Natriuretic Peptides and Risk of Type 2 Diabetes: Results From the Biomarkers for Cardiovascular Risk Assessment in Europe (BiomarCaRE) Consortium

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OBJECTIVE

Natriuretic peptide (NP) concentrations are increased in cardiovascular diseases (CVDs) but are associated with a lower diabetes risk. We investigated associations of N-terminal pro-B-type NP (NT-proBNP) and midregional proatrial NP (MR-proANP) with incident type 2 diabetes stratified by the presence of CVD.

RESEARCH DESIGN AND METHODS

Based on the Biomarkers for Cardiovascular Risk Assessment in Europe (BiomarCaRE) Consortium, we included 45,477 participants with NT-proBNP measurements (1,707 developed type 2 diabetes over 6.5 years of median follow-up; among these, 209 had CVD at baseline) and 11,537 participants with MR-proANP measurements (857 developed type 2 diabetes over 13.8 years of median follow-up; among these, 106 had CVD at baseline). The associations were estimated using multivariable Cox regression models.

RESULTS

Both NPs were inversely associated with incident type 2 diabetes (hazard ratios [95% CI] per 1-SD increase of log NP: 0.84 [0.79; 0.89] for NT-proBNP and 0.77 [0.71; 0.83] for MR-proANP). The inverse association between NT-proBNP and type 2 diabetes was significant in individuals without CVD but not in individuals with CVD (0.81 [0.76; 0.86] vs. 1.04 [0.90; 1.19]; *P* multiplicative interaction = 0.001). There was no significant difference in the association of MR-proANP with type 2 diabetes between individuals without and with CVD (0.75 [0.69; 0.82] vs. 0.81 [0.66; 0.99]; *P* multiplicative interaction = 0.236).

CONCLUSIONS

NT-proBNP and MR-proANP are inversely associated with incident type 2 diabetes. However, the inverse association of NT-proBNP seems to be modified by the presence of CVD. Further investigations are warranted to confirm our findings and to investigate the underlying mechanisms.

B-type natriuretic peptide (BNP) and atrial natriuretic peptide (ANP) are cardiac hormones that exert physiological actions not only on cardiovascular homeostasis but also on glucose and lipid metabolism. Both natriuretic peptides (NPs) increase mitochondrial fat oxidative capacity in skeletal muscle and promote lipolysis,

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browning of white adipocytes, oxygen consumption, glucose uptake in adipose tissue and also modulate cytokine and adipokine responses (1,2). Altogether, these biological effects ameliorate insulin resistance and blood glucose control (3).

In previous epidemiological studies, higher concentrations of N-terminal pro-BNP (NT-proBNP) (4–9) and midregional pro-ANP (MR-proANP) (4,10–12), the inactive fragments of BNP and ANP, respectively, were associated with a lower risk of type 2 diabetes. However, circulating concentrations of both NPs are elevated in cardiovascular diseases (CVDs) to compensate for cardiac pressure overload (2) and predict CVD prognosis (13). CVDs, such as heart failure (HF), myocardial infarction (MI), and stroke, can give rise to abnormalities in glucose metabolism (14–16). For instance, HF invokes a compensatory neurohumoral response, which increases free fatty acids, thereby inhibiting muscular glucose uptake and insulin signaling (14). These effects, in turn, predispose to insulin resistance and type 2 diabetes. To date, it remains uncertain whether high NP concentrations are also associated with a lower risk of diabetes in individuals with CVD. Existing studies investigating the association of NPs with diabetes have only included individuals without diabetes and without prevalent CVD or did not report the association separately for individuals with and without prevalent CVD.

The current study aimed to investigate the prospective associations of NT-proBNP and MR-proANP with incident type 2 diabetes in several population-based studies from the multinational Biomarkers for Cardiovascular Risk Assessment in Europe (BiomarCaRE) Consortium (17). We specifically aimed to assess whether these associations differed by the presence of CVD. Additionally, to allow a more robust analysis, we applied two-sample Mendelian randomization (MR) approaches by using published data on genetic variants that are specific for NT-proBNP or MR-proANP.

RESEARCH DESIGN AND METHODS

Study Design and Population

BiomarCaRE is based on the Monitoring of Trends and Determinants in Cardiovascular Diseases (MONICA) Risk Genetics Archiving and Monograph (MORGAM) Project (18), which has harmonized data from a large number of population-based cohorts. Our study complied with the Declaration of Helsinki. All participating cohorts were approved by local ethical review boards, and written informed consent was obtained from all study participants.

To investigate the association between NT-proBNP and incident type 2 diabetes, we included five BiomarCaRE population-based cohorts comprising 45,477 participants initially without diabetes and who had baseline measurements of NT-proBNP. The participating cohorts were the Cooperative Health Research in the Region of Augsburg Study Survey 3 and 4 (KORA S3-S4), the 1997 survey of the FINRISK Study, the Prospective Epidemiological Study of Myocardial Infarction (PRIME) Belfast, the Moli-sani Study, and the Northern Sweden MONICA Study. To investigate the association between MR-proANP and incident type 2 diabetes, we included three BiomarCaRE population-based cohorts involving 11,537 participants who initially did not have diabetes and who had baseline measurements of MR-proANP. The participating cohorts were the reexamination study of KORA S4 in 2006–2008 (KORA F4), FINRISK, and PRIME Belfast. An overview of each participating cohort is provided in Supplementary Table 1. The exclusion criteria for analyzing NT-proBNP and MR-proANP are described in Supplementary Figs. 1 and 2, respectively.

For each cohort, the following harmonized variables were available at baseline: age, sex, BMI, systolic blood pressure, antihypertensive medication, smoking status, total and HDL cholesterol, diabetes status, and history of CVD. History of CVD was defined as having documented or self-reported history of HF, MI, or stroke.

Assessment of Type 2 Diabetes

Prevalent diabetes was defined as a documented diagnosis of diabetes at baseline, either identified by record linkage or through self-report of the participants. In some cohorts, self-reported data were verified by medical record review or through information obtained from the treating physician. Incident type 2 diabetes was defined as a new diagnosis of type 2 diabetes during follow-up, either identified by record linkage or through self-report of the participants without prevalent diabetes at baseline. Details on the assessment of type 2 diabetes and the general follow-up procedures in each cohort are provided in Supplementary Table 1.

Laboratory Measurements

Baseline concentrations of NT-proBNP were measured using electrochemiluminescence immunoassay (ECLIA; Roche Diagnostics GmbH, Mannheim, Germany) on the Elecsys 2010 or the cobas e411 system. Baseline concentrations of MR-proANP were measured using an immunoluminometric assay (B·R·A·H·M·S/Thermo Fisher Scientific, Hennigsdorf, Berlin, Germany) on the B·R·A·H·M·S KRYPTOR automated system. The study-specific intra- and interassay coefficients of variation for each NP are described in Supplementary Table 2. Description of laboratory procedures in detail are provided in Supplementary Text 1.

Statistical Analysis

Participant characteristics stratified by history of CVD were calculated separately for the study sample with baseline measurements of NT-proBNP and MR-proANP.

In our data, we distinguished between missing values, which were below the limit of detection (LOD); that is, below the range to which the assay has been calibrated and missing values due to

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other reasons (e.g., samples were not available, sample volumes were inadequate, sample mix-up or a technical problem). Only missing values due to NP values below the LOD ($n = 2{,}725$ for NT-proBNP and $n = 5$ from the FINRISK study for MR-proANP) were imputed to the lower LOD (i.e., 5 pg/mL for NT-proBNP and 4.6 pmol/L for MR-proANP).

The associations of NT-proBNP and MR-proANP with incident type 2 diabetes were estimated by calculating hazard ratios (HRs) with 95% CIs in Cox proportional hazard models. Age (continuous, in years) was used as the time scale. The models were stratified by study cohort and were adjusted for sex (men/women) in model 1 and were further adjusted for BMI (continuous, in kg/m^2), current smoking (yes/no), systolic blood pressure (continuous, in mmHg), use of antihypertensive medication (yes/no), total and HDL cholesterol (continuous, in mmol/L), and history of CVD (yes/no) in model 2. Additionally, we included history of CVD as a time-varying covariate in a sensitivity analysis of model 2. The distributions of NT-proBNP and MR-proANP were right-skewed (Supplementary Fig. 3). Thus, both NPs were log-transformed and (0,1)-standardized in the overall study population to approximate normality and to evaluate the HRs per 1-SD increase. These associations were further investigated for nonlinearity with restricted cubic spline regressions, with three knots at the 10th, 50th, and 90th percentiles applied to model 2. The proportional hazard assumption was tested by plotting scaled Schoenfeld residuals against follow-up time for each covariate. No indication of nonproportionality was observed.

To examine possible differences in the association of NPs with incident type 2 diabetes by CVD status at baseline, we conducted separate analyses for individuals with and without CVD history. Because some individuals may experience more than one CVD at baseline, which was seen in our data, history of CVD was defined as the composite history of HF, MI, and stroke. We also tested for multiplicative and additive interactions between NPs and CVD history in model 2. The multiplicative interaction was examined by incorporating both factors and their cross-product term in the same model. We calculated the additive interaction by estimating the relative excess risk due to interaction (RERI). RERI was calculated by comparing the joint and separate regression coefficients of NPs and CVD history from the same model using the following formula:

$$RERI = e^{(\beta_{NPs} + \beta_{CVD\ \text{history}} + \beta_{\text{NPs}*CVD\ \text{history}})} - e^{\beta_{NPs}} - e^{\beta_{CVD\ \text{history}}} + 1.$$

To test the null hypothesis that RERI $= 0$, we computed the 95% CIs and P values using the delta method (19). To further evaluate whether other diabetes-related biomarkers might account for the observed associations, we additionally included the baseline measurement of the estimated glomerular filtration rate (eGFR), hs-CRP, leptin, and adiponectin individually in model 2. We log-transformed hs-CRP, leptin, and adiponectin to approximate normality. The distribution of eGFR was approximately normal and was therefore not log-transformed. We further examined the potential interactions of NPs with BMI and sex in individuals with and without CVD history separately. False discovery rate with the Benjamini-Hochberg method was used to correct for multiple testing. An interaction was considered statistically significant at a false discovery rate of <0.05.

As a sensitivity analysis, we examined the associations of NT-proBNP and MR-proANP with incident type 2 diabetes in the same individuals by including only participants with data on both NPs. We also calculated the HRs for each participating cohort and used the Cochran Q to evaluate heterogeneity between cohorts. To account for death without experiencing diabetes as a competing event, we conducted competing-risk analyses using Fine and Gray models.

Finally, we performed two-sample univariate MR analyses using results from published genome-wide association (GWA) studies to examine the associations between genetically predicted NPs and type 2 diabetes risk. We identified single nucleotide polymorphisms (SNPs) with effects specific to either NT-proBNP or MR-proANP at a P value of $<5E{-}8$ as the genetic instrumental variables (IVs) from a published GWA study of European ancestry from Salo et al. (20). The association estimates of the IVs with type 2 diabetes were extracted from a meta-analysis of GWA studies by Xue et al. (21) because of the data availability for populations of European ancestry and the large sample size (62,892 case subjects and 596,424 control subjects). The procedure for the MR analysis is provided in detail in Supplementary Text 2.

All statistical analyses were performed using R 4.0.3 software (22). P values <0.05 were considered statistically significant.

RESULTS

Participant Characteristics

Characteristics of the study participants stratified by CVD history for the study samples with data on NT-proBNP and MR-proANP, respectively, are presented in Table 1. At baseline, compared with participants without CVD, participants with CVD had higher concentrations of NT-proBNP and MR-proANP, were on average older and more frequently male, had a higher BMI and systolic blood pressure, were more likely to take antihypertensive medication, had lower eGFR, had lower concentrations of HDL cholesterol and adiponectin, and had higher concentrations of leptin and hs-CRP. Throughout the follow-up period, participants with CVD were more likely to develop type 2 diabetes than participants without CVD. Characteristics of the study participants in the quarters of baseline NT-proBNP and MR-proANP concentrations are shown in Supplementary Tables 3 and 4, respectively. Characteristics for each participating cohort are provided in Supplementary Table 5.

Associations of NT-proBNP and MR-proANP With Incident Type 2 Diabetes

During a median follow-up of 6.5 years (interquartile range [IQR] 9.9), among the 45,477 participants with NT-proBNP data, 1,707 developed type 2 diabetes. Of these, 209 had a history of CVD at baseline. Among the 11,537 participants with MR-proANP data, 857 developed type 2 diabetes during a median follow-up of 13.8 years (IQR 5.0). Of these, 106 had a history of CVD at baseline.

Both NT-proBNP and MR-proANP were inversely associated with incident type 2 diabetes in model 1 in the overall study population. The HRs (95% CIs) were 0.89 (0.84; 0.94) per 1-SD increase of log NT-proBNP and 0.79 (0.73; 0.86) per 1-SD increase of log MR-proANP. The associations remained significant after additional adjustment according to model 2 (HRs

Table 1—Participant characteristics in the total study population and stratified by history of CVD

	Study population with NT-proBNP measurement			Study population with MR-proANP measurement		
	Overall *n* = 45,477	With CVD* *n* = 1,995	Without CVD *n* = 43,482	Overall *n* = 11,537	With CVD† *n* = 783	Without CVD *n* = 10,754
Incident type 2 diabetes	1,707 (3.8)	209 (10.5)	1,498 (3.4)	857 (7.4)	106 (13.5)	751 (7.0)
NT-proBNP, pg/mL (antilog SD)	41.3 (3.0)	122.7 (3.6)	39.3 (2.9)	39.3 (2.9)‡	107.8 (3.4) ‡	36.2 (2.8)‡
MR-proANP, pmol/L (antilog SD)	47.9 (1.6)‡	76.7 (1.8)‡	46.1 (1.6)‡	49.9 (1.6)	82.3 (1.8)	47.9 (1.6)
Study cohort						
KORA S3-S4	5,130 (11.3)	328 (16.4)	4,802 (11.0)	NA	NA	NA
KORA F4	NA	NA	NA	2,265 (19.6)	128 (16.3)	2,137 (19.9)
FINRISK	7,240 (15.9)	518 (26.0)	6,722 (15.5)	7,301 (63.3)	532 (67.9)	6,769 (62.9)
PRIME Belfast	2,332 (5.1)	147 (7.4)	2,185 (5.0)	1,971 (17.1)	123 (15.7)	1,848 (17.2)
Moli-sani	21,357 (47.0)	589 (29.5)	20,768 (47.8)	NA	NA	NA
Northern Sweden	9,418 (20.7)	413 (20.7)	9,005 (20.7)	NA	NA	NA
Age, years (SD)	51.5 (12.7)	62.7 (10.1)	51.0 (12.6)	49.9 (12.0)	60.9 (9.7)	49.1 (11.8)
Male	23,045 (50.7)	1,386 (69.5)	21,659 (49.8)	6,677 (57.9)	552 (70.5)	6,125 (57.0)
BMI, kg/m^2 (SD)	27.2 (4.6)	28.7 (4.6)	27.2 (4.6)	26.6 (4.3)	28.4 (4.6)	26.5 (4.3)
Current smoking	11,333 (24.9)	367 (18.4)	10,966 (25.2)	2,998 (26.0)	166 (21.2)	2,832 (26.3)
Systolic blood pressure, mmHg (SD)	135.5 (20.6)	142.2 (22.4)	135.2 (20.5)	132.5 (20.3)	140.3 (22.4)	132.0 (20.0)
Use of antihypertensive medication	8,424 (18.5)	964 (48.3)	7,460 (17.2)	1,533 (13.3)	331 (42.3)	1,202 (11.2)
Total cholesterol, mmol/L (SD)	5.67 (1.13)	5.59 (1.20)	5.67 (1.13)	5.58 (1.05)	5.61 (1.01)	5.58 (1.05)
HDL cholesterol, mmol/L (SD)	1.45 (0.40)	1.31 (0.38)	1.45 (0.40)	1.38 (0.37)	1.26 (0.37)	1.39 (0.37)
eGFR, mL/min/1.73 m^2 (SD)§	94.5 (17.3)	82.8 (18.7)	95.1 (17.0)	88.6 (19.3)	78.1 (18.9)	89.4 (19.1)
hs-CRP, mg/L (antilog SD)|	1.35 (3.03)	1.99 (3.00)	1.34 (3.03)	1.26 (3.03)	1.97 (3.00)	1.22 (3.00)
Leptin, ng/mL (antilog SD)¶	7.77 (2.36)	9.30 (2.36)	7.69 (2.36)	8.67 (2.56)	10.59 (2.59)	8.58 (2.53)
Adiponectin, μg/mL (antilog SD)#	5.42 (1.88)	4.90 (1.95)	5.47 (1.88)	5.64 (1.90)	5.31 (1.99)	5.64 (1.90)

Data are presented as *n* (%) for categorical variables and as mean (SD) for continuous variables. Continuous variables with skewed distributions are presented as geometric mean (antilog SD). NA, data not available. *Among 1,995 participants with CVD history and NT-proBNP measurement, 570 had HF (120 with MI, 28 with stroke, 16 with MI and stroke), 1,114 had MI (120 with HF, 65 with stroke, and 16 with HF and stroke), and 556 had stroke (28 with HF, 65 with MI and 16 with HF and MI). †Among 783 participants with CVD history and MR-proANP measurement, 315 had HF (88 with MI, 34 with stroke, 10 with MI and stroke), 411 had MI (88 with HF, 19 with stroke and 10 with HF and stroke), and 218 had stroke (34 with HF, 19 with MI and 10 with HF and MI). ‡Data were available and calculated in 8,695 (612 with and 8,083 without a history of CVD). §Data were available and calculated in 44,219 (1,922 with and 42,297 without a history of CVD) participants with NT-proBNP measurement and 11,341 (764 with and 10,577 without a history of CVD) participants with MR-proANP measurement. |Data were available and calculated in 45,032 (1,981 with and 43,051 without a history of CVD) participants with NT-proBNP measurement and 11,073 (758 with and 10,315 without a history of CVD) participants with MR-proANP measurement. ¶Data were available and calculated in 17,927 (1,038 with and 16,889 without a history of CVD) participants with NT-proBNP measurement and 10,311 (734 with and 9,577 without a history of CVD) participants with MR-proANP measurement. #Data were available and calculated in 8,669 (611 with and 8,058 without a history of CVD) participants with NT-proBNP measurement and 9,673 (738 with and 8,935 without a history of CVD) participants with MR-proANP measurement.

0.84 [95% CI 0.79; 0.89] per 1-SD increase of log NT-proBNP and 0.77 [0.71; 0.83] per 1-SD increase of log MR-proANP). The results were similar when we included history of CVD as a time-varying covariate (HR 0.84 [95% CI 0.79; 0.89] per 1-SD increase of log NT-proBNP and 0.77 [0.71; 0.83] per 1-SD increase of log MR-proANP). The associations of NT-proBNP and MR-proANP with incident type 2 diabetes were also examined in each cohort without significant heterogeneity (Supplementary Figs. 4 and 5).

We observed a significant interaction between NT-proBNP and history of CVD on both multiplicative and additive scales with respect to incident type 2 diabetes ($P = 0.001$ for interaction on multiplicative scale and $P = 0.015$ on additive scale) (Table 2). When stratified by CVD history, NT-proBNP was significantly inversely associated with incident type 2 diabetes in participants without but not in participants with CVD history. The association between NT-proBNP and incident type 2 diabetes in participants without CVD was approximately linear (Fig. 1*A*). The multi-variable HRs (95% CIs) per 1-SD increase were 0.81 (0.76; 0.86) and 1.04 (0.90; 1.19) in participants without and with CVD history, respectively. These results were consistent after further adjustment for eGFR, hs-CRP, leptin, and adiponectin (Supplementary Table 6). In our subgroup analyses, we observed a significant interaction of NT-proBNP with BMI and sex in participants without CVD history, with a stronger association in women than in men and in obese than in nonobese participants (Supplementary Fig. 6).

For MR-proANP, we did not observe a significant difference in the association with incident type 2 diabetes between individuals with and without CVD history

Table 2—Association between NPs and incident type 2 diabetes

	Cases/person-years (*n*)	HR (95% CI) per 1-SD increase	*P* value	Multiplicative interaction	*P* value	Additive interaction*	*P* value
NT-proBNP							
Overall	1,707/429,620	0.84 (0.79; 0.89)	<0.001				
History of CVD				1.25 (1.09; 1.43)	0.001†	0.20 (0.04; 0.37)	0.015†
Yes	209/18,249	1.04 (0.90; 1.19)	0.608				
No	1,498/411,372	0.81 (0.76; 0.86)	<0.001				
MR-proANP							
Overall	857/141,206	0.77 (0.71; 0.83)	<0.001				
History of CVD				1.12 (0.93; 1.36)	0.236	0.08 (−0.12; 0.27)	0.441
Yes	106/8,441	0.81 (0.66; 0.99)	0.042				
No	751 / 132,765	0.75 (0.69; 0.82)	<.001				

The Cox models used age (continuous, in years) as time scale and were stratified by study cohort and adjusted for sex (men/women), BMI (continuous, in kg/m^2), current smoking (yes/no), systolic blood pressure (continuous, in mmHg), use of antihypertensive medication (yes/no), total and HDL (continuous, in mmol/L), and history of CVD (yes/no). NT-proBNP and MR-proANP were log-transformed and (0,1)-standardized in the total study population to approximate normality and to evaluate the HRs per 1-SD increase. *Interaction on additive scale was estimated with RERI (95% CI). †False discovery rate-adjusted *P* values <0.05 using Benjamini-Hochberg method.

($P = 0.236$ for interaction on the multiplicative scale and $P = 0.441$ on the additive scale) (Table 2). The multivariable HRs (95% CIs) per 1-SD increase were 0.81 (0.66; 0.99) and 0.75 (0.69; 0.82) in participants with and without CVD history, respectively. Inspection of restricted cubic splines indicated an inverse linear relationship between MR-proANP and incident type 2 diabetes in participants with and without CVD history (Fig. 1*B*). Further individual adjustment for eGFR, hs-CRP, leptin, and adiponectin only marginally affected the association (Supplementary Table 6). No significant differences in the association between MR-proANP and incident type 2 diabetes were observed across BMI and sex categories (Supplementary Fig. 7).

In a sensitivity analysis including only participants with complete data on both NT-proBNP and MR-proANP ($n = 8,695$), the results were consistent. We only observed a significant difference by CVD history in the association between NT-proBNP and incident type 2 diabetes (Supplementary Table 7). Our competing risk analyses yielded similar results (Supplementary Table 8).

Two-Sample MR Analyses on the Associations of Genetically Predicted NT-proBNP and MR-proANP With Type 2 Diabetes Risk

We included one SNP located in the natriuretic peptide precursor B (*NPPB*) gene (rs198379) for NT-proBNP and two independent SNPs in the natriuretic peptide precursor A (*NPPA*) gene for MR-proANP (rs4845875 and rs3753584) as the genetic IVs. The genetic associations with each NP and with type 2 diabetes were extracted from the previously mentioned GWA studies (20,21) and are provided in Supplementary Table 9. In line with the results from the survival analysis, our MR analyses showed that genetically predicted NT-proBNP and MR-proANP were inversely associated with type 2 diabetes risk. The odds ratios (95% CIs) were 0.93 (0.87; 0.98) for NT-proBNP and 0.91 (0.86; 0.97) for MR-proANP. Sensitivity analyses using the likelihood-based and the weighted mode-based methods yielded similar results (Table 3). We did not observe significant heterogeneity between the two IVs for MR-proANP with respect to the association with type 2 diabetes (Table 3 and Supplementary Fig. 8).

CONCLUSIONS

Our results show that higher circulating concentrations of NT-proBNP and MR-proANP were significantly associated with a lower incidence of type 2 diabetes. We were able to show for the first time that the association between NT-proBNP and incident type 2 diabetes was modified by the presence of CVD, while there was no significant difference in the inverse association of MR-proANP with incident type 2 diabetes between individuals with and without CVD history. We only observed an inverse association of NT-proBNP with incident type 2 diabetes in individuals without but not in individuals with CVD history. Further adjustment for eGFR, hs-CRP, leptin, and adiponectin did not substantially alter the results. In addition, our MR analyses yielded significant associations of genetically predicted NT-proBNP and MR-proANP with the risk of type 2 diabetes.

Our findings support the growing evidence associating high concentrations of NT-proBNP and MR-proANP with a lower risk of type 2 diabetes in individuals without CVD at baseline (5–12) and provide further information regarding these associations in individuals with CVD. Furthermore, our MR analyses corroborate findings from previous studies (5,23) suggesting a potential causal relationship between higher concentrations of NT-proBNP and a lower risk of type 2 diabetes in individuals without prevalent diabetes and CVD and additionally provide the same evidence for MR-proANP.

The underlying mechanisms whereby higher concentrations of BNP and ANP are associated with a lower risk of type 2 diabetes are not fully understood. In adipose tissue, ANP stimulates lipolysis via cyclic guanosine monophosphate–mediated phosphorylation thereby inhibits visceral adipocyte hypertrophy (6), while BNP induces browning of white adipose tissue. ANP also inhibits leptin release, and BNP and ANP both reduce the secretion of proinflammatory cytokines from adipose tissue and enhance adiponectin secretion via the activation of NP receptor A, which suppresses low-grade inflammation of the adipose tissue (24). Thus, BNP and ANP may counteract insulin res-

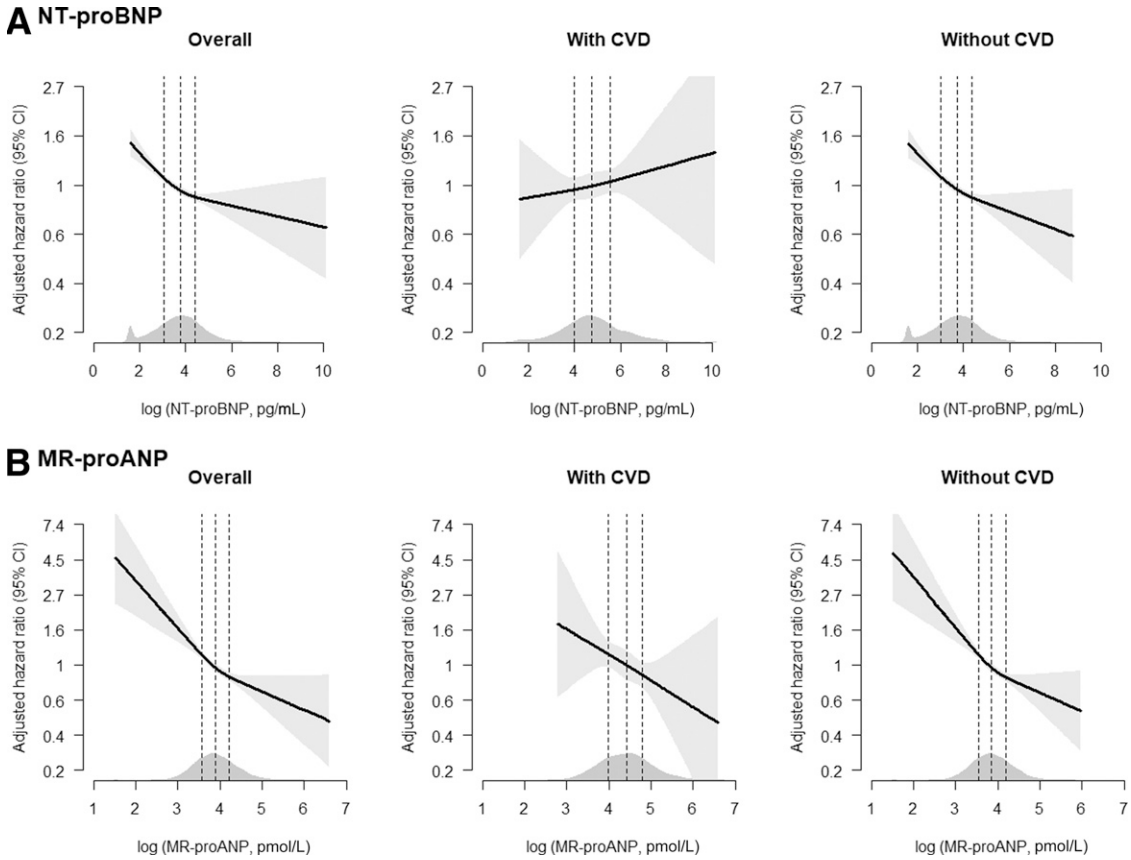

Figure 1—Shape of the association between NPs and incident type 2 diabetes in the total study population and stratified by history of CVD. The linearity was assessed with restricted cubic splines with three knots at the 10th, 50th, and 90th percentiles. Data and the smoothed splines are fitted using Cox models. The models used age as the time scale and were stratified by study cohort. The models were adjusted for sex (men/women), BMI (continuous, in kg/m^2), current smoking (yes/no), systolic blood pressure (continuous, in mmHg), use of antihypertensive medication (yes/no), total and HDL cholesterol (continuous, in mmol/L), and history of CVD (yes/no). NT-proBNP and MR-proANP were log-transformed and (0,1)-standardized in the total study population to approximate normality and to evaluate the HRs per 1-SD increase. Shaded areas around the curves depict the 95% CI. Kernel density plots are imposed along the *x* axis, with vertical dotted lines depicting (from the left) the 25th, 50th, and 75th percentiles of the population.

istance. However, in our study, the inverse association of NT-proBNP and MR-proANP concentrations with incident type 2 diabetes remained stable after further adjustment for hs-CRP, leptin, and adiponectin.

Another potential mechanism for a lower risk of type 2 diabetes is via the direct effects of BNP and ANP on the oxidative metabolism of skeletal muscles (1). NP receptor A is upregulated in the muscle of exercise-trained individuals, suggesting that some of the metabolic adaptations of skeletal muscle in response to exercise may be mediated by NPs (1,24). In healthy individuals, increased NT-proBNP concentrations are also associated with prolonged physical activity (25). In contrast, the concentrations of NPs are reduced in obesity (26), possibly due to the deleterious effects of cardiac ectopic fat and the upregulation of the NP receptor C in adipose tissue that increases NPs clearance (24). Moreover, evidence from previous epidemiological studies suggests that NPs are inversely associated with insulin resistance and obesity (26,27). Intriguingly, we observed a stronger association of NT-proBNP and incident type 2 diabetes in obese than in nonobese participants without CVD history. Of note, a recent study indicates that the inverse association between NT-proBNP and obesity could be modified by sex, with a more pronounced association in women than in men (28), which could be explained by the sex differences in body composition and fat distribution. This observation is in line with our findings and a previous study (9) reporting a stronger inverse association between NT-proBNP and incident type 2 diabetes in women than in men without CVD history, which could possibly be further explained by sex hormones, especially testosterone. Testosterone suppresses NT-proBNP production (29) and, in turn, may partially account for higher circulating NT-proBNP concentrations in women than in men (24). Interestingly, in men, testosterone was inversely associated with type 2 diabetes, while this association in women was positive in cross-sectional settings (30). This evidence is similar in prospective studies; however, the positive association in women was no longer significant after controlling for diabetes risk factors (30,31). The apparent sex-specific associations between testosterone and type 2 diabetes may be driven by the extreme spectrum of testosterone concentrations; for instance, abnormally high testosterone concentrations (hyperandrogenism) in women and abnormally low testosterone concentrations (hypogonadism) in men are associated with a higher risk of

Table 3—MR results of the association between genetically predicted NPs and the risk of type 2 diabetes

Phenotype	No. of IVs	Methods	MR estimates on odds ratio scale (95% CI)	*P*	Cochran's Q	*P* for Cochran *Q*	I^2 (%)
NT-proBNP	1 (rs198379)	Wald ratio	0.93 (0.87; 0.98)	0.012	—	—	—
		Maximum likelihood	0.93 (0.87; 0.98)	0.013	—	—	—
MR-proANP	2 (rs4845875 & rs3753584)	IVW fixed effect model	0.91 (0.86; 0.97)	0.002	0.701	0.402	0
		Maximum likelihood	0.91 (0.85; 0.97)	0.003	0.649	0.421	—
		Weighted mode	0.92 (0.86; 0.98)	0.016	—	—	—

Cochran *Q* and I^2 statistics to test for heterogeneity were calculated when more than one IV was included in the analysis. IVW, inverse-variance weighted.

type 2 diabetes (32). However, in the previous study reporting sex-specific associations between NT-proBNP and incident type 2 diabetes (9), the sex differences were still observed after adjustment for testosterone and other sex hormones, suggesting other possible explanations.

Furthermore, previous studies have shown that elevated blood pressure is associated with increased NP concentrations, which reflects a compensatory response to restrain blood pressure (2,26). Cardiovascular and metabolic regulations are tightly linked; therefore, lowering blood pressure may lower type 2 diabetes risk (2,33). However, some classes of antihypertensive medication may exhibit differential effects on type 2 diabetes risk. Thiazides and β-blockers tend to increase diabetes risk, while neprilysin blockers, angiotensin receptor blockers, ACE inhibitors, and calcium channel blockers decrease the risk (34,35). Due to lack of data on specific antihypertensive medications, we were unable to examine the differential effects of antihypertensive medication classes on the association between NPs and type 2 diabetes.

Differences between BNP and ANP in their cardiometabolic effects have not been widely studied. Within the heart, ANP is considered to be mainly secreted from the atria, while BNP is mainly from the ventricles (36). Although both NPs are known to lower blood pressure, data from animal models (37) and a recent GWA study (20) implicate ANP rather than BNP as a strong blood pressure-lowering hormone. However, in individuals with left ventricular dysfunction, BNP concentrations are markedly increased compared with ANP, suggesting BNP rather than ANP as an emergency defense against ventricular overload (36). Elevated BNP concentrations are also strongly correlated with the severity of CVD (38), which is associated with a higher risk of type 2 diabetes (14,39,40). This could have attenuated the inverse association of NT-proBNP with incident type 2 diabetes in individuals with CVD and could thus explain the difference in the association between individuals with and without CVD seen in our study. Unfortunately, due to lack of relevant data, we were unable to further examine whether the observed associations could be influenced by the severity of CVD. Furthermore, as NT-proBNP concentrations are higher in individuals with CVD compared with individuals without, one could speculate that there is a plateau effect and that the inverse association between NT-proBNP and incident type 2 diabetes is only seen in the lower concentration range. However, our results did not support this hypothesis. An inverse association between NT-proBNP and incident type 2 diabetes in individuals without CVD was also observed within the concentration range seen in individuals with CVD, although with some uncertainty due to the wide 95% CIs at the upper end of NT-proBNP concentrations (Fig. 1*A*). Of note, a nonsignificant association is not evidence for no association. Indeed, based on the 95% CIs from the present analysis, we cannot rule out a small effect of NT-proBNP on type 2 diabetes risk in individuals with CVD. Furthermore, our interaction analyses for MR-proANP may have been underpowered to detect differences between individuals with and without CVD history. More studies with larger study populations, particularly with a large number of incident type 2 diabetes cases in individuals with CVD history are needed to confirm our findings.

The strengths of the current study include the prospective, population-based design, the large sample size, and the thorough adjustment for different cardiometabolic risk factors. Since 1998, we have harmonized data from population-based cohort studies in the MORGAM Data Centre in Helsinki, providing the best possible exposure and covariate alignment as well as end point validation. Standardized epidemiological and laboratory procedures based on individual level data also allow for the best possible data analyses.

Our study has some limitations that merit consideration. Although the assessment of type 2 diabetes incidence was systematic and detailed, it was mainly based on medical reviews and for a small number of participants on self-report, which may have led to misclassification of incident cases. However, since we expect people under regular review by their physician for CVD to have more opportunities for the detection of diabetes, any bias introduced by these means of ascertainment could not explain the lower risk of diabetes seen in individuals with elevated NP concentrations. History of CVD was based on medical review or self-report; therefore, it is possible that some of the individuals classified as having no CVD could have had underlying undiagnosed CVD. We had only a single measurement of NT-proBNP and MR-proANP at baseline, and therefore, intraindividual variation could not be taken into account. This could have led to misclassification of participants and biased the estimates toward the null. Harmonized data on other known cardiometabolic risk factors, such as physical activity and diet, were lacking in the current study, which could have led to some degree of residual confounding. Furthermore, the exclusion of eligible individuals due to

missing values of the NPs or of cardiometabolic risk factors (10.1% in the subsample for NT-proBNP and 10.7% in the subsample for MR-proANP) decreased the statistical power of the analyses and could have led to biased association estimates if the data were not missing completely at random. Finally, due to a limited number of genetic IVs, we were unable to perform more robust sensitivity analyses for our MR.

In conclusion, our findings suggest that NT-proBNP and MR-proANP are inversely associated with incident type 2 diabetes. However, the inverse association of NT-proBNP seems to be modified by the presence of CVD. Future studies are needed to examine the underlying mechanisms, the differences in the metabolic actions between both NPs, and their potential as targets for therapeutic interventions of type 2 diabetes.

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