both ARIC and SHHS visits, 201 with prevalent CHD or HF at the time of the last visit performed of either SHHS or ARIC visit 4 were excluded. Forty-six were excluded due to missing hs-TnT data, leaving 1645 participants in the hs-TnT analysis, and one additional patient had missing NT-proBNP data leaving 1644 participants in the NT-proBNP analysis. (Supplemental Data: Supplemental Figure 1)

Polysomnography

All participants underwent one overnight full polysomnography which was centrally interpreted as previously published.[14] Apnea was defined as a cessation or nearly complete cessation of airflow. Hypopnea was defined as a ≤70% reduction from baseline airflow for at least 10 seconds. Only events associated with a ≥4% oxygen desaturation were included in the Respiratory Disturbance Index (RDI), a measure of OSA severity.[19] The severity of OSA by RDI was defined using conventional clinical categories: none (RDI≤5), mild (RDI >5 and ≤15), moderate (RDI >15 to ≤30), and severe (RDI>30).

Cardiac Biomarkers

We assessed hs-TnT as a marker of subclinical myocardial injury and NT-proBNP as a marker of increased ventricular wall stress. Importantly, both biomarkers are prognostic of incident heart failure and mortality.[7,9] Blood samples were taken at the time of ARIC visit 4 and plasma was stored centrally at -80°C. Hs-TnT was measured using a highly sensitive assay (Elecsys Troponin T, Roche diagnostics, Indianapolis, IN) with a lower limit of measurement, as defined by the manufacturer, of 0.003μg/L).[7] NT-proBNP was measured using electrochemiluminescent immunoassay (Roche Diagnostics) with a lower detection limit of ≤5 pg/mL.[7] Participants with undetectable NT-proBNP were considered to have a level of 2.5 pg/mL.

Clinical Outcomes

Cardiovascular outcomes assessed were all-cause mortality or incident CHD, all-cause mortality or incident HF, all-cause mortality, and the composite of all-cause mortality, incident CHD and incident HF, occurring after the later of ARIC visit 4 or the SHHS visit.

Statistical Analysis

Summary data are presented as the mean and standard deviation for data that is normally distributed and median and interquartile range for non-normally distributed data. Categorical variables are expressed as proportions. For regression modeling, hs-TnT and NT-proBNP were modeled separately as outcome variables. RDI and was modeled continuously using the log transformed value to achieve normality and was modeled categorically using clinically defined thresholds as noted above. NT-proBNP was modeled continuously using log transformed values. Hs-TnT was heavily skewed and was modeled as an ordinal categorical variable using 5 categories, as explained in Supplemental data. As the lower limit of measurement may differ from the lower limit of detection for the Roche hsTnT assay[20] we repeated our analysis using a higher threshold, the rational and results of which are shown as shown in the Supplemental Data. As many variables associated with OSA may act as either confounders or mediators of the OSA-biomarker relationship, we employed several additive multivariable models adjusting for sequentially more variables. Model covariates were selected based on *a priori* knowledge and variables significantly associated with the predictor variable of interest in univariate analysis (see Supplemental Data section). For NT-proBNP, linear regression was employed. For hs-TnT, ordinal logistic regression was used. As an independent relationship was noted between hs-TnT and OSA measures, the association of hs-TnT levels with risk of cardiovascular events within categories of OSA severity (defined by RDI) was investigated using univariate and multivariable

Cox proportional hazards models. To address potential limitations to our analysis we performed three different sensitivity analysis to support the strength of our results, as described in the Supplemental Data section. All analysis was performed using STATA 11.1 (StataCorp LP. 2009. Texas).

Results

Demographic, clinical characteristics, and cardiac biomarker levels by OSA category are summarized in Table 1 (and Supplemental Table 1). More severe OSA was associated with older age, male gender, higher BMI, a higher prevalence of previous smoking, hypertension, and diabetes, and a lower eGFR. In unadjusted analysis, higher RDI was associated with higher hs-TnT levels (Spearman correlation coefficient= 0.25, $p<0.0001$; Table 2, Supplemental Table 2 Figure 1). Similarly, based on ordinal logistic regression models, a doubling of RDI was associated with an odds ratio of 1.24 for being in a higher hs-TnT category. A change from a lower OSA category to a more severe category was associated with an odds ratio of 1.45 [1.32-1.60] for being in a higher hs-TnT category. The relationship between RDI and hs-TnT remained significant in multivariable ordinal logistic regression models adjusting for age, gender, and BMI (Model 2, $p = 0.007$; Table 2, Supplemental Table 2) as well as in fully adjusted models (Model 5, $p = 0.02$; Table 2, Supplemental Table 2). This association between RDI and hs-TnT was driven largely by significantly higher hs-TnT levels in the severe compared to no OSA group (severe vs no OSA: age-, gender-, BMI-adjusted $p=0.03$; fully adjusted $p = 0.06$; Figure 1).

In unadjusted analysis, a weak, but significant negative correlation between RDI and NT-proBNP was noted (Pearson correlation coefficient=-0.11, $p<0.0001$), suggesting higher RDI

was associated with lower NT-proBNP. This association remained significant after adjusting for gender and age (p=0.0007; Table 2, Supplemental Table 2), but was greatly attenuated after additional adjustment for BMI (p=0.05), and was no longer significant after further adjustment (p=0.19 in Model 5; Table 2, Supplemental Table 2).

Participants were followed up for a median of 12.4 [IQR 11.6-13.1] years with a total of 222 deaths, 212 participants experiencing incident CHD events, and 122 participants experiencing incident HF. A total of 427 participants died or experienced an incident CV event during the follow-up period. Within each OSA group, higher hs-TnT level was associated with a higher hazard ratio for death or incident HF, death or incident CHD, and the composite of death, incident HF, or incident CHD, consistently from the unadjusted to the fully adjusted model (Table 3, Supplemental Table 3). For death or incident HF in particular, this relationship was most robust in the severe OSA group and least robust in the no OSA group (p for interaction = 0.04).

Similar results to the primary analysis were found when the analysis was repeated using 0.005 µg/L as the limit of detection, instead of 0.003 µg/L (Supplemental Tables 1, 2 and 3). Sensitivity analyses restricting the population to participants with RDI and biomarker measurement performed within 12 months of each other (n=1,025), to participants with complete data (n=1,630), or to participants with eGFR ≥60 ml/min/1.73 m2 (n=1,568) were all consistent with the results found in the overall study population. Similarly, sensitivity analysis using uniform cut-offs for hs-TnT categories for both genders demonstrated consistent results (see Supplemental data).

Discussion

Among 1,655 community dwelling participants without prevalent CHD or HF, more severe OSA was significantly associated with higher hs-TnT levels, even after adjusting for 17 potential confounders, a relationship that was particularly strong among women compared to men. Furthermore, hs-TnT levels were associated with incident cardiovascular disease events or death in each category of OSA severity, especially for incident HF. This association seemed to be largely driven by higher hs-TnT in participants with severe OSA compared with the no OSA group. In contrast, no association was noted between OSA and NT-proBNP levels after adjusting for potential confounders, most notably BMI.

To our knowledge, this community-based study is one of the first to demonstrate an independent association between sleep apnea severity and circulating levels of hs-TnT after adjusting for potential confounders. Since OSA is significantly associated with multiple established CV risk factors there has been controversy over whether OSA is causally related to incident CHD or HF.[2,3] OSA is characterized by repetitive episodes of nocturnal hypoxemia, with associated sympathetic activation, hypertension, and tachycardia. The nocturnal hypoxemia likely contributes to ischemia, as supported by several publications demonstrating ECG changes consistent with ischemia occurring in association with apneas, although this finding has not been universal.[21] OSA may also cause myocardial stress and injury due to the increased load on both the right and left ventricles resulting from marked swings in intra-thoracic pressure during obstructed breathing, as well as associated paroxysmal nocturnal and more chronic systemic and pulmonary hypertension, a mechanism supported by the association of OSA with biventricular hypertrophy.[22,23] The independent relationship founded between OSA severity and higher circulating hs-TnT would therefore help inform our understanding of the association between

OSA and CV outcomes by suggesting that subclinical myocardial injury may be a possible causal link.

Although troponin assays are used commonly in cardiovascular research and clinical settings, there has been little prior research that has addressed this marker in association with OSA. Previous studies have not demonstrated a significant relationship between TnT levels and OSA severity,[6] however, newer hs-TnT assays detect TnT levels in a much higher proportion of disease-free subjects than traditional TnT assays.[8] Similar to our study, using an hs-TnT limit of measurement of 0.003 µg/L, Randby *et al* recently evaluated the association between OSA severity and the presence of detectable hs-TnT in 505 individuals from a community-based cohort.[8] The association of OSA with hs-TnT was not significant after adjustment of potential confounders. Importantly, unlike our study, their population was younger (30-65 years old), and was enriched for prevalent cardiovascular disease. Possibly related to the younger age and lower prevalence of hypertension and diabetes in their population, only 43% of subjects had detectable hs-TnT, compared to 65% of subjects in our study. Additionally, they examined the association of OSA severity with the presence of measurable hs-TnT, while we assessed its relationship with both the presence and the magnitude of hs-TnT level, which should enhance our study's power.

Further supporting a mechanistic link between OSA, hs-TnT, and CV events – and consistent with findings in the overall ARIC population – hs-TnT level was a significant predictor of incident CHD and HF in our study population. In addition, hs-TnT remained a significant predictor within each category of OSA severity, with greater risk associated with elevated hs-TnT levels in more severe OSA categories. The significant interaction found between OSA severity and hs-TnT levels in predicting incident HF suggests the possibility that hs-TnT levels may be a particularly important prognostic marker in patients with severe OSA.

We observed a negative association between OSA severity and NT-proBNP levels in unadjusted analysis. However, BMI is a key confounder of this relationship, as obesity is a powerful risk factor for OSA[24] but also associated with inappropriately low NT-proBNP levels.[25] Indeed, in our study, the negative association between OSA severity and NT-proBNP levels was markedly attenuated after adjustment by BMI and no longer significant after further adjustment. Although previous studies have shown conflicting results,[10,11,12] our results are concordant with those of the largest prior study by Patwardham *et al* who found no independent association between OSA severity and circulating natriuretic peptides levels in the Framingham-Offspring/SHHS study.[11]

Several limitations of this analysis should be noted. Our analysis was cross-sectional in design and precludes conclusions regarding causality. While multiple additive multivariable models were employed, residual confounding cannot be excluded. Conversely, many potential confounders may also act as mediators between OSA and the outcomes of interest, potentially leading to greater Type 2 error. Biomarkers were not measured coincident with polysomnography, with a difference between the two measurements of greater than one year in many participants. Although biomarker levels may change over time, individuals with intercurrent cardiovascular events between polysomnography and biomarker assessment were excluded. In addition, prior studies suggest that sleep apnea classification remains largely stable over several months to years[26,27] suggesting that at the time of biomarkers determination OSA status was similar that assessed at the time of the polysomnography. Additionally, a sensitivity analysis restricting the population to those with sleep variables and soluble biomarkers ascertained within 1 year of each other demonstrated concordant results with the primary analysis. Information regarding the time of collection of blood was not available. Although NT-

proBNP has the longest half-life of the natriuretic peptide biomarkers, it is still short at approximately 120 minutes,[28] This may diminish our ability to detect an association of OSA severity with NT-proBNP levels.[11] Although our study is one of the largest to our knowledge to assess the relationship between uniformly assessed OSA severity and hsTnT, the limited number of participants in the most severe OSA category may limit our power to detect associations.

Conclusions

After adjustment for potential confounders, OSA severity is associated with higher levels of hs-TnT in middle aged to older individuals, suggesting that subclinical myocardial injury caused by OSA may play a role in the subsequent risk of HF. Further research is needed to identify the role of subclinical ischemia in OSA, and the potential utility of monitoring hs-TnT levels as a prognostic marker in individuals with OSA but without prevalent cardiovascular disease.

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Figure Legends

Figure 1. Whisker box-plot of hs-TnT levels by OSA category. Hs-TnT is shown using a logarithmic scale. Values under the limit of detection (0.003 µg/L) are assigned to a value of 0.002 µg/L). *Unadjusted ordinal logistic regression. †Multivariable ordinal logistic regression adjusted by age, BMI, smoking status, alcohol intake, hypertension, diabetes, chronic lung disease, pulmonary function tests, eGFR, systolic blood pressure and blood levels of total cholesterol, LDL, HDL, triglycerides and insulin (model 5).

Tables

Table 1. Baseline demographics, clinical characteristics, and cardiac biomarker levels in the study population overall and by category of OSA severity.

	Overall (n=1655)	OSA Severity				P for trend
		None (n=910)	Mild (n=476)	Moderate (n=168)	Severe (n=101)	
Age (years)	62.5±5.5	61.8±5.5	63.3±5.4	63.4±5.3	64.2±5.3	<0.0001
Female	897 (54%)	595 (65%)	208 (44%)	59 (35%)	35 (35%)	<0.0001
White	1640 (99%)	908 (99.8%)	465 (98%)	167 (99%)	100 (99%)	0.01*
Co-morbidities						
Hypertension	621 (38%)	301 (33%)	195 (41%)	71 (42%)	54 (53%)	<0.0001*
Diabetes	180 (11%)	65 (7%)	73 (15%)	25 (15%)	17 (17%)	<0.0001*
Prior stroke	23 (1.4%)	10 (1.1%)	8 (1.7%)	3 (1.8%)	2 (2%)	0.26*
Atrial fib/flutter	13 (0.8%)	8 (0.9%)	3 (0.6%)	1 (0.6%)	1 (1%)	0. 88*
Smoking						
Current	169 (10%)	118 (13%)	29 (6%)	14 (8%)	8 (8%)	0.0002*
Former	773 (47%)	392 (43%)	247 (52%)	91 (54%)	51 (51%)	0.0004*
Asthma	122 (7%)	62 (7%)	37 (8%)	18 (11%)	5 (5%)	0.37*

COPD	119 (7%)	66 (7%)	39 (8%)	11 (7%)	3 (3%)	0.55*
BMI (kg/m2)	28.6±5.0	27.0±4.3	29.6±4.8	31.8±5.3	33.4±5.0	<0.0001
SBP (mmHg)	126±18	123±17	128±18	128±18	130±16	<0.0001
DBP (mmHg)	71±9	70±9	71±10	73±10	73±10	<0.0001
FEV1 (L)	2.90±0.71	2.84±0.69	2.97±0.71	3.00±0.74	2.93±0.63	<0.0001
FVC (L)	3.91±0.93	3.85±0.91	4.00±0.93	4.04±0.90	3.91±0.83	<0.0003
eGFR (mL/min/1.73 m2)	83.3±13.1	83.9±13.0	82.5±13.4	83.7±13.0	81.5±12.4	0.03
NT-proBNP (pg/mL)	67 (34 – 122)	71 (39 – 129)	67 (33 – 119)	50 (24 – 95)	52 (24 – 118)	<0.001†
Hs-TnT (µg/L)	0.004 (<0.003-0.007)	0.004 (<0.003 – 0.006)	0.005 (<0.003 – 0.008)	0.005 (0.003 – 0.009)	0.006 (0.004 – 0.010)	<0.0001¥
Hs-TnT category						

Undetectable (< 0.003 µg/L)	575 (35%)	381 (42%)	132 (28%)	41 (25%)	21 (21%)	<0.0001
M: 0.003 – 0.005 µg/L F:0.003 –0.004 µg/L	370 (22%)	198 (22%)	117 (25%)	39 (23%)	16 (16%)	
M: 0.006 – 0.008 µg/L F: 0.005 ng/L	277 (17%)	139 (15%)	84 (18%)	31 (19%)	23 (23%)	
M: 0.009 – 0.013 µg/L F: 0.006 – 0.007 µg/L	235 (14%)	108 (12%)	77 (16%)	34 (20%)	16 (16%)	
M: ≥0.014 µg/L F: ≥0.008 µg/L	188 (11%)	78 (9%)	65 (14%)	21 (13%)	24 (24%)	

*Based on two sample Wilcoxon rank-sum test. † Based in logarithmic transformed values for biomarkers. ¥ Based in non-parametric trend test.

Table 2: Univariate and multivariable models assessing the relationship between RDI and cardiac biomarkers.

	Hs-TnT			NT-proBNP		
	N	**Beta coefficient ± Std Error**	**P value**	**N**	**Beta coefficient ± Std Error**	**P value**
Unadjusted	1645	0.27 ± 0.03	<0.0001	1644	-0.08 ± 0.02	<0.0001
Model 1	1645	0.15 ± 0.03	<0.0001	1644	-0.06 ± 0.02	0.0007
Model 2	1642	0.10 ± 0.04	0.007	1641	-0.04 ± 0.02	0.05
Model 3	1637	0.08 ± 0.04	0.03	1636	-0.04 ± 0.02	0.04
Model 4	1633	0.09 ± 0.04	0.02	1632	-0.03 ± 0.02	0.08
Model 5	1631	0.09 ± 0.04	0.02	1630	-0.02 ± 0.02	0.19

Analysis for hs-TnT based on ordinal logistic regression. Analysis for NT-proBNP based on linear regression using logarithmic transformed values. Regression models: Model 1: adjusted by age and gender; Model 2: additionally adjusted by BMI; Model 3: additionally adjusted by

smoking status, alcohol intake, hypertension and diabetes; Model 4: additionally adjusted by pulmonary function tests (FEV1 and FVC) and chronic lung disease; Model 5: additionally adjusted by systolic blood pressure, estimated glomerular filtration rate (eGFR) and blood levels of insulin, total cholesterol, LDL, HDL and triglycerides. Reported regression coefficients are those associated with log(RDI).

Table 3. Multivariable adjusted hazard ratios for incident death or CV events associated with hs-TnT level by category of OSA severity.

	Number of events/total at risk	Hazard Ratio (95% CI)	P values
CHD/Death			
Overall	380/1631	1.17 (1.07-1.26)	<0.001
Category of OSA Severity			
None	182/891	1.13 (1.01-1.28)	0.04
Mild	116/472	1.18 (1.02-1.36)	0.03
Moderate	49/165	1.32 (1.04-1.70)	0.03
Severe	33/99	1.89 (1.28-2.80)	0.001
HF/Death			
Overall	283/1627	1.27 (1.16-1.39)	<0.0001
Category of OSA Severity			
None	132/891	1.19 (1.04-1.36)	0.009
Mild	92/472	1.31 (1.11-1.53)	0.001
Moderate	33/165	1.34 (1.00-1.80)	<0.05
Severe	26/99	2.30 (1.42-3.72)	0.001
Death			

Overall	216/1627	1.19 (1.07-1.32)	0.001
Category of OSA Severity			
None	101/891	1.12 (0.96-1.30)	0.16
Mild	67/472	1.12 (0.94-1.36)	0.23
Moderate	29/165	1.17 (0.85-1.63)	0.34
Severe	19/99	1.86 (1.08-3.22)	0.02
CHD/HF/Death			
Overall	418/1627	1.22 (1.13-1.31)	<0.0001
Category of OSA Severity			
None	199/891	1.16 (1.04-1.30)	0.009
Mild	132/472	1.25 (1.09-1.43)	0.001
Moderate	51/165	1.39 (1.09-1.78)	0.008
Severe	36/99	1.91 (1.31-2.81)	0.001

Estimates derived from multivariable Cox proportional hazards models with the following model covariates: age, gender, body mass index, smoking status, hypertension, diabetes, alcohol intake, pulmonary function variables (FEV1 and FVC), COPD status, systolic blood pressure, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, insulin level, and estimated glomerular filtration rate (eGFR).

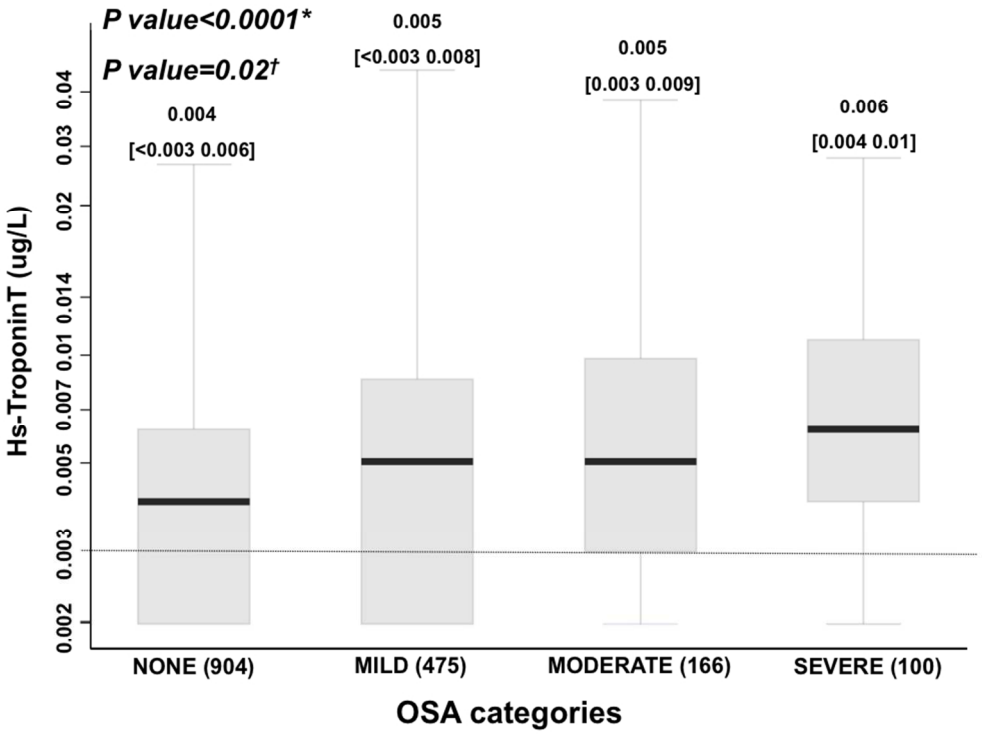

Figure 1. Whisker box-plot of hs-TnT levels by OSA category. Hs-TnT is shown using a logarithmic scale. Values under the limit of detection (0.003 µg/L) are assigned to a value of 0.002 µg/L). *Unadjusted ordinal logistic regression. †Multivariable ordinal logistic regression adjusted by age, BMI, smoking status, alcohol intake, hypertension, diabetes, chronic lung disease, pulmonary function tests, eGFR, systolic blood pressure and blood levels of total cholesterol, LDL, HDL, triglycerides and insulin (model 5).
352x264mm (72 x 72 DPI)

SUPLEMENTAL DATA:

Methods:

As the distribution of hs-TnT was heavily skewed and thus could not be transformed to achieve normality, hs-TnT was modeled as an ordinal categorical variable using 5 categories based on our population's hs-TnT distribution. As the population distribution of hs-TnT is known to vary by gender,[1,2] we employed gender-specific hs-TnT categories: the first category was defined by undetectable values based on limit of measurement provided by the manufacturer (0.003 μg/L), the fifth category was defined by the 90th percentile (≥0.014 μg/L for males and ≥0.008 μg/L for females), and the remainder of participants were divided into tertiles (for males: 0.003-0.005, 0.006-0.008, and 0.009-0.013 μg/L; for females: 0.003-0.004, 0.005, and 0.006-0.007 μg/L).

Although the limit of measurement for the Roche hs-TnT assay used in this study is 0.003 μg/L, the concordance of hs-TnT values using the assay employed in this study compared to the newer 4th generation assay by Roche is worse for values <0.005 μg/L. As a result, this higher threshold of 0.005 μg/L has been proposed as a more appropriate limit of detection for this hs-TnT assay.(3) Therefore, we repeated our analysis using a limit of detection of 0.005 μg/L, instead of 0.003 μg/L, as shown in the supplemental data. In this analysis, hs-TnT was modeled as an ordinal categorical variable using 5 categories employing gender-specific cutoffs: first category was defined by undetectable values based on limit of quantification (0.005 μg/L), the fifth category was defined by the 90th percentile (≥0.014 μg/L for males and ≥0.008 μg/L for females), and the remainder of participants were divided into tertiles (for males: 0.005-0.006, 0.007-0.009, and 0.010-0.013 μg/L; for females: 0.005, 0.006, and 0.007 μg/L).

Therefore five regression models were constructed: Model 1 included age and gender; Model 2 additionally adjusted for body mass index; Model 3 additionally adjusted for smoking status, hypertension, diabetes and alcohol intake; Model 4 additionally adjusted for pulmonary function variables (FEV1 and FVC) and COPD status; Model 5 additionally adjusted for systolic blood pressure, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, insulin level, and estimated glomerular filtration rate (eGFR) measured at ARIC visit 4.[4]

As polysomnography and cardiac biomarkers were not assessed at the same time point, we performed a sensitivity analysis to assess the potential impact of this temporal difference in the relationship between OSA and cardiac biomarkers, restricting the analysis to the 1,025 participants with the OSA assessment and biomarker assessment occurring within one year of each other. To assess the potential impact of missing data, all analyses were also repeated including only the 1,630 participants with complete data for all covariates. A third sensitivity analysis was performed excluding 87 participants with eGFR lower than 60 ml/min to assess the potential impact of renal dysfunction on biomarker levels. Finally, we performed a sensitivity analysis using uniform cut-offs for hs-TnT categories for both genders (Supplemental Table 4).

Supplemental Tables and Figures

Supplemental Table 1. Distribution of hs-TnT categories in the overall population and by category of OSA severity using a limit of detection of 0.005 µg/L, instead of 0.003 µg/L.

	Overall (n=1645)	OSA Severity				P for trend
		None (n=904)	Mild (n=475)	Moderate (n=166)	Severe (n=100)	
Hs-TnT category						
Undetectable (< 0.005 µg/L)	853 (52%)	538 (60%)	210 (44%)	72 (43%)	33 (33%)	<0.0001
M: 0.005 – 0.006 µg/L F: 0.005 µg/L	253 (15%)	133 (15%)	80 (17%)	23 (14%)	17 (17%)	
M: 0.007 – 0.009 µg/L F: = 0.006 µg/L	217 (13%)	105 (12%)	68 (14%)	29 (17%)	15 (15%)	
M: 0.010 – 0.013 µg/L F:= 0.007 µg/L	134 (8%)	50 (6%)	52 (11%)	21 (13%)	11 (11%)	
M:>0.013 µg/L F: >0.008 µg/L	188 (11%)	78 (9%)	65 (14%)	21 (13%)	24 (24%)	

*Based on two sample Wilcoxon rank-sum test. † Based in logarithmic transformed values for biomarkers. ¥ Based in non-parametric trend test.

Supplemental Table 2: Univariate and multivariable models assessing the relationship between RDI and hs-TnT using a limit of detection of 0.005 µg/L, instead of 0.003 µg/L.

	Hs-TnT		
	N	**Beta coefficient ± Std Error**	**P value**
Unadjusted	1645	0.29 ± 0.03	<0.0001
Model 1	1645	0.15 ± 0.04	<0.0001
Model 2	1642	0.09 ± 0.04	0.02
Model 3	1637	0.07 ± 0.04	0.08
Model 4	1633	0.08 ± 0.04	0.05
Model 5	1631	0.08 ± 0.04	0.04

Analysis for hs-TnT is based on ordinal logistic regression. Regression models: Model 1: adjusted by age and gender; Model 2: additionally adjusted by BMI; Model 3: additionally adjusted by smoking status, alcohol intake, hypertension and diabetes; Model 4: additionally adjusted by pulmonary function tests (FEV1 and FVC) and chronic lung disease; Model 5: additionally adjusted by systolic blood pressure, estimated glomerular filtration rate (eGFR) and blood levels of insulin, total cholesterol, LDL, HDL and triglycerides. Reported regression coefficients are those associated with log(RDI).

Supplemental Table 3. Multivariable adjusted hazard ratios for incident death or CV events associated with hs-TnT level by category of OSA severity, using an hsTnT limit of detection of 0.005 µg/L, instead of 0.003 µg/L. Estimates derived from multivariable Cox proportional hazards models with the following model covariates: age, gender, body mass index, smoking status, hypertension, diabetes, alcohol intake, pulmonary function variables (FEV1 and FVC), COPD status, systolic blood pressure, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, insulin level, and estimated glomerular filtration rate (eGFR). P for interaction between hs-TnT categories and OSA severity when predicting HF or death=0.09

	Number of events/total at risk	**Hazard Ratio (95% CI)**	**P values**
CHD/Death			
Overall	380/1631	1.16 (1.08-1.25)	<0.001
Category of OSA Severity			
None	182/891	1.17 (1.05-1.31)	0.006
Mild	116/472	1.13 (1.00-1.29)	0.06
Moderate	49/165	1.25 (1.01-1.56)	0.04
Severe	33/99	1.73 (1.26-2.38)	0.001
HF/Death			
Overall	283/1627	1.23 (1.14-1.34)	<0.0001
Category of OSA Severity			

None	132/891	1.17 (1.03-1.33)	0.01
Mild	92/472	1.23 (1.08-1.42)	0.004
Moderate	33/165	1.29 (1.00-1.66)	0.05
Severe	26/99	1.91 (1.29-2.83)	0.001
Death			
Overall	216/1627	1.15 (1.05-1.27)	0.004
Category of OSA Severity			
None	101/891	1.15 (0.99-1.32)	0.06
Mild	67/472	1.08 (0.91-1.28)	0.37
Moderate	29/165	1.20 (0.92-1.56)	0.18
Severe	19/99	1.60 (1.07-2.40)	0.02
CHD/HF/Death			
Overall	418/1631	1.20 (1.12-1.29)	<0.0001
Category of OSA Severity			
None	199/891	1.18 (1.06-1.31)	0.003
Mild	132/472	1.21 (1.07-1.37)	0.001
Moderate	51/165	1.31 (1.05-1.62)	0.02
Severe	36/99	1.72 (1.26-2.35)	0.001

Supplemental Table 4. Univariate and multivariable models assessing the relationship between RDI and hs-TnT, using uniform hsTnT category cut-offs between genders. hsTnT limit of detection is 0.003 μg/L.

	Hs-TnT with gender-specific hs-TnT category cut-offs			**Hs-TnT with the same categories' cut-off by gender**		
	N	**Beta coefficient ± Std Error**	**P value**	**N**	**Beta coefficient ± Std Error**	**P value**
Unadjusted	1645	0.27 ± 0.03	<0.0001	1645	0.31 ± 0.03	<0.0001
Model 1	1645	0.15 ± 0.03	<0.0001	1645	0.15 ± 0.03	<0.0001
Model 2	1642	0.10 ± 0.04	0.007	1642	0.09 ± 0.04	0.02
Model 3	1637	0.08 ± 0.04	0.03	1637	0.07 ± 0.04	0.07
Model 4	1633	0.09 ± 0.04	0.02	1633	0.07 ± 0.04	0.05
Model 5	1631	0.09 ± 0.04	0.02	1631	0.08 ± 0.04	0.04

Supplemental References:

[1] Keller T, Ojeda F, Zeller T, Wild PS, Tzikas S, Sinning CR, Peetz D, Münzel T, Blankenberg S, Lackner KJ. Defining a reference population to determine the 99th percentile of a contemporary sensitive cardiac troponin I assay. *Int. J. Cardiol.* 2013; 167:1423-9.

[2] Eggers KM, Jaffe AS, Lind L, Venge P, Lindahl B. Value of Cardiac Troponin I Cutoff Concentrations below the 99th Percentile for Clinical Decision-Making. *Clinical Chemistry*. 2008;55:85–92

[3] Saenger AK, Beyrau R, Braun S, Cooray R, Dolci A, Freidank H, Giannitsis E, Gustafson S, Handy B, Katus H, Melanson SE, Panteghini M, Venge P, Zorn M, Jarolim P, Bruton D, Jarusch J, Jaffe AS. Multicenter analytical evaluation of a high-sensitivity troponin T assay. *Clin Chimic Acta.* 2011; 412: 748-754.

[4] Matsushita K, Selvin E, Bash LD, Astor BC, Coresh J. Risk implications of the new CKD Epidemiology Collaboration (CKD-EPI) equation compared with the MDRD Study equation for estimated GFR: the Atherosclerosis Risk in Communities (ARIC) Study. *Am J Kidney Dis*. 2010;55:648–659.

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Supplemental Tables and Figures

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M: 0.007 – 0.009 µg/L F: = 0.006 µg/L	217 (13%)	105 (12%)	68 (14%)	29 (17%)	15 (15%)	
M: 0.010 – 0.013 µg/L F:= 0.007 µg/L	134 (8%)	50 (6%)	52 (11%)	21 (13%)	11 (11%)	
M:>0.013 µg/L F: >0.008 µg/L	188 (11%)	78 (9%)	65 (14%)	21 (13%)	24 (24%)	

*Based on two sample Wilcoxon rank-sum test. † Based in logarithmic transformed values for biomarkers. ¥ Based in non-parametric trend test.

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	Hs-TnT		
	N	**Beta coefficient ± Std Error**	**P value**
Unadjusted	1645	0.29 ± 0.03	<0.0001
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Analysis for hs-TnT is based on ordinal logistic regression. Regression models: Model 1: adjusted by age and gender; Model 2: additionally adjusted by BMI; Model 3: additionally adjusted by smoking status, alcohol intake, hypertension and diabetes; Model 4: additionally adjusted by pulmonary function tests (FEV1 and FVC) and chronic lung disease; Model 5: additionally adjusted by systolic blood pressure, estimated glomerular filtration rate (eGFR) and blood levels of insulin, total cholesterol, LDL, HDL and triglycerides. Reported regression coefficients are those associated with log(RDI).

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	Number of events/total at risk	**Hazard Ratio (95% CI)**	**P values**
CHD/Death			
Overall	380/1631	1.16 (1.08-1.25)	<0.001
Category of OSA Severity			
None	182/891	1.17 (1.05-1.31)	0.006
Mild	116/472	1.13 (1.00-1.29)	0.06
Moderate	49/165	1.25 (1.01-1.56)	0.04
Severe	33/99	1.73 (1.26-2.38)	0.001
HF/Death			
Overall	283/1627	1.23 (1.14-1.34)	<0.0001
Category of OSA Severity			

None	132/891	1.17 (1.03-1.33)	0.01
Mild	92/472	1.23 (1.08-1.42)	0.004
Moderate	33/165	1.29 (1.00-1.66)	0.05
Severe	26/99	1.91 (1.29-2.83)	0.001
Death			
Overall	216/1627	1.15 (1.05-1.27)	0.004
Category of OSA Severity			
None	101/891	1.15 (0.99-1.32)	0.06
Mild	67/472	1.08 (0.91-1.28)	0.37
Moderate	29/165	1.20 (0.92-1.56)	0.18
Severe	19/99	1.60 (1.07-2.40)	0.02
CHD/HF/Death			
Overall	418/1631	1.20 (1.12-1.29)	<0.0001
Category of OSA Severity			
None	199/891	1.18 (1.06-1.31)	0.003
Mild	132/472	1.21 (1.07-1.37)	0.001
Moderate	51/165	1.31 (1.05-1.62)	0.02
Severe	36/99	1.72 (1.26-2.35)	0.001

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	Hs-TnT with gender-specific hs-TnT category cut-offs			Hs-TnT with the same categories' cut-off by gender		
	N	Beta coefficient ± Std Error	P value	N	Beta coefficient ± Std Error	P value
Unadjusted	1645	0.27 ± 0.03	<0.0001	1645	0.31 ± 0.03	<0.0001
Model 1	1645	0.15 ± 0.03	<0.0001	1645	0.15 ± 0.03	<0.0001
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Model 5	1631	0.09 ± 0.04	0.02	1631	0.08 ± 0.04	0.04

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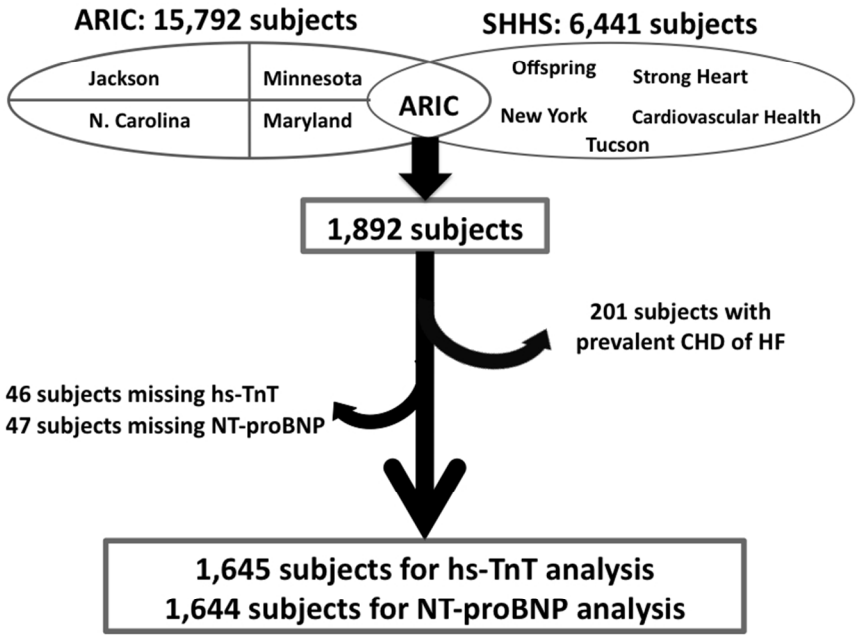

Study Population
352x264mm (72 x 72 DPI)