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Longitudinal Assessment of N-Terminal Pro-B-Type Natriuretic Peptide and Risk of Diabetes in Older Adults: The Cardiovascular Health Study

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Abstract

Introduction—Natriuretic peptides have a well-recognized role in cardiovascular homeostasis. Recently, higher levels of B-type natriuretic peptide (BNP) have also been associated with decreased risk of diabetes in middle-aged adults. Whether this association persists into older age, where the pathophysiology of diabetes changes, has not been established, nor have its intermediate pathways.

Methods—We investigated the relationship between N-terminal (NT)-proBNP and incident diabetes in 2359 older adults free of cardiovascular disease or chronic kidney disease in the Cardiovascular Health Study.

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Results—We documented 348 incident cases of diabetes over 12.6 years of median follow-up. After adjusting for age, sex, race, body mass index, systolic blood pressure, anti-hypertensive treatment, smoking, alcohol use, and LDL, each doubling of NT-proBNP was associated with a 9% lower risk of incident diabetes (HR=0.91 [95% CI: 0.84–0.99]). Additional adjustment for waist circumference, physical activity, estimated glomerular filtration rate or C-reactive protein did not influence the association. Among putative mediators, HDL and triglycerides, adiponectin, and especially homeostasis model assessment of insulin resistance, all appeared to account for a portion of the lower risk associated with NT-proBNP.

Conclusion—In older adults without prevalent cardiovascular or kidney disease, higher NT-proBNP is associated with decreased risk of incident diabetes even after adjustment for traditional risk factors. These findings suggest that the metabolic effects of natriuretic peptides persist late in life and offer a potential therapeutic target for prevention of diabetes in older people.

1.0 Introduction

Brain (B-type) natriuretic peptide (BNP) is one of the three characterized human natriuretic peptides.[1, 2] It is produced primarily by cardiomyocytes and has well-known effects on heart and vascular function. Released in response to ventricular stretch, BNP promotes vasodilation and natriuresis.[2] In the clinical setting, BNP is used to assess the presence and severity of heart failure, in which it is pathologically elevated.[2]

In addition to its effects on cardiovascular homeostasis, accumulating data show that natriuretic peptides (NPs) have metabolic effects. NP receptors are expressed in adipose tissue and skeletal muscle, and NPs have been shown to promote adipocyte browning, foster adipokine secretion and increase oxidative capacity in muscle.[3–8] In clinical studies, higher levels of N-terminal proBNP (NT-proBNP), a cleavage product of proBNP, are associated with less obesity and metabolic syndrome,[9–12] and a decreased risk of incident type 2 diabetes.[13–16] Moreover, studies of genetic variants in the natriuretic peptide precursor A (*NPPA*) and B (*NPPB*) loci suggest that mild, lifelong elevations in natriuretic peptides may protect against type 2 diabetes.[15, 17]

Such epidemiological evidence linking lower natriuretic peptide levels to increased risk of incident diabetes comes primarily from middle-aged cohorts. As compared with middle-aged individuals, however, the pathophysiology of diabetes in older adults has an important component of aging-related decline in skeletal muscle mass and quality, which results in peripheral insulin resistance.[18, 19] With aging there is also central fat redistribution, accompanied by a decrease in brown fat in favor of expansion of white fat,[20, 21] findings similarly associated with diabetes.[22] Because natriuretic peptides have been shown in experimental models to promote fatty acid oxidation and mitochondrial biogenesis in skeletal muscle[3] and to foster adipocyte browning,[7, 8] their favorable metabolic properties could be especially relevant in older age. Prior work from our group has indeed documented a positive association of circulating NT-proBNP with various measures of insulin sensitivity, although a relationship for genetically determined levels could not be demonstrated.[23] As diabetes is especially common in adults ≥65, with roughly one third in the U.S. affected,[24] assessing whether the previously reported association applies to older people is of particular

importance. In this study, we investigate whether lower NT-proBNP is associated with increased risk of incident diabetes in a prospective study of community-dwelling older adults.

2.0 Methods

2.1 Study population

The Cardiovascular Health Study (CHS) is a longitudinal population-based cohort study investigating risk factors for cardiovascular disease (CVD) in older adults.[25] Participants age 65 and older residing in the community were identified using Medicare eligibility lists and recruited from 4 field centers in the United States (Washington County, MD; Allegheny County, PA; Forsyth County, NC; Sacramento County, California). An initial cohort of 5,201 predominantly white individuals was recruited in 1989–90 (original cohort), and an additional cohort of 687 mostly African-American individuals was recruited in 1992–93 (supplemental cohort). Participants received standardized health evaluations at site clinics as previously described.[25, 26] All centers obtained institutional review board approval for the study and participants gave informed consent.

For the present analysis, we used the 1992–93 visit as our baseline exam to allow incorporation of Centers for Medicare and Medicaid claims data for ascertainment of diabetes, information on which was available starting in 1991. As detailed in Figure 1, of the 5,533 CHS participants alive at the 1992–93 visit, 4,147 had NT-proBNP measurements available. Participants with available NT-proBNP measurements were younger and more commonly female, had less hypertension, diabetes, and self-reported fair/poor health status, and exhibited lower prevalence of cardiovascular disease, in comparison to those without available NT-proBNP measurements. Of participants with available NT-proBNP values, we excluded individuals who had prevalent diabetes mellitus (DM) or unknown DM status and those without diabetes follow-up after 1992–93. Since cardiovascular disease and chronic kidney disease can result in pathologic elevations in NT-proBNP levels,[2] those with prevalent atherosclerotic cardiovascular disease (CVD) (myocardial infarction and stroke), heart failure (HF), atrial fibrillation and estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 were also excluded. Therefore, a total of 2,359 individuals were included in the analysis (2,059 original cohort, 300 supplemental cohort)(Figure 1).

2.2 Measurement of NT-proBNP

NT-proBNP was measured in serum specimens collected from both the original and supplemental cohort in 1992–93, which were stored at −70°C to −80°C and thawed before testing. NT-proBNP measurements were made on the Elecsys 2010 system (Roche Diagnostics, Indianapolis, Indiana). The analytical measurement range was 5 to 35,000 pg/ml, and the coefficient of variation was 2–5%.[27]

2.3 Measurement of covariates

Demographic, lifestyle and clinical characteristics were recorded during field center visits using standardized questionnaires along with blood pressure and anthropometric assessments, as previously described.[25] Laboratory specimen collection and biochemical

testing procedures were performed as reported elsewhere.[28] Estimated glomerular filtration rate (eGFR) was calculated using cystatin C.[29] Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as fasting glucose(mmol/l)×fasting insulin(mU/l)/22.5.[30] Total adiponectin was measured in serum as previously described.[31] All laboratory measurements were taken from the 1992–1993 visit.

2.4 Ascertainment of diabetes

Glucose was measured on blood specimens collected during annual clinic visits in 1992–93, 1994–95, 1996–97, 1998–99, and 2005–06. Information on prescription medications taken in the previous 2 weeks was collected annually using standardized methods at clinic visits for the first 10 years, and by telephone contact thereafter. Medicare claims data for inpatient (hospital, skilled nursing facility, or home health) and outpatient (outpatient or carrier) health care services were available beginning in 1991. Hypertension was defined by systolic blood pressure ≥140 and/or diastolic blood pressure ≥90 mm Hg or by self-report and use of antihypertensive medication. Diabetes was defined as single measure of fasting glucose ≥126 mg/dL (7.0 mmol/L), nonfasting glucose ≥200 mg/dL (11.1 mmol/L), or use of insulin or oral hypoglycemic medication, or the existence of ≥ 2 inpatient or ≥ 3 inpatient or (≥ 1 inpatient and ≥ 1 outpatient) or Medicare claims during a 2-year time period which included a diagnostic International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code of 250.xx.

2.5 Statistical analysis

Baseline covariates were examined by quartiles of NT-proBNP. Cox models were used to calculate adjusted relative risks for incident diabetes by quartile of NT-proBNP and by NT-proBNP doubling. The functional form of the association between NT-proBNP and new-onset diabetes was evaluated with generalized additive models, and non-linearity assessed with the gain statistic. The proportional hazards assumption was tested using Schoenfeld's goodness-of-fit; this revealed no material violations.

To adjust for confounding, models were constructed that included relevant covariates based on previously demonstrated relations with outcomes in CHS or other cohorts. The first model included age, sex and race. This was followed by addition of clinical and laboratory variables, including body mass index (BMI), systolic blood pressure, use of anti-hypertensive medication, smoking, alcohol consumption, and LDL cholesterol. Additional adjustment for waist circumference, leisure-time physical activity, cystatin-based eGFR or C-reactive protein was then undertaken. Next, we explored the impact of factors documented or presumed to be influenced by BNP that could therefore, at least in part, act as potential causal intermediates in the relationship of BNP with diabetes. Three separate models therefore added HDL cholesterol and triglycerides, adiponectin, or HOMA-IR to assess their effect on the association of interest.

First-order interactions of NT-proBNP with age, sex, race, BMI, physical activity level, and hypertension status were examined. In addition, sensitivity analysis excluded participants with NT-proBNP ≥190 pg/ml, levels at which an elevated risk of heart failure has been previously observed in the CHS cohort.[27] Analyses were conducted with Stata version 13.0

(Statacorp, College Station, TX). A two-sided P value <0.05 was considered statistically significant.

3.0 Results

The median age of the study sample was 74 (range, 64 to 103) years, with men constituting 33.8% and African Americans 15.6%. The distribution of baseline characteristics by quartiles of NT-proBNP is presented in Table 1. There was an increase in age, hypertension, fair or poor self-reported health, HDL cholesterol, C-reactive protein and total adiponectin across higher quartiles of NT-proBNP. By contrast, there were smaller proportions of men and African Americans with higher quartiles of NT-proBNP, as well as lower levels of adiposity, LDL cholesterol, triglycerides, eGFR, and HOMA-IR.

During 12.6 median years of follow-up, 348 new cases of diabetes occurred. As shown in Table 2, the incidence of diabetes was progressively lower across increasing quartiles of NT-proBNP. The relative risk estimates for incident diabetes by quartiles and by continuous levels of NT-proBNP are also presented in Table 3. The incidence of diabetes was inversely associated with BNP. Generalized additive models did not reveal significant departure from a linear relationship (p=0.45). In the model adjusting for age, sex, race, systolic blood pressure, hypertension medication, smoking status, alcohol consumption, and LDL, every doubling of NT-proBNP concentration was associated with a 9% lower risk of new-onset diabetes. Additional adjustment for waist circumference, physical activity, eGFR or C-reactive protein did not meaningfully affect the risk estimate. There was no statistically significant difference between quartiles of NT-proBNP in risk of diabetes despite the consistent trend towards lower relative risk of diabetes with increasing quartiles in all models.

Figure 2 displays the results of additional adjustment for potential causal intermediates of the relationship between NT-proBNP and incident diabetes. Addition of HDL cholesterol and triglycerides or adiponectin to the confounder-adjusted model modestly attenuated the association, and statistical significance was lost. Adjustment for HOMA-IR in addition to potential confounders more substantially attenuated the association, moving it closer to null.

Assessment for effect-modification did not reveal an interaction between NT-proBNP and age, sex, race, BMI, physical activity or hypertension status. Exclusion of participants with NT-proBNP ≥190 pg/ml did not materially alter the risk estimate for continuous NT-proBNP level (per doubling) in relation to incident diabetes.

4.0 Discussion

4.1 Principal Findings

The present report shows that in a cohort of community-dwelling older adults without prevalent cardiovascular disease or chronic kidney disease, higher levels of NT-proBNP were associated with a lower risk of incident diabetes. Our study demonstrates that this relationship was independent of various potential confounders and consistent across a variety of subgroups.

Although analysis by quartiles of NT-proBNP suggested an inverse association with incident diabetes, a significant relationship was only observed when NT-proBNP levels were modeled continuously, likely due to the less robust power associated with categorization. Furthermore, the association, which was marginally non-significant after adjustment for demographic covariates, became statistically significant only after additional adjustment for potential clinical and laboratory confounders. This finding reflects the positive association of NT-proBNP with hypertension, which acted as a negative confounder of NT-proBNP's inverse relationship with diabetes.

As hypothesized, the association was weakened after adjustment for several putative mediators. This included HDL cholesterol and triglycerides, lipid subfractions that are closely linked to insulin resistance,[32] as well as adiponectin and, particularly, HOMA-IR itself.

4.2 Previous Studies

Previous prospective studies have examined the association between natriuretic peptides and incident diabetes in predominantly middle-aged populations.[13–17] Among Finnish participants in the FINRISK97 and HEALTH 2000 longitudinal studies, with mean (geometric) ages of ~46 and ~53 years, respectively, every SD increment in NT-proBNP was associated with an 18% lower risk of incident diabetes.[14] This inverse relationship was replicated among participants in the EPIC-Norfolk study, ages 39 to 79 years, which documented a 21% lower adjusted risk of diabetes per SD increment in log-transformed NT-proBNP.[17] The Malmo Diet and Cancer study also reported an inverse association between NT-proBNP and development of diabetes among participants with a mean age of ~57 years, but this fell short of statistical significance (adjusted odds ratio [OR] per SD increment, 0.92 [95% CI, 0.80–1.06]).[13] There was, however, a significant association between mid-regional atrial natriuretic peptide and new-onset diabetes (adjusted OR per SD increment, 0.85 [95% CI 0.73–0.99]).[13]

Recent reports from U.S. cohorts have also provided support for an inverse association. The Women's Health Study documented a significant relationship among middle-aged women, with a 22% lower adjusted risk of diabetes per SD increment in logarithm-transformed NT-proBNP.[15] Likewise, the Atherosclerosis Risk in Communities (ARIC) study reported a significant 35% decrease in adjusted risk of incident diabetes in comparison of extreme quartiles among men and women with a mean age of ~62 years, although there was flattening of the association starting at levels within the third quartile.[16] Such findings linking natriuretic peptides with onset of diabetes have been buttressed by analyses of genetic variants in natriuretic peptide precursor (NPP) genes, *NPPA* and *NPPB*, associated with higher levels of NT-proBNP. Two separate studies have reported such variants to be associated with reduced risk of diabetes,[15, 17] providing population-level evidence for the potentially causal influence of relative natriuretic peptide deficiency on the development of diabetes.

Lately, the Multi-Ethnic Study of Atherosclerosis also found an inverse association between NT-proBNP and incident diabetes among individuals ages 45–84.[33] Comparison of the upper versus the lowest three sextiles of baseline NT-proBNP was associated with a 32%

lower adjusted risk of this outcome, but attenuation of the association occurred at levels toward the upper limit of the fifth sextile (>150 pg/ml),[33] consistent with similar flattening of NT-proBNP's associations with metabolic risk factors as concentrations reached a higher range.[11, 12] The same study[33] reported a U-shaped association for subsequent 3-year interval change in NT-proBNP and diabetes. Taken together with the ARIC results, these findings are consistent with the adverse metabolic impact of pathologic elevations of NT-proBNP into the higher range, as compared with physiologic elevations.

The present results extend these previous findings to an older population with a mean age of 74 years, showing that after exclusion of cardiovascular and kidney disorders apt to confound any inverse association of physiologic natriuretic peptide levels with diabetes,[34, 35] such protective association holds for individuals late in life. Unlike previous reports, there was no evidence of attenuation of the association at the upper range of the NT-proBNP distribution, but the smaller number of incident diabetes cases may have limited the current study's ability to detect such an effect. Regardless, the current findings building on our separate report[23] of inverse associations between NT-proBNP and various measures of insulin resistance are important. Not only is diabetes more prevalent in older adults than in any other age group, [24] but it is also characterized by distinct pathogenetic features, including aging-related decline in beta-cell function and loss of skeletal muscle mass with attendant skeletal muscle insulin resistance.[18] Moreover, abnormal glucose regulation is well documented to heighten risk of cardiovascular disease and mortality in elders, much as it does in middle-aged adults.[36, 37] Hence, our findings have implications for harnessing natriuretic peptides and related pathways as potential therapeutic targets in the segment of the population with the greatest burden of disorders of glucose regulation.

4.3 Potential Mechanisms

The mechanisms behind the association between NT-proBNP and decreased risk for diabetes are not well understood. Recently discovered effects of NPs on metabolism and energy expenditure raise the intriguing possibility that NPs play a causal role in protecting against obesity and dysmetabolism, and may affect pathways that are involved in age-related insulin resistance and dysglycemia.[6, 38] It was discovered over a decade ago that adipocytes express natriuretic peptide receptor A (NPR-A) and that BNP induces lipolysis in cultured adipocytes.[5] Subsequent experiments demonstrated that transgenic mice overexpressing BNP are protected from obesity and insulin resistance, and have less ectopic and visceral fat accumulation when fed a high-fat diet.[3] More recent work has documented that activation of NPR-A on adipocytes by BNP also induces transcription of genes, including *PGC1-α* and *UCP1*, that enhance energy expenditure and adipocyte browning.[7] With aging, there are changes in adipose tissue distribution associated with an adverse metabolic profile, including an increase in visceral fat and loss of brown adipose tissue.[21, 22, 39] Thus, it is possible that BNP may help to protect against such changes in humans. Although we adjusted for waist circumference, which had no meaningful impact on the observed association, we lacked reliable measures of adipocyte browning to support or refute this specific hypothesis.

Another mechanism by which BNP might decrease the risk of diabetes is through effects on skeletal muscle. ANP and BNP are released from the heart during exercise[40, 41] and in

response to exercise training, obese individuals up-regulate *NPR-A*, *PGC1-α* and genes involved in oxidative phosphorylation.[42] Studies in rodents show that long-term exposure to increased BNP increases oxidative capacity in skeletal muscle and protects against skeletal muscle atrophy.[3, 8] Such skeletal muscle effects may be especially important in older adults, who experience decline in skeletal muscle mass and quality,[19] and are therefore particularly susceptible to skeletal muscle insulin resistance.[18] We examined levels of self-reported physical activity in our analyses as a surrogate for skeletal muscle health, as well as a stimulus for natriuretic peptide secretion, but did not find these to influence our findings. We lacked direct measures of skeletal muscle mass or quality, however, and therefore had limited ability to evaluate the interrelationship between natriuretic peptides, skeletal muscle, and metabolic risk in our study.

Finally, BNP may exert some of its metabolic effects is through release of adipokines. BNP is positively correlated with adiponectin,[43–45] and in vitro studies of cultured human adipocytes show that ANP and BNP enhance adiponectin secretion via NPR-A. ANP infusion also raises adiponectin plasma levels in healthy adults and those with heart failure.[4, 46] These findings have led to speculation that the metabolic effects of BNP may be partially mediated by adiponectin. Indeed, our data show a positive association between NT-proBNP and suggest some, but not complete, attenuation of the association between BNP and incident diabetes by adiponectin in older adults. A recent cross-sectional study showed that the association between higher BNP and a favorable fat distribution profile persisted even after adjustment for adipokine levels.[43]

4.4 Strengths and Weaknesses

Our study strengths include its prospective, population-based design, its long-term follow-up, and its focus on adults late in life. The present investigation is also subject to several limitations. NT-proBNP was not available for all participants at the 1992–93 visit. Participants with missing NT-proBNP measurements tended to be less healthy than those with available values. This is, however, precisely the population we sought to exclude to avoid confounding by pathologic elevations of NT-proBNP. The outcome measure was based on a combination of glucose measurements, medication use, and CMS diagnostic codes. Although this affords good accuracy for diabetes diagnosis, lack of additional measures at follow-up, such as glycated hemoglobin, may have decreased sensitivity. The resulting misclassification, however, would generally tend to bias the association of interest toward the null. Finally, the results were based on a single measure of NT-proBNP, which has been shown to have some degree of intraindividual variability.[47] While use of genetic variants influencing plasma NT-proBNP can provide a better measure of long-term levels, we lacked sufficient power in the present analysis to undertake this type of evaluation, which will require meta-analytic approaches for meaningful investigation specifically in elders.

5.0 Conclusions

In conclusion, our findings show that higher circulating NT-proBNP levels are associated with lower risk of incident diabetes in older adults. These results add to the growing evidence that the heart acts, through release of natriuretic peptides, as an important

endocrine organ in metabolic homeostasis, even in the setting of advanced age. Further studies are necessary to assess whether direct pharmacologic administration of natriuretic peptides, or interventions to raise their levels, represent effective new strategies for the prevention or treatment of diabetes.

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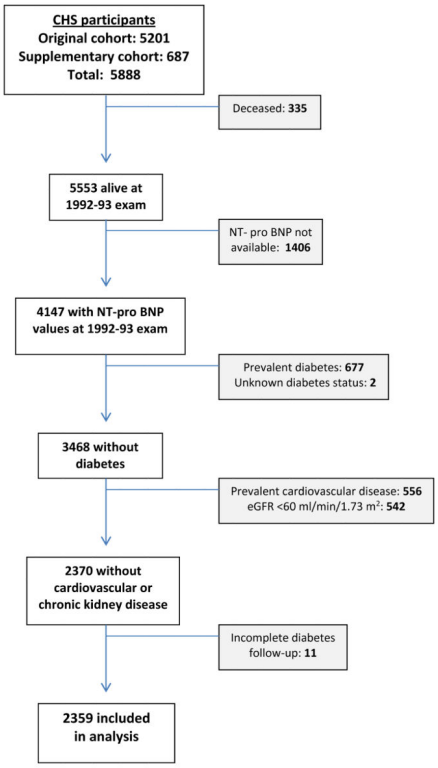

Figure 1.
Number of participants after exclusion by each criteria.

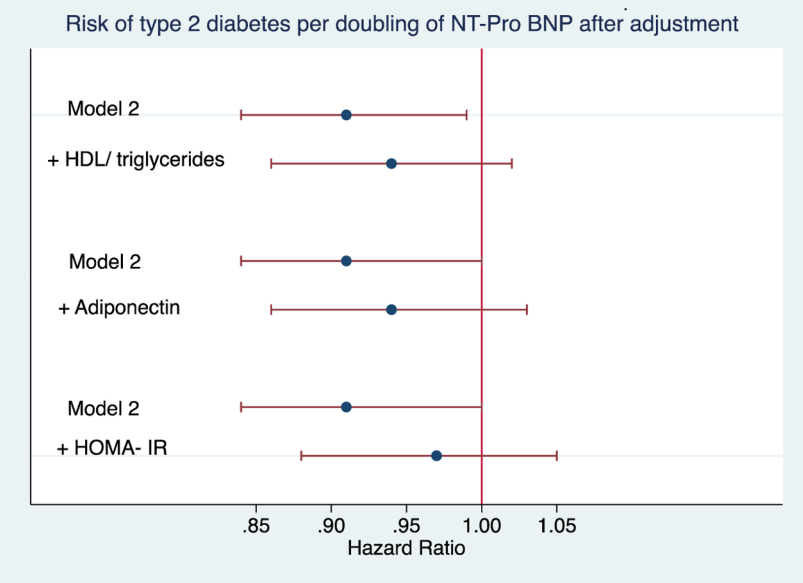

Figure 2.

Impact of additional adjustment for putative mediators of the relationship between NT-proBNP and diabetes. Model 2 is the same as in Table 3, and includes adjustment for age, sex, race, body mass index, systolic blood pressure, smoking, alcohol, and LDL cholesterol. Data available in n=2,359 participants for HDL cholesterol and triglycerides; n=2,343 participants for adiponectin; and n=2,347 participants for HOMA-IR. Horizontal bars represent 95% confidence intervals.

Table 1

Baseline characteristics by quartile of NT-proBNP

NT-proBNP	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P value
Range, pg/ml	≤60.6	>60.6–111.5	>111.5–203.8	>203.8	
Age, years	72 ± 3	73 ± 4	74 ± 5	76 ± 5	<0.001
Male sex, %	45.3	34.6	27.1	28.4	<0.001
Black race, %	24.7	16.3	12.4	8.8	<0.001
BMI, kg/m^2	27.1 ± 4.2	26.7 ± 4.5	25.8 ± 4.4	25.5 ± 4.6	<0.001
Waist circumference, cm	97.8 ± 11.5	95.9 ± 12.7	93.4 ± 12.8	93.2 ±13.7	<0.001
Physical activity, kcal	1601 ± 1644	1574 ± 1861	1672 ± 1963	1447 ± 1639	0.27
Systolic blood pressure, mmHg	129 ± 18	134 ± 19	136 ± 20	142 ± 22	<0.001
Anti-hypertensive medication, %	34.1	34.2	38.8	47.9	<0.001
Hypertension status, %	41.9	48.4	53.1	62.7	<0.001
Alcohol >7 drink/week, %	13.1	14.1	16.6	13.2	0.63
Current smoker %	9.8	9.5	10.3	10.5	0.60
Self-reported health fair/poor, %	12.3	12.5	13.9	17.5	0.009
LDL cholesterol, mg/dl	133 ± 33	129 ± 31	127 ± 31	124 ± 35	<0.001
HDL cholesterol, mg/dl	54 ± 14	56 ± 14	58 ± 15	58 ± 15	<0.001
Triglycerides, mg/dl	142 ± 75	131 ± 64	128 ± 68	126 ± 62	<0.001
eGFR, ml/min/1.73 m^2	84 ± 15	81 ± 14	80 ± 13	78 ± 14	<0.001
CRP, mg/l	3.9 ± 5.3	4.4 ± 8.9	4.4 ± 7.3	4.7 ± 8.8	0.10
Total adiponectin, mg/l	11.3 ± 5.8	14.0 ±.6.7	15.7 ± 7.6	17.7 ± 9.1	<0.001
HOMA-IR	3.1 ± 1.8	2.5 ± 1.4	2.4 ± 1.5	2.2 ± 1.3	<0.001

Continuous variables presented as mean ± standard deviation.

BMI= Body mass index. LDL= Low density lipoprotein.

CRP= C-reactive protein.

eGFR= Estimated glomerular filtration rate.

HOMA-IR= Homeostatic model assessment of insulin resistance

HDL= High density lipoprotein.

NT-ProBNP= N-terminal Pro B-type Natriuretic Peptide.

Table 2

Association of NT-proBNP with incident diabetes

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	Overall
Events/Individuals at risk (n)	105/590	95/590	85/590	63/589	348/2359
Incidence (per 1000 py) *	14.0	13.3	12.2	10.5	12.6
	HR vs. referent (95% CI), p Value				**HR per doubling (95% CI), p Value**
Model 1 †	1.00 (Ref.)	0.99 (0.75 – 1.31) p=0.93	0.92 (0.68 – 1.24) p=0.59	0.82 (0.59 – 1.13) p=0.24	0.93 (0.85 – 1.01) p=0.10
Model 2 ‡	1.00 (Ref.)	0.95 (0.71 – 1.26) p=0.71	0.93 (0.69 – 1.25) p=0.62	0.76 (0.54 – 1.07) p=0.11	0.91 (0.84 – 0.99) p=0.039

* p=0.060 for trend across quartiles.

† Adjusted by age, sex, race.

‡ Adjusted by age, sex, race, body mass index, systolic blood pressure, antihypertensive medication, smoking status, alcohol consumption, and low density lipoprotein cholesterol.

CI=Confidence interval. HR=Hazard ratio. PY= Person-years.