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CLINICAL RESEARCH

Plasma Amyloid-β in Relation to Cardiac Function and Risk of Heart Failure in General Population

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ABSTRACT

BACKGROUND Amyloid-β (Aβ) may be related to cardiac function. However, there are limited data on the association of plasma Aβ with cardiac function and risk of heart failure (HF) in the general population.

OBJECTIVES This study sought to determine the associations of plasma amyloid-β40 (Aβ40) and amyloid-β42 (Aβ42) with echocardiographic measurements of cardiac dysfunction and with incident HF in the general population.

METHODS The study included 4,156 participants of the population-based Rotterdam Study (mean age: 71.4 years; 57.1% women), who had plasma Aβ samples collected between 2002 and 2005 and had no established dementia and HF at baseline. Multivariable linear regression models were used to explore the cross-sectional association of plasma Aβ with echocardiographic measures. Participants were followed up until December 2016. Cox proportional hazards models were used to assess the association of Aβ levels with incident HF. Models were adjusted for cardiovascular risk factors.

RESULTS A per 1-SD increase in log-transformed plasma Aβ40 was associated with a 0.39% (95% CI: −0.68 to −0.10) lower left ventricular ejection fraction and a 0.70 g/m^2 (95% CI: 0.06-1.34) larger left ventricular mass indexed by body surface area. Aβ42 was not significantly associated with echocardiographic measures cross-sectionally. During follow-up (median: 10.2 years), 472 incident HF cases were identified. A per 1-SD increase in log-transformed Aβ40 was associated with a 32% greater risk of HF (HR: 1.32; 95% CI: 1.15-1.51), and the association was significant in men, but not in women. Higher plasma Aβ42 levels were associated with an increased risk of HF (HR: 1.12; 95% CI: 1.02-1.24), although the association was attenuated after further adjustment for concomitant Aβ40 (HR: 1.03; 95% CI: 0.92-1.16).

CONCLUSIONS Higher levels of Aβ40 were associated with worse cardiac function and higher risk of new onset HF in the general population, in particular among men. (J Am Coll Cardiol HF 2023;11:93-102) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Brain accumulation of amyloid-β (Aβ) is the major hallmark of the Alzheimer disease (AD) amyloid hypothesis.[1] Given the cleavage at variable sites, γ-secretase yields Aβ peptides of different lengths, with amyloid-β40 (Aβ40) and amyloid-β42 (Aβ42) the predominant isoforms.[2] Aβ peptides, in particular Aβ40, are produced not only in the central nervous system but also peripherally.

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ABBREVIATIONS AND ACRONYMS

Aβ = amyloid-β
AD = Alzheimer disease
AF = atrial fibrillation
BSA = body surface area
CVD = cardiovascular disease
HF = heart failure
LAD = left atrial diameter
LV = left ventricular
LVEF = left ventricular ejection fraction

Aβ40 is mostly found in vascular lesions, and Aβ42, the most aggregation prone and neurotoxic isoform of Aβ, mainly deposits in brain lesions.[3] The Aβ42/Aβ40 ratio is considered a surrogate biomarker for cortical Aβ deposition, which can also be used to aid in the diagnosis of AD.[4]

Aβ peptides have primarily been studied for their roles in neuronal dysfunction, whereas emerging evidence indicates the potential link between Aβ and cardiac function. First, Aβ has been found to accumulate in the heart of patients with AD and induce AD-related cardiac amyloidosis,[5,6] findings raising a novel hypothesis that Aβ disorder is a multiple organ syndrome. Second, the toxic effects of Aβ preamyloid oligomers on cardiomyocytes have been demonstrated, causally linking cardiac Aβ-amyloidosis with cardiac dysfunction.[7,8] Moreover, Aβ40 is suggested to be involved in vascular aging. The accumulation of Aβ40 in blood, vascular wall, and heart tissues has been associated with cardiac dysfunction,[3,5,9] coronary heart disease,[10] cardiovascular mortality,[10,11] and adverse outcomes among patients with heart failure (HF).[11] So far, research on the association between plasma Aβ40, Aβ42, and the Aβ42/Aβ40 ratio with cardiac function and HF in the general population is limited. The pathogenesis and clinical relevance of these biomarkers for cardiac function remain unclear.

Using data from the prospective population-based Rotterdam Study cohort in the Netherlands, we investigated the cross-sectional association of plasma levels of Aβ40, Aβ42, and the Aβ42/Aβ40 ratio with echocardiographic parameters of cardiac function and structure. We further assessed their associations with incident HF among participants free of dementia and HF at baseline.

METHODS

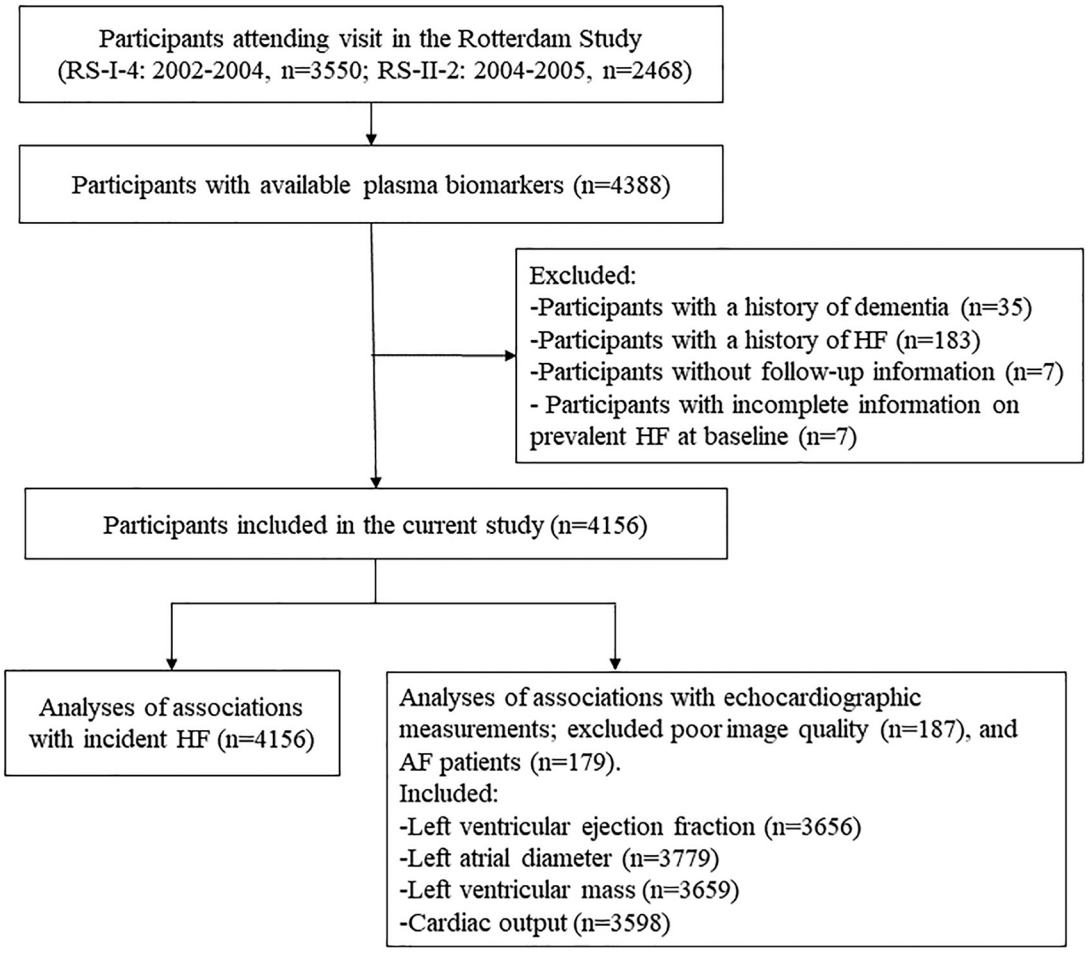
STUDY PARTICIPANTS. This study was embedded within the Rotterdam Study, an ongoing prospective population-based cohort in adults aged 40 years or older. The cohort started in 1990 and has undergone 3 extensions, in 2000, 2006, and 2016. Detailed rationale and design of the Rotterdam Study have been described previously.[12] Participants undergo examination at baseline and during subsequent follow-up visits every 4 to 5 years. The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus Medical Center (registration number: MEC 02.1015) and by the Dutch Ministry of Health, Welfare, and Sport (Population Screening Act WBO, license number: 1071272-159521-PG). The Rotterdam Study has been entered into the Netherlands National Trial Register and into the WHO International Clinical Trials Registry Platform under shared catalog number NTR6831. All participants provided written informed consent to participate in the study and to have their information obtained from their treating physicians.

We conducted current research using data from the fourth visit of the original cohort (RS [Rotterdam Study]-I-4: 2002-2004; n = 3,550) and the second visit of the extended cohort (RS-II-2: 2004-2005; n = 2,468). Of these participants, 4,388 had available measurements of plasma Aβ40 and Aβ42. We excluded participants with a diagnosis of dementia (n = 35), a history of HF (n = 183), incomplete information on the prevalence of HF at their baseline visit (n = 7), or lack of informed consent for follow-up (n = 7). As a result, a total of 4,156 participants were included in the current study. Regarding echocardiographic assessments, we excluded 366 individuals because of poor image quality or a history of atrial fibrillation (AF). Therefore, information on echocardiographic assessments was available on left ventricular ejection fraction (LVEF) for 3,656 participants, on left atrial diameter (LAD) for 3,779 participants, on left ventricular (LV) mass for 3,659 participants, and on cardiac output for 3,598 participants (**Figure 1**).

ASSESSMENT OF PLASMA Aβ40 AND Aβ42. Details of plasma Aβ40 and Aβ42 measurements have been described elsewhere.[13] EDTA plasma was sampled, aliquoted, and frozen according to standard procedures. All measurements were performed at Quanterix on a single molecule array HD-1 analyzer platform, using a Simoa Human Neurology 3-Plex A (N3PA) assay (Quanterix). Samples were tested in duplicate. Two quality control samples were run on each plate for each analyte. When either or both measurements were missing or the concentration coefficient of variation exceeded 20% or control samples were out of range, samples were set as unreliable and were excluded from the analysis.[13]

ASSESSMENT OF CARDIAC FUNCTION AND ASCERTAINMENT OF HF. Echocardiographic measurements and plasma Aβ measurements (blood samples) were obtained from the same visit in the Rotterdam Study. A total of 1,953 (47%) of the participants underwent these 2 measurements on the same day, and the overall average time interval between the 2 measurements was 13 days. The echocardiograms were obtained by 4 certified, experienced echocardiographers according to a standardized protocol.[14] Echocardiograms were performed with a commercially available ultrasonography

FIGURE 1 Flowchart of the Study Group



AF = atrial fibrillation; HF = heart failure; RS = Rotterdam Study.

system (AU3 Partner, Esaote Biomedica, with a 3.5/2.5-MHz transducer) and Acuson Cypress (with a 3V2c transducer).[14] As previously reported in detail,[15] the inter-reader and intrareader agreements were good. Several structural parameters were measured in the parasternal long-axis view with the use of M-mode and 2-dimensional guidance, including LAD, left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), end-diastolic interventricular septum thickness (IVST), and end-diastolic left ventricular posterior wall thickness (LVPWT). LV mass, in grams, was calculated as follows, according to Devereux et al[16]:

$$0.8 \times (1.04 \times [\{\text{LVEDD} + \text{IVST} + \text{LVPWT}\}^3 - \text{LVEDD}^3]) + 0.6$$

End-diastolic volume (EDV) and end-systolic volume (ESV) were used to calculate LVEF on the basis of the Teichholz formula.[17] Cardiac output (L/min) was calculated as follows:

$$(\text{EDV} - \text{ESV}) \times \text{heart rate}$$

Cardiac output and LV mass were both indexed to body surface area (BSA).

The Rotterdam Study participants are monitored continuously for incident cardiovascular events through automated linkage of files from general practitioners, including all information from medical specialist consultation.[18] Incident HF was defined as a combination of the presence of typical

symptoms or signs of HF on the basis of the criteria of the European Society of Cardiology and was confirmed by medical specialists.[18] Study subjects were observed for the occurrence of the HF event, death, or end of follow-up time (December 2016), whichever came first.

ASSESSMENT OF MORTALITY. Information on vital status of participants of the Rotterdam Study is obtained from municipal health authorities in Rotterdam and is updated monthly for all-cause mortality.

ASSESSMENT OF COVARIATES. Procedures for physical examination, clinical testing, and laboratory testing and definitions of cardiovascular outcomes in the Rotterdam Study have been previously described.[12,18] In short, information on a history of cardiovascular disease (CVD) (defined as coronary heart disease or stroke) and AF was verified from the medical records of the general practitioners. Prevalent coronary heart disease was defined as a history of myocardial infarction or revascularization.[18] Stroke was defined using criteria as a syndrome of rapidly developing symptoms of focal or global cerebral dysfunction lasting 24 hours or longer or leading to death, with no other apparent cause than vascular origin.[19] AF was defined in accordance with the European Society of Cardiology guideline.[20] Participants were screened for dementia by using the Mini-Mental State Examination and the Geriatric Mental Schedule organic level.[21] All participants suspected of having dementia are reviewed by a consensus panel that adheres to applied standard criteria for dementia to come to a final diagnosis.[21]

Blood pressure was measured using a random-zero sphygmomanometer on the right arm twice, and the average of the 2 measurements was used. Diabetes mellitus was defined as a fasting glucose level ≥7 mmol/L or a nonfasting glucose level ≥11.1 mmol/L, and/or the use of glucose-lowering medication. Serum total cholesterol and high-density lipoprotein cholesterol values were assessed using comparable enzymatic procedures. Estimated glomerular filtration rate was calculated according to the Chronic Kidney Disease Epidemiology Collaboration formula.[22] Trained interviewers administered standardized questionnaires to obtain information on medical history, smoking status, and pharmacy prescription records. Height and weight were measured, and body mass index was calculated as weight (kg)/(height [m])^2. BSA was calculated by using the Mosteller formula:

$$\text{BSA} = 0.016667 \times \text{weight (kg)}^{0.5} \times \text{height (cm)}^{0.5}$$

STATISTICAL ANALYSIS. Baseline characteristics of the study participants were presented as mean ± SD for normally distributed variables, median (IQR) for skewed variables, and number (percentage) for categorical variables. Aβ40 and Aβ42 were natural log-transformed for all analyses to approximate normal distribution. Pearson correlation coefficients between log-transformed plasma Aβ40 and log-transformed Aβ42 were calculated.

First, we used multivariable linear regression to determine the cross-sectional associations of plasma Aβ40, Aβ42, and the Aβ42/Aβ40 ratio with echocardiographic measures, including LVEF, LAD, BSA-indexed LV mass, and BSA-indexed cardiac output. Plasma Aβ biomarkers were set as exposure variables, and echocardiographic measurements were set as outcome variables. Aβ40 and Aβ42 were standardized (mean centered and then divided by the SD of the variable), and the standardized β-coefficients were presented. Models were adjusted for traditional cardiovascular risk factors, including age, sex, smoking status, body mass index, systolic blood pressure, diabetes mellitus, total and high-density lipoprotein cholesterol levels, lipid-lowering medication use, blood pressure-lowering medication use, and history of CVD. We did not include education level, physical activity, and estimated glomerular filtration rate in the final model because these, variables did not show significant association with incident HF ($P > 0.20$) and they had a high missing rate (>15%). Natural cubic spline function was used to specify the nonlinear effect for age (3 knots).

Next, we determined the association of plasma Aβ biomarkers with incident HF, by using cause-specific hazard models (on the basis of Cox proportional hazards models) and considering that death could be a competing event for incident HF. We reported the HRs and 95% CIs of per 1-SD increase of log-transformed Aβ biomarkers. The proportional hazards assumption was tested using the Schoenfeld residuals, and the assumption was not violated. We constructed crude (unadjusted) cumulative incidence plots to show the incidence of HF among study subjects in each quartile of biomarkers. Gray's test was used to test the equality of cumulative incidence curves among quartile groups.[23] In addition to the aforementioned potential confounders, we further

TABLE 1 Baseline Characteristics of the Study Group (N = 4,156)

Age, y	71.4 ± 7.2
Women	2,373 (57.1)
Body mass index, kg/m^2	27.6 ± 4.0
BSA, m^2	1.9 ± 0.2
Total cholesterol, mmol/L	5.7 ± 1.0
High-density lipoprotein cholesterol, mmol/L	1.5 ± 0.4
Systolic blood pressure, mm Hg	149.1 ± 20.8
Hypertension	3,215 (77.4)
Diabetes mellitus	527 (13.1)
Blood pressure lowering medication	1,752 (42.5)
Lipid-lowering medication	913 (22.1)
Current smoker	509 (12.5)
History of coronary heart disease or stroke	485 (11.8)
History of AF	193 (4.6)
Echocardiographic measurements	
LVEF, %	63.0 ± 9.0
Left atrial diameter, cm	4.0 ± 0.6
LV mass, g	143.6 ± 41.5
LV mass indexed by BSA	76.0 ± 19.8
Cardiac output, L/min	5.8 ± 1.5
Cardiac output indexed by BSA	3.1 ± 0.8
Plasma levels of Aβ biomarkers	
Aβ40, pg/mL	256.4 (227.9-289.0)
Aβ42, pg/mL	10.3 (8.8-11.9)
Aβ42/Aβ40	0.04 ± 0.01

Values are mean ± SD, n (%), or median (IQR).

Aβ = amyloid-β; Aβ40 = amyloid-β40; Aβ42 = amyloid-β42; AF = atrial fibrillation; BSA = body surface area; LV = left ventricular; LVEF = left ventricular ejection fraction.

adjusted these models for a history of AF because AF is associated with a risk of HF and concentrations of Aβ.[24] To determine whether associations would be affected by sex, we tested interaction effects between sex and biomarkers.

Sensitivity analyses were conducted. First, we concomitantly included plasma Aβ40 and Aβ42 into the models, on top of other model adjustments. Second, we repeated analyses by excluding participants with prevalent CVD at baseline. The maximum missing information on covariates was up to 5.7% of the participants. Missing values in covariates were imputed using the multiple imputation method. Five imputed data sets were generated, and the summarized estimates were calculated on the basis of Rubin's rule by using the pool function in mice software.[25] A 2-sided *P* value was considered significant at $P < 0.05$. Statistical analyses were performed with the use of R software version 4.0.5 (R Project).

RESULTS

BASELINE CHARACTERISTICS. The study group included 4,156 participants with a mean (± SD) age of 71.4 ± 7.2 years, and 57.1% were women. Hypertension and diabetes were present in 77.4% and 13.1% of the participants at baseline (Table 1). Log-transformed Aβ40 and Aβ42 were moderately correlated (Pearson coefficient r = 0.57; $P < 0.001$).

ASSOCIATION OF PLASMA Aβ BIOMARKERS WITH CARDIAC FUNCTION. After adjustments for potential confounders, higher levels of Aβ40 were significantly associated with lower LVEF (β: −0.39; 95% CI: −0.68 to −0.10) and larger BSA-indexed LV mass (β: 0.70; 95% CI: 0.06-1.34), but not with LAD or cardiac output (Table 2). None of the echocardiographic parameters were independently associated with either plasma Aβ42 or the Aβ42/Aβ40 ratio.

ASSOCIATION OF PLASMA Aβ BIOMARKERS WITH INCIDENT HEART FAILURE. During a median of 10.2 years of follow-up, HF developed in a total of 472 (11.4%) participants. Cumulative incidence curves showed that incident HF significantly differed among participants in quartiles of Aβ40 and Aβ42 ($P < 0.001$) (Figure 2). Table 3 displays HRs of risk of HF and its competing event for plasma Aβ biomarkers. After adjusting for cardiovascular risk factors, higher levels of Aβ40 were associated with a greater risk for HF (HR: 1.32; 95% CI: 1.15-1.51), and the association was significant only in men (*P* value for sex interaction = 0.02). We subsequently performed analyses in women and men separately. A 1-SD increase in log-transformed Aβ40 was associated with a 31%

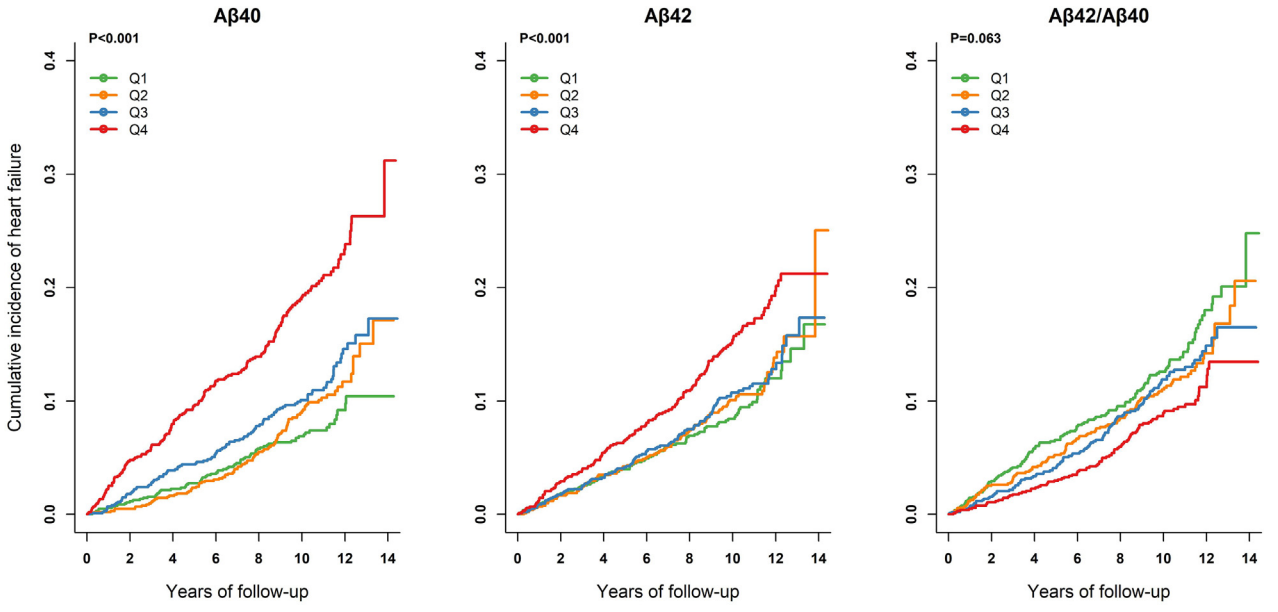
TABLE 2 Associations of Plasma Amyloid-β With Echocardiographic Parameters of Cardiac Function in Total Population

	LVEF (%) (n = 3,656)		LAD (n = 3,779)		BSA-Indexed LV Mass (n = 3,659)		BSA-Indexed Cardiac Output (n = 3,598)	
	β[a] (95% CI)	*P* Value	β[a] (95% CI)	*P* Value	β[a] (95% CI)	*P* Value	β[a] (95% CI)	*P* Value
Aβ40 (log transformed)	−0.39 (−0.68 to −0.10)	0.008	−0.01 (−0.02 to 0.01)	0.660	0.70 (0.06 to 1.34)	0.031	−0.02 (−0.04 to 0.01)	0.212
Aβ42 (log transformed)	−0.24 (−0.51 to 0.03)	0.086	−0.01 (−0.02 to 0.01)	0.320	−0.06 (−0.66 to 0.54)	0.845	−0.02 (−0.05 to 0.01)	0.094
Aβ42/Aβ40	0.04 (−0.23 to 0.32)	0.747	−0.01 (−0.02 to 0.01)	0.317	−0.46 (−1.06 to 0.14)	0.130	−0.01 (−0.03 to 0.02)	0.702

[a]β represents changes in echocardiographic parameters of cardiac function per 1-SD increase in plasma biomarkers. Models were adjusted for age (with 3 natural spline knots), sex, smoking status, body mass index, systolic blood pressure, diabetes mellitus, total and high-density lipoprotein cholesterol levels, lipid-lowering medication use, blood pressure-lowering medication use, history of cardiovascular disease.

LAD = left atrial diameter; other abbreviations as in Table 1.

FIGURE 2 Crude Cumulative Incidence Plots for Heart Failure



Aβ40 = amyloid-β40; Aβ42 = amyloid-β42; Q1, Q2, Q3, Q4 = quartiles 1 to 4 (Q1 represents the lowest quartile).

greater risk for HF in men (HR: 1.31; 95% CI: 1.14-1.54), but not in women (HR: 1.06; 95% CI: 0.93-1.22). Higher levels of Aβ42 were significantly associated with an increased risk of HF (HR: 1.12; 95% CI: 1.02-1.24), but this was largely explained by concurrent levels of Aβ40, as described in the later discussion of sensitivity analysis. There was no significant association between the Aβ42/Aβ40 ratio and the risk of HF. No significant interaction effects of sex with Aβ42 or the Aβ42/Aβ40 ratio were observed.

TABLE 3 Cause-Specific Cox Proportional Hazard Models for the Associations Between Plasma Amyloid-β With Incident Heart Failure and Mortality

Biomarkers	Outcome	HR (95% CI)	*P* Value
Aβ40 (log transformed)[a]	Heart failure	1.32 (1.15-1.51)[a]	<0.001
	Mortality	1.19 (1.17-1.27)	<0.001
Aβ42 (log transformed)	Heart failure	1.12 (1.02-1.24)	0.023
	Mortality	1.01 (0.96-1.07)	0.638
Aβ42/Aβ40	Heart failure	0.99 (0.91-1.08)	0.786
	Mortality	0.90 (0.85-0.95)	<0.001

HRs for outcomes were calculated per 1-SD increase in biomarkers. Models were adjusted for age (with 3 natural spline knots), sex, smoking status, body mass index, systolic blood pressure, diabetes mellitus, total and high-density lipoprotein cholesterol levels, lipid-lowering medication use, blood pressure-lowering medication use, history of cardiovascular disease, and history of AF. [a]There was a significant interaction between sex (women) and Aβ40 (HR: 0.81; 95% CI: 0.68-0.97; $P = 0.022$). In women: HR: 1.06; 95% CI: 0.93-1.22; $P = 0.371$; in men: HR: 1.31; 95% CI: 1.14-1.54; $P < 0.001$.

Abbreviations as in Table 1.

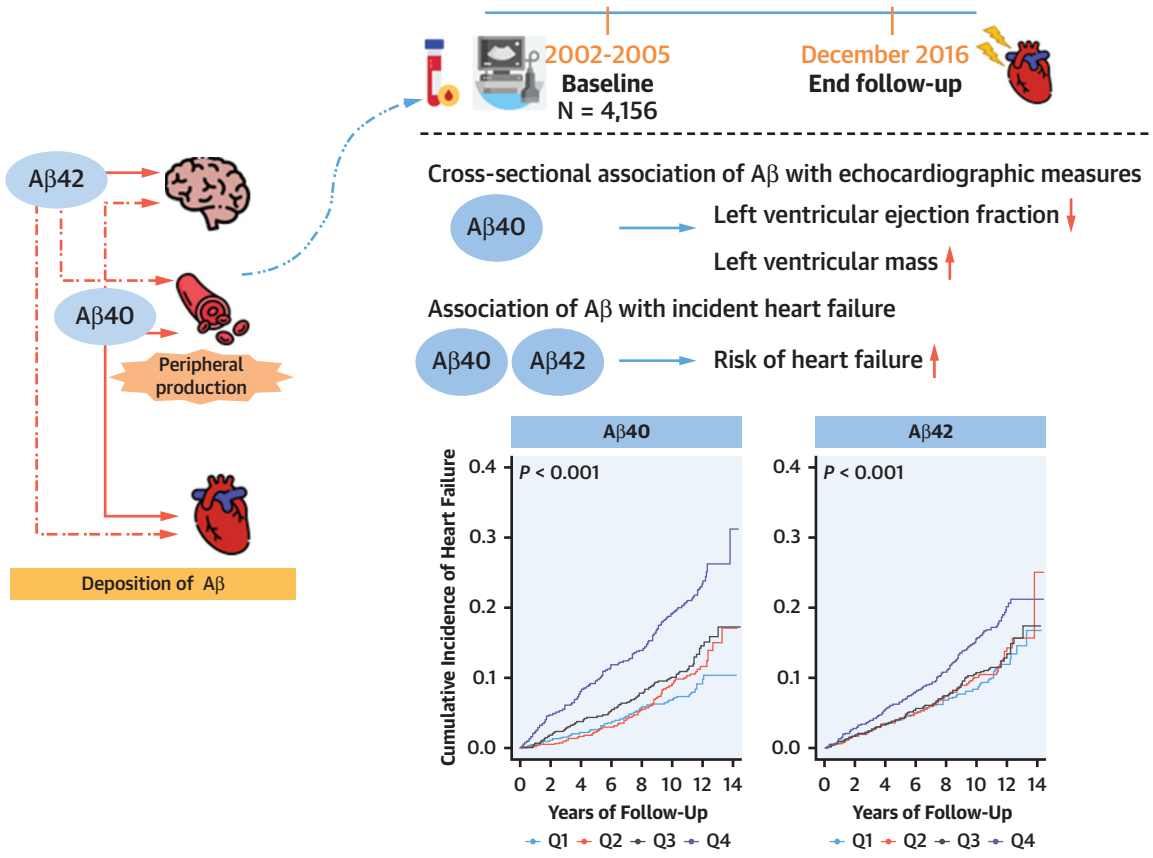
COMPETING RISK OF MORTALITY. A total of 1,449 (34.8%) participants died during the entire follow-up period. We found that participants with higher levels of Aβ40 and participants with lower levels of Aβ42/Aβ40 ratio had a greater risk of death, whereas plasma Aβ42 levels were not significantly associated with mortality (Table 3).

SENSITIVITY ANALYSIS. In sensitivity analysis, we concomitantly included Aβ40 and Aβ40 into the models (Supplemental Tables 1 and 2), and we performed analyses among participants free of CVD at baseline (Supplemental Tables 3 and 4). The association of plasma Aβ40 and the Aβ42/Aβ40 ratio with echocardiographic measurements and incident HF did not change materially compared with main results. However, the association of plasma Aβ42 with incident HF, after additional adjustment for Aβ40, was no longer significant (HR: 1.03; 95% CI: 0.92-1.16). Moreover, among participants without prevalent CVD at baseline, the concentrations of plasma Aβ42 were not associated with incident HF.

DISCUSSION

Using data from the Rotterdam Study cohort, we found that higher levels of plasma Aβ40 were associated with a slightly lower LVEF, a slightly higher LV mass, and a higher risk of incident HF, independent of traditional cardiovascular risk factors, and in

CENTRAL ILLUSTRATION **Plasma Amyloid-β in Relation to Cardiac Function and Risk of Heart Failure in the General Population**



Zhu F, et al. J Am Coll Cardiol HF. 2023;11(1):93–102.

Aβ = amyloid-β; Aβ40 = amyloid-β40; Aβ42 = amyloid-β42; Q1, Q2, Q3, Q4 = quartiles 1 to 4 (Q1 represents the lowest quartile).

particular among men. Higher plasma levels of Aβ42 were associated only with a higher risk of incident HF (Central Illustration).

Our observation that higher plasma levels of Aβ40 were associated with a worse LVEF, a larger LV mass, and a higher risk of HF aligns with a previous study that reported worse HF symptoms with higher levels of plasma Aβ40 among 939 patients with HF.[11] Meanwhile, Stamatelopoulos et al[9] found that plasma Aβ40 levels were significantly associated with levels of N-terminal pro-B-type natriuretic peptide and high-sensitivity cardiac troponin T, findings suggesting the involvement of this biomarker in an early subclinical rise in filling pressure and myocardial injury. A significant association between elevated Aβ40 and worse left atrial function (ie, left atrial emptying fraction) has also been reported.[9] Previous research indicated the direct and indirect role of Aβ40 in accelerating arterial aging and various stages of atherosclerosis.[3] Mechanistically, circulating Aβ40 activates numerous vascular cells and leads to vascular inflammation.[26] It could stimulate platelet activation and adhesion and induce matrix metalloproteinases by human monocytes to increase plaque vulnerability.[27] Moreover, concentrations of Aβ40 are related with the progression of arterial stiffness.[28] Atherosclerosis and arterial stiffness, by decreasing blood flow and increasing cardiac afterload, can raise the risk of HF. Increased arterial stiffness also promotes LV hypertrophy (defined as an LV mass that exceeds the normal range) and reduce coronary perfusion, thereby leading to LV diastolic dysfunction and HF.[29] In addition, abnormal aggregation of Aβ peptides may disrupt calcium (Ca^{2+}) homeostasis in cardiomyocytes,[30] and altered Ca^{2+} homeostasis is recognized as a contributor to HF.[31]

Therefore, we speculate that Aβ40 and Aβ42, as major isoforms of Aβ peptides, may exert similar effects. Notably, the effect sizes of plasma Aβ40 with LVEF and LV mass were small, and we observed no significant associations with other echocardiographic measurements such as cardiac output or LAD. This may be because we assessed only the association at baseline in a group without overt HF, so late changes were not discernible. Longitudinal studies with repeated echocardiographic measurements are further needed to evaluate the association of plasma Aβ40 with cardiac dysfunction and remodeling changes.

To our knowledge, there is no published research on the association of plasma Aβ42 with incident HF. Meakin et al[32] demonstrated that metabolic disorders, including obesity and diabetes, can result in elevated plasma Aβ42 levels. In contrast, Roeben et al[33] reported that plasma Aβ42 concentrations were associated neither with coronary artery disease nor with any cardiovascular risk factors, including hypertension and hyperlipidemia. Compared with Aβ40, aggregated Aβ42 is the primary constituent of amyloid plaques in the brain. Generally speaking, deposition of Aβ42 as cerebral plaques leads to lower plasma levels of Aβ42 (and a lower Aβ42/Aβ40 ratio) because the more brain amyloid is deposited in plaques, the less is available for secretion to the cerebrospinal fluid and blood.[34] As such, the observed higher risk of HF with *higher* plasma Aβ42 levels is unexpected if it is based only on the link between AD and HF. One possible explanation could be that the levels of Aβ42 in the blood not only reflect neurodegeneration, but also are also involved in pathologic pathways leading to cardiac dysfunction. In addition, the probability of a biologic link between Aβ42 and HF was further undermined by strong attenuation after additional adjustment for plasma Aβ40. This finding could suggest that the link between plasma Aβ and HF is mainly driven by vascular amyloid disease, rather than the type of aggregated amyloid deposits seen in the brain of patients with AD.

Plasma Aβ42/Aβ40 is also a robust measure for detecting amyloid plaques and can be used to aid in the diagnosis of AD.[4,13] However, we did not find it to be related to cardiac dysfunction or incident HF. This finding suggests that the plasma Aβ42/Aβ40 ratio may not be a useful marker of cardiac dysfunction or HF risk.

Interestingly, sex differences were observed in the association of plasma Aβ40 with incident HF in our study. Plasma Aβ40 showed significant associations with incident HF only in men. Although this finding is incompletely understood, there are several potential explanations for the underlying mechanisms. First, men have higher plasma Aβ40 levels, which may reflect sex differences in blood-brain barrier permeability (eg, men could have higher concentrations of cerebrospinal fluid–specific isoforms in the blood).[35] Second, HF is demonstrated to have a stronger relationship with dementia in men than in women, on the basis of previous research.[35] So it seems plausible that the association between plasma AD biomarkers and incident HF was more profound in men. In addition, differences between men and women in genetic factors (eg, family history), sex hormonal factors (eg, menopause), and lifestyle factors (eg, smoking, diet, exercise) could partly account for the observed sex differences.

Neprilysin is a circulating transmembrane protease with a broad range of substrates including Aβ peptides.[36] Considering its role in the metabolism of cardiovascular peptides and Aβ peptides, neprilysin has gained interest as a potential, but controversial, pharmaceutical target for AD as well as for HF.[37] Notably, Aβ levels in brain and plasma are not simply linearly correlated, and more data are needed to support how circulatory neprilysin directly and indirectly affects plasma Aβ levels and further affects HF. However, we did not have data on neprilysin in our study group to help elucidate the potential role of neprilysin in the treatment of HF through an Aβ pathogenic mechanism.

This is the first study examining associations between plasma concentrations of Aβ40, Aβ42, and the Aβ42/Aβ40 ratio and cardiac function and risk of HF among the community-dwelling population without previous dementia or HF. The strengths of our study include a well-characterized cohort with availability of plasma Aβ biomarkers, various cardiovascular risk factors, and echocardiographic assessment of cardiac function, as well as detailed information on HF status and long follow-up. Moreover, plasma Aβ biomarkers were evaluated with stringent quality control procedures.

STUDY LIMITATIONS. First, the study group comprised an older adult population of mostly White European ancestry. Therefore, our results may not be generalizable to younger populations and other ancestries. Second, we assessed only the associations of plasma Aβ biomarkers with echocardiographic measurements in the baseline study group without overt HF, and late changes in cardiac function and cardiac remodeling were not discernible. Third, we measured LVEF and cardiac output by using the Teichholz method, whereas the volumetric method to measure LVEF[38] and the velocity time integral method to

measure cardiac output[39] are more recommended. This approach may have introduced measurement error, resulting in a loss of statistical power. Fourth, we did not have data for distinction of HF phenotypes (HF with preserved ejection fraction vs HF with reduced ejection fraction). Focusing on subtypes of HF in future studies would be warranted and would help to explore further and compare the underlying mechanisms. Fifth, although we adjusted for several potential confounders, we cannot rule out the possibility of residual or unmeasured confounding.

CONCLUSIONS

In this prospective, population-based study, higher levels of plasma Aβ40 were associated with worse cardiac function and a higher risk of HF in the general population, independent of traditional cardiovascular risk factors, and especially among men. Higher plasma levels of Aβ42 were associated only with a higher risk of HF. The potential roles of plasma Aβ40 and Aβ42 as biomarkers for subclinical cardiac dysfunction warrant further investigation.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: It has been suggested that Aβ may be associated with cardiac function. In particular, Aβ40 can be produced peripherally and is involved in vascular aging. However, there are limited data on the relation of plasma Aβ with cardiac function and risk of HF in the general population. We found that, after accounting for cardiovascular risk factors, higher plasma Aβ40 levels were associated with worse cardiac function and higher risk of new onset HF in the general population, in particular among men. The link between plasma Aβ and HF was primarily driven by Aβ40 rather than by Aβ42.

TRANSLATIONAL OUTLOOK: These findings carry the premise for understanding the pathogenesis of Aβ involvement in cardiac dysfunction and have the potential to be taken forward in identifying individuals at higher risk for HF.

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KEY WORDS amyloid-β40, amyloid-β42, cardiac function, echocardiography, heart failure

APPENDIX For supplemental tables, please see the online version of this paper.