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Serum Brain-derived Neurotrophic Factor and Risk of Atrial Fibrillation

Faisal Rahman, BM BCh^a, Jayandra J. Himali, PhD^{b,c}, Xiaoyan Yin, PhD^{b,d,e}, Alexa S. Beiser, PhD^{b,c,d}, Patrick T. Ellinor, MD, PhD^f, Steven A. Lubitz, MD, MPH^f, Ramachandran S. Vasan, MD^{b,e,g}, Jared W. Magnani, MD, MSc^h, David D. McManus, MD, ScM^{b,i,j}, Sudha Seshadri, MD^{#b,c}, and Emelia J. Benjamin, MD, ScM^{#b,e,g}

^a Department of Medicine, Boston University Medical Center, Boston, MA, USA

^b National Heart Lung and Blood Institute's and Boston University's Framingham Heart Study, Framingham, MA, USA

^c Department of Neurology, Boston University School of Medicine, Boston, MA, USA

^d Department of Biostatistics, Boston University, Boston, MA, USA

^e Section of Cardiovascular Medicine, Preventive Medicine and Epidemiology, Department of Medicine, Boston University School of Medicine, Boston, MA, USA

^f Cardiovascular Research Center, Massachusetts General Hospital, Charlestown, MA, USA

^g Department of Epidemiology, Boston University School of Public Health, Boston, MA, USA

^h Department of Medicine, Division of Cardiology, UPMC Heart & Vascular Institute, University of Pittsburgh, Pittsburgh, Pennsylvania

ⁱ Departments of Medicine and Quantitative Health Sciences, University of Massachusetts, Worcester, MA, USA

^j Department of Biomedical Engineering, Worcester Polytechnic Institute, Worcester, MA, USA

[#] These authors contributed equally to this work.

Abstract

Background and objective—Brain-derived neurotrophic factor (BDNF) is expressed by endothelial cells and can affect cardiovascular function. We examined if serum BDNF was associated with risk of incident atrial fibrillation (AF) in the Framingham Heart Study.

Corresponding author Emelia J. Benjamin, Professor of Medicine and Epidemiology, Boston University Schools of Medicine and Public Health, Framingham Heart Study, 73 Mount Wayte Avenue, Suite 2, Framingham, MA 01702-5827, Fax: 617 638 8969, Telephone: 617-638-8968, emelia@bu.edu.

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DISCLOSURES

Dr. Ellinor is the PI on a grant from Bayer HealthCare to the Broad Institute focused on the genetics and therapeutics of atrial fibrillation.

Methods—We studied individuals without an AF diagnosis at baseline from the Framingham Original and Offspring cohorts. We used age- and sex-adjusted, and multivariable-adjusted Cox proportional hazard regression models to examine the association of serum BDNF concentrations with 10-year risk of incident AF.

Results—We studied 3457 participants (mean age 65±11 years, 58% women). During follow-up 395 participants developed AF. In unadjusted analysis, higher mean serum BDNF concentration was associated with lower incidence of AF (hazard ratio 0.89 per SD, 95% confidence interval 0.80 to 0.99). In multivariable-adjusted analyses, serum BDNF concentration was not significantly associated with incident AF (hazard ratio 0.98 per SD, 95% confidence interval 0.88 to 1.09). Compared with the lowest quartile, BDNF levels in the other quartiles were not associated with risk of AF in multivariable-adjusted analyses. No interactions between sex or age with serum BDNF concentrations and risk of AF were found.

Conclusions—In our prospective, community-based sample we did not find a statistically significant association of serum BDNF levels with risk of incident AF.

Keywords

Atrial fibrillation; brain-derived neurotrophic factor; epidemiology

Atrial fibrillation (AF) is the most common cardiac arrhythmia, and the prevalence is increasing worldwide.¹ AF is associated with multiple adverse outcomes including embolic stroke,² cognitive impairment,³ heart failure,⁴ myocardial infarction,⁵ chronic kidney disease,⁶ and mortality.^{2,7} Over the past few decades, several studies have defined major risk factors for AF including body mass index, hypertension, diabetes mellitus, history of cardiovascular disease, genetic factors, and various circulating biomarkers.⁷⁻¹¹

Brain-derived neurotrophic factor (BDNF), is a growth factor with roles within the nervous system¹² and cardiovascular system.¹³ BDNF is expressed in endothelial cells, and its release is modified by stimuli including laminar shear stress and changes in intracellular calcium.^{13,14} Further, decreased BDNF levels reduce endothelial cell survival and reduce cardiac contractility, whereas activation of trk B receptors by BDNF is associated with angiogenesis.¹³ It is unclear if these effects of BDNF on the cardiovascular system may modify the risk of AF. However, lower BDNF concentrations have been associated with known risk factors for AF including advancing age,^{15,16} male sex,¹⁶ alcohol consumption,¹⁷ smoking,¹⁸ and diabetes mellitus (**Figure 1**).¹⁹ Circulating BDNF levels were higher among individuals with higher mean physical activity,²⁰ diastolic blood pressure, and body mass index.¹⁶ In contrast, lower serum BDNF levels have been associated with adverse outcomes, including cardiovascular events²¹ and dementia.²² BDNF may have a role in the development of acute coronary syndrome, which may be partly through modulation of associated inflammatory pathways.²³⁻²⁵

Due to BDNF's association with multiple AF risk factors, inflammatory pathways, and its role in the cardiovascular system, we hypothesized that lower BDNF concentrations are associated with increased risk of developing AF prospectively. Thus, we sought to determine

if serum BDNF concentrations are associated with 10-year incidence of AF in the community.

Methods

Study Sample

The Framingham Heart Study (FHS) is a longitudinal community-based epidemiological cohort study. Details of the FHS Original and Offspring cohorts have been described previously.^{26,27} During 1948-1953, 5,209 participants between the ages of 28-62 years were enrolled into the Original cohort. In addition, 5,124 children of the Original cohort and their spouses were recruited into the Offspring cohort between 1971 and 1975. Participants have undergone routine follow-up examinations biennially for the Original cohort, and every 4-8 years for the Offspring cohort. Six hundred sixty-nine of the 1026 participants from the Original cohort who attended examination 23 (1992-1996), and 3020 of 3539 participants from the Offspring cohort who attended examination 7 (1998-2001) had circulating BDNF measurements. We excluded participants with prevalent AF (n=214) and those younger than 40 years of age (n=18) at BDNF measurements (baseline), resulting in a sample of 3457 for our study. All participants gave informed consent. The study protocol was approved by the Institutional Review Board of Boston University Medical Center.

Clinical variables

Participants' medical history, physical examination, blood tests, and 12-lead electrocardiogram were obtained routinely at each FHS examination. In addition, records including electrocardiograms from outpatient visits or hospitalizations between examinations were routinely retrieved and reviewed. Participants were defined to have AF if AF or atrial flutter was confirmed by a FHS cardiologist on review of electrocardiograms, as detailed previously.²⁷

We included clinical covariates from the FHS AF risk score²⁸ assessed at baseline by standardized protocols. Body mass index (weight [in kilograms] divided by height [in meters] squared) was calculated. The PR interval was measured from the beginning of the P-wave deflection to the end of the PR-segment at the junction with the QRS complex. Body mass index and PR interval were natural log-transformed to normalize the skewed distributions. Systolic blood pressure and self-reported use of anti-hypertensive and diabetes medications were recorded. Diabetes mellitus was diagnosed if the participant used insulin or oral hypoglycemic agents, had fasting glucose level ≥ 126 mg/dl, or random blood glucose ≥ 200 mg/dl at FHS examination. We defined valvular heart disease as grade III/VI systolic murmur or any diastolic murmur auscultated at FHS examination. Myocardial infarction and heart failure were diagnosed by review of hospital records and physician reports, and adjudicated by three FHS investigators.²⁹

Laboratory Measurements of BDNF

Fasting blood tests were obtained, frozen, and stored at -70°C until assayed. Serum BDNF concentrations were measured using enzyme-linked immunosorbent assay (ELISA) kits

(R&D Systems, Minneapolis, MN). The intra-assay and interassay coefficients of variation for BDNF were 4.8% and 7.6%, respectively.

Statistical Analyses

We followed up participants for 10 years to evaluate for risk of incident AF. We used unadjusted, age- and sex-adjusted, and multivariable-adjusted Cox proportional hazard regression models to examine the association of change in serum BDNF concentrations (per standard deviation) with 10-year risk of incident AF. Multivariable models adjusted for age, sex, FHS cohort (Original vs. Offspring), body mass index, PR interval, systolic blood pressure, hypertension treatment, diabetes mellitus, significant heart murmur, history of myocardial infarction, and history of heart failure. Estimates were adjusted for competing risk of death. In addition, in exploratory analyses we adjusted for each individual covariate separately to understand if any potential relationship existed between a specific risk factor, serum BDNF concentrations, and risk of incident AF.

In secondary analyses we considered non-linear associations and divided participants into quartiles using serum BDNF concentrations. In previous studies lower concentrations of BDNF were associated with higher risk of dementia.²² Thus, the lowest quartile, Q1, was used as the reference to compare with each individual quartile and a combined Q2 to Q4. Subsequently, the highest quartile (Q4) was used as reference and compared to the other quartiles pooled. The same analyses were performed on all models after exclusion of participants with history of myocardial infarction or heart failure. We also evaluated if there was an interaction of sex and age < or ≥ 65 years with BDNF for the risk of AF.

Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC) and 2-sided $P < .05$ was considered statistically significant for all models and $P < .10$ for analyses assessing interactions. We estimate that our study had 90% power to detect a hazard ratio as large as 0.86 for AF incidence with one standard deviation change of BDNF.

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Results

Of the 3,457 participants included in the study, the mean age was 64.5 ± 11.3 years and 58% were women. **Table 1** shows the baseline characteristics of the study participants.

During up to 10-years of follow-up, 395 individuals developed AF. **Table 2** shows the association of serum BDNF concentrations and risk of incident AF. In unadjusted analysis, higher mean serum BDNF concentration was associated with lower incidence of AF (hazard ratio [HR] per standard deviation change 0.89, 95% confidence interval [CI] 0.80-0.99, $P=.02$). In exploratory analyses, after adjustment for age or sex, there was no statistically significant association of serum BDNF concentrations and risk of incident AF (**Supplementary Table 1**).

In secondary analysis examining for nonlinear associations, in unadjusted analyses a statistically significant lower risk of incident AF was noted with higher BDNF quartiles. However, we did not observe any statistically significant difference among BDNF quartiles in the risk of incident AF in age- and sex-adjusted or multivariable-adjusted analyses. Comparing Q1 with pooled Q2 to Q4 there was borderline statistically significant association with AF incidence in unadjusted analysis, but no statistically significant association was observed after multivariable adjustment (**Table 2**). Compared to the 4th quartile, the risk of incident AF in the other 3 quartiles did not differ, either. (**Supplementary Table 2**).

There was no significant interaction of sex ($P=.86$) or age (< 65 years, $P=.45$) with BDNF levels and risk of AF. If participants with history of myocardial infarction or heart failure were excluded ($n=179$), there continued to be no statistically significant association of BDNF and 10-year risk of AF (per standard deviation age- and sex-adjusted HR [95% CI] 0.95 [0.86-1.06], $P=.36$; and multivariable-adjusted HR [95% CI], 0.97 [0.88-1.08], $P=.61$).

Discussion

Our study evaluated if serum BDNF concentrations were associated with 10-year risk of incident AF in the FHS. Although in unadjusted analyses higher mean serum BDNF concentrations were associated with lower risk of incident AF, after adjustment for age or sex no persistent association was found. As noted above in **Figure 1**, serum BDNF concentrations were lower with higher mean age and were lower in men compared with women.^{15,16}

BDNF is expressed by endothelial cells¹³ and lower serum BDNF levels are associated with higher risk of cardiovascular events.²¹ BDNF modulates cadherin expression and shedding^{30,31} and interacts with tumor necrosis factor- α .^{32,33} Both cadherin³⁴ and tumor necrosis- α ³⁵⁻³⁷ contribute to atrial structural remodeling in human and animal studies, and therefore changes in BDNF may promote development of a substrate vulnerable to AF. We hypothesized that BDNF is associated with incident AF, possibly through modulation of endothelial cells. However, our findings in a prospective, community-based cohort did not support our hypothesis. Further, we failed to find a threshold effect, or interactions with sex or age.

Our study has several strengths including the availability of long-term follow-up, comprehensive evaluation of clinical covariates and adjudication of cardiovascular outcomes, and consistent FHS adjudication of electrocardiograms for AF by a cardiologist.

However, there are several limitations. The generalizability of the study is potentially limited by the largely white, middle-aged and older adults included in the FHS, and therefore our findings may not be translated to younger individuals or other races/ethnicities. Further, we measured BDNF concentration at a single point, and it is possible that the longitudinal trend in BDNF concentrations or levels at an earlier age are more important (mean age in our study was 65 ± 11 years). Single point BDNF measurements may be affected by recent patient factors, e.g. exercise, diet, or time of measurement. In addition, we examined circulating BDNF, and cannot comment on the relation of left atrial tissue BDNF and risk of AF. AF in the population is known to be underdiagnosed, which may be the case in the FHS leading to possible misclassification bias.³⁸ Our follow-up period was 10 years, but a longer duration of follow-up may provide different findings. We did not distinguish between AF and atrial flutter and between AF types; we cannot exclude variation in the relation between BDNF and subtypes of AF.

Conclusion

In our moderate-sized community-based sample, serum BDNF concentrations were not associated with 10-year risk of incident AF. Given BDNF's role as a growth factor, future studies may investigate if tissue levels of BDNF or circulating BDNF levels during early adulthood, or serial BDNF concentrations influence AF risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

None

Abbreviations

AF	atrial fibrillation
BDNF	brain-derived neurotrophic factor
FHS	Framingham Heart Study

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Figure 1. The factors and outcomes associated with BDNF

BDNF is released in the nervous system and by endothelial cells. Several factors can increase or decrease BDNF levels. Serum BDNF levels have been demonstrated to be associated with dementia and cardiovascular events. The grey boxes include continuous variables in which increases in the risk factors are associated with changes in BDNF levels. BDNF = brain-derived neurotrophic factor.

Table 1

Baseline characteristics of the study sample.

Sample characteristics (n=3457)	
Age, years	65±11
Women, n (%)	1992 (58)
Original cohort, n (%)	580 (17)
Body mass index, kg/m ²	27.2 [24.3 – 30.5]
Electrocardiographic PR interval, ms	160 [150 – 180]
Systolic blood pressure, mmHg	130±20
Treatment for hypertension, n (%)	1231 (36)
Diabetes, n (%)	417 (12)
Significant heart murmur [*] , n (%)	111 (3)
Myocardial infarction, n (%)	160 (5)
Heart failure, n (%)	37 (1)
BDNF, pg/mL	23431 [18026 – 28925]

BDNF = brain-derived neurotrophic factor.

Values are presented as median [25th-75th percentile], mean ± standard deviation, or number (%).^{*} Defined as any diastolic murmur or a systolic murmur of grade 3 of 6

Table 2

Serum BDNF concentration and 10-year risk of atrial fibrillation

BDNF	Atrial fibrillation (395/3457)	
	Hazard ratio (95% CI)	P-value
Per SD *		
Unadjusted	0.89 (0.80-0.99)	0.02
Age- and sex-adjusted	0.97 (0.87-1.08)	0.59
Multivariable-adjusted †	0.98 (0.88-1.09)	0.70
Quartiles (unadjusted)		
Q1	Reference	-
Q2	0.95 (0.73-1.24)	0.71
Q3	0.73 (0.55-0.97)	0.03
Q4	0.74 (0.56-0.97)	0.03
Quartiles (age- and sex-adjusted)		
Q1	Reference	-
Q2	1.01 (0.77-1.32)	0.96
Q3	0.86 (0.64-1.14)	0.29
Q4	0.94 (0.71-1.25)	0.66
Quartiles (Multivariable-adjusted)		
Q1	Reference	-
Q2	1.02 (0.78-1.35)	0.87
Q3	0.85 (0.64-1.15)	0.29
Q4	0.97 (0.72-1.30)	0.82
Q1 vs. Q2 to Q4		
Unadjusted	1.25 (1.00-1.56)	0.05
Age- and sex-adjusted	1.07 (0.85-1.34)	0.56
Multivariable-adjusted	1.05 (0.84-1.33)	0.66

BDNF = brain-derived neurotrophic factor; CI = confidence interval;

* Hazard ratios per standard deviation increase in serum BDNF concentrations

† Multivariable-adjusted for age, sex, Framingham cohort, body mass index, PR interval, systolic blood pressure, treatment for hypertension, diabetes mellitus, significant murmur, history of myocardial infarction, and history of heart failure. Analyses account for death as a competing event.