

Parental history of premature coronary artery disease does not affect plasma levels of asymmetric dimethylarginine in young healthy adults

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KEY WORDS

asymmetric dimethylarginine, carotid intima-media thickness, coronary artery disease, positive family history

ABSTRACT

INTRODUCTION Family history of premature coronary artery disease (CAD) is a risk factor of atherogenesis and adverse coronary events.

OBJECTIVES The aim of the study was to establish whether asymmetric dimethylarginine (ADMA), an endogenous inhibitor of nitric oxide formation, might be elevated in the asymptomatic offspring of patients with early-onset CAD and whether it might contribute to subclinical atherosclerosis.

PATIENTS AND METHODS We studied 20 healthy subjects (10 men and 10 women) aged from 19 to 30 years with a parental history of documented CAD before 60 years of age, and 20 controls with no evidence of parental CAD. ADMA and its isomer, symmetric dimethylarginine (SDMA), were determined by enzyme-linked immunosorbent assays. Mean intima-media thickness (IMT) of the common carotid arteries was assessed by B-mode ultrasound.

RESULTS Characteristics of the 2 groups were similar, except for insignificant tendencies towards higher low-density lipoprotein (LDL) cholesterol ($P = 0.07$) and estimated glomerular filtration rate (eGFR) ($P = 0.06$) in the group with a positive family history. Compared with controls, subjects with a parental history of premature CAD had increased IMT (0.54 ± 0.05 vs. 0.48 ± 0.05 mm; $P < 0.001$) and similar levels of ADMA (0.66 ± 0.17 vs. 0.74 ± 0.15 $\mu\text{mol/l}$; $P = 0.14$) and SDMA (0.49 ± 0.07 vs. 0.50 ± 0.07 $\mu\text{mol/l}$; $P = 0.61$). The results did not change substantially on adjustment for LDL cholesterol and eGFR. In a multivariate analysis, parental CAD ($P = 0.005$) and LDL cholesterol ($P = 0.06$), but not ADMA, were independent positive IMT predictors.

CONCLUSIONS Our preliminary data suggest that elevated ADMA is not a part of the proatherogenic risk profile in the young adult offspring of patients with premature CAD.

INTRODUCTION Almost 50 years ago, Slack and Evans¹ described a 2.7- to 7-fold increased risk of death from coronary events in middle-aged first-degree relatives of patients with the onset of clinical coronary artery disease (CAD) manifestations at less than 55 to 65 years of age compared with those with no parental history of CAD. Parental history of myocardial infarction (MI)

below the age of 60 to 70 years conferred mean relative risks of MI of 1.8 and 2.8 in the Health Professionals Follow-up Study² and the Nurses' Health Study,³ respectively, which increased with decreasing age of parents at the time of MI and remained almost unchanged after multivariate adjustment. In 14,538 participants of the Atherosclerosis Risk in Communities study free of

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prevalent CAD, a quantitative measure of family history of CAD – standardized for sex and age at disease onset for each of parents and siblings – was associated with a significant increase in incident MI and cardiac death largely independently of coexisting risk factors, including subclinical carotid atherosclerosis.⁴ In 12,082 individuals from the same cohort, about half of the relationship of carotid intima-media thickness (IMT) with family history in middle-aged whites was explained by the familial aggregation of major cardiovascular (CV) risk factors.⁵ As family history is not included in the Framingham or SCORE risk models, the assessment of emerging CV risk factors among the asymptomatic offspring of patients with premature CAD might improve risk prediction.

To the best of our knowledge, until recently the levels of asymmetric dimethylarginine (ADMA), an endogenous inhibitor of nitric oxide formation, had not been reported in adults with a parental history of premature CAD, known to exhibit impaired coronary⁶ and peripheral^{7,8} vasodilatory endothelial dysfunction and increased carotid IMT.^{5,8-10} Elevated ADMA concentrations are associated with both traditional and some of the novel CV risk factors, endothelial dysfunction, and carotid IMT in subjects without pre-existing atherosclerotic CV disease,¹¹⁻²⁰ as well as with adverse CV outcome across a wide spectrum of CV risk.²¹

Recently, an insignificant tendency towards higher ADMA in the presence of familial predisposition to CAD has been described.²² However, young adults with a family history of premature MI differed significantly from their control counterparts in several characteristics linked with an adverse risk profile, which could limit the interpretation of the results.²² Therefore, our aim was to test the hypothesis that ADMA might be independently related to parental history of premature CAD and could contribute to increased carotid IMT in this condition.

PATIENTS AND METHODS **Subjects** The study included 20 healthy subjects (10 men and 10 women) aged from 19 to 30 years with a positive parental history of documented CAD established before 60 years of age^{8,9} and without major CV risk factors. Additionally, we recruited 20 healthy controls aged from 21 to 30 years with no evidence of established or suspected CAD in their parents. Established CAD was defined as MI, coronary angioplasty, or coronary-artery bypass grafting.

The exclusion criteria were common for both groups and included clinical evidence of atherosclerotic CV disease, arterial hypertension, body mass index of 30 kg/m² or higher, abnormal serum glucose or creatinine levels, total cholesterol above 6.5 mmol/l, high-sensitivity C-reactive protein (hs-CRP) above 5 mg/l, any current medication and coexistent chronic diseases.

Protocol The procedure was performed in agreement with the Declaration of Helsinki. The protocol was approved by the ethics committee of our university, and written informed consent was obtained from each participant. The subjects were studied in the morning after an overnight fasting in an outpatient clinic of our department. Demographic and clinical characteristics including self-reported current smoking were recorded; family history was assessed with a standard questionnaire. Then, participants underwent ultrasonography of the common carotid arteries and blood sampling for biochemical assays.

Ultrasonography of the common carotid arteries

The right and left common carotid arteries were visualized by B-mode imaging in the longitudinal plane using a high-resolution ultrasound device equipped with a 4.0–10.0 MHz vascular transducer (GE Vivid 7, GE Healthcare, Chalfont St. Giles, United Kingdom) by an investigator (T.R.) who was unaware of the family history of the subjects. The image was recorded and stored for an off-line analysis by an automated edge-detection and wall-tracking software program (EchoPAC; GE Healthcare). The final IMT value was averaged from end-diastolic semiautomatic measurements (about 200 per each side) of the distance between the lumen-intima interface and media-adventitia interface at the far arterial wall (distal to the skin) within a manually selected 1-cm segment immediately caudal to the carotid bulb outside atherosclerotic plaques (if present) (FIGURE 1).²³ Plaques were defined as focal echogenic encroachments into the vessel lumen with a distinct area at least 50% thicker than the surrounding wall, as proposed previously.²⁴

Biochemical assays Blood samples were drawn from an antecubital vein for measurements of serum total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, glucose, homocysteine, creatinine, and hs-CRP. We calculated the estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration formula, which is superior to the Modification of Diet in Renal Disease study equation, especially in normal renal function.²⁵

A portion of plasma for future determinations of dimethylarginines was separated and frozen at –70°C until assayed. Commercially available enzyme-linked immunosorbent assays (ELISA) were used to measure ADMA and its stereoisomer, symmetric dimethylarginine (SDMA) (DLD Diagnostika GmbH, Hamburg, Germany). The ADMA ELISA had previously shown high agreement with liquid chromatography-tandem mass spectrometry, the golden standard for ADMA determinations.²⁶ The lower detection limits were 0.05 µmol/l for ADMA and SDMA and intra-assay and inter-assay coefficients of variation averaged 5.7% and 10.3% (ADMA), and 6.1% and 9.8% (SDMA). According to the manufacturer,



FIGURE 1 Representative value of intima-media thickness (IMT) averaged from about 200 semiautomatic measurements within a manually selected 1-cm segment of the common carotid artery; IMT P Pts indicates the number of points corresponding to respective IMT measurements. Abbreviations: Avg – average, Max – maximum, Min – minimum, P – posterior wall, Pts – points, SD – standard deviation

TABLE 1 Characteristics of subjects by parental history of coronary artery disease

Characteristic	Parental history		P
	premature CAD (n = 20)	no CAD (n = 20)	
age, y	26 ± 3	25 ± 3	0.15
female sex	12 (60)	10 (50)	0.55
current smoking	5 (25)	4 (20)	0.73
body mass index, kg/m ²	23.3 ± 3.3	22.6 ± 2.9	0.48
systolic blood pressure, mmHg	116 ± 12	116 ± 8	0.94
diastolic blood pressure, mmHg	76 ± 7	74 ± 8	0.34
eGFR, ml/min/1.73 m ^{2a}	117 ± 11	109 ± 12	0.06
total cholesterol, mmol/l	5.0 ± 0.9	4.5 ± 0.7	0.05
LDL-C, mmol/l	3.1 ± 0.9	2.7 ± 0.6	0.07
HDL-C, mmol/l	1.3 ± 0.4	1.3 ± 0.3	0.43
triglycerides, mmol/l	1.1 ± 0.6	1.1 ± 0.6	0.92
glucose, mmol/l	4.5 (4.2–4.9)	4.7 (4.5–4.9)	0.68
homocysteine, μmol/l	9.9 ± 1.7	9.6 ± 1.5	0.67
hs-CRP, mg/l	0.7 (0.3–1.1)	0.7 (0.4–1.2)	0.49

Values are expressed as means ± standard deviation, medians (interquartile range), or numbers (percentages).

a by the Chronic Kidney Disease Epidemiology Collaboration formula²⁵

Abbreviations: CAD – coronary artery disease, eGFR – estimated glomerular filtration rate, HDL – high-density lipoprotein-cholesterol, hs-CRP – high-sensitive C-reactive protein, LDL-C – low-density lipoprotein-cholesterol

cross-reactivity with L-arginine and other methylarginines averaged <0.01%–0.02% (SDMA or ADMA vs. L-arginine), 0.44%–1.2% (ADMA vs. SDMA), and 0.7%–1.0% (SDMA or ADMA vs. N^G-monomethyl-L-arginine).

Homocysteine was measured by a chemiluminescent microparticle immunoassay (ARCHITECT Homocysteine Reagent Kits, Abbott Diagnostics Division, Abbott Park, Illinois, United States).

Statistical analysis Data are presented as means ± standard deviation (SD) unless otherwise indicated for continuous variables with normal distribution, medians (interquartile range) for not normally distributed parameters or in the case of the lack of homogeneity of variances (heteroscedasticity), and numbers (percentages) for categorical data. The agreement with normal distribution was validated by the Shapiro-Wilk's test and uniformity of variance by the Levene's test. Intergroup differences in continuous variables were assessed by the unpaired two-tailed *t* test or the Mann-Whitney *U* test for not normally distributed (hs-CRP) or heteroscedastic data (glucose). Categorical variables were compared by the two-tailed Fisher's exact test.

The analysis of variance (ANOVA) and covariance (ANCOVA) were applied to estimate interaction effects between family history and sex or self-reported smoking on IMT and ADMA as well as to adjust for selected covariates. To identify independent determinants of carotid IMT in both groups pooled together, we applied a multiple linear regression with backward stepwise covariate selection; the variables were removed from the model at a *P*-value of 0.15. Exclusively, the covariates for which the intergroup *P*-value was below 0.15 entered the ANCOVA and multiple regression. As LDL cholesterol and total cholesterol were closely interrelated (Pearson's correlation coefficient, 0.93; *P* < 0.0001), only LDL cholesterol was considered as a covariate in addition to eGFR.

On the basis of our previous ADMA measurements by ELISA in 80 subjects with CAD (0.48 ± 0.12 μmol/l),²⁷ the study design allowed to detect an increase in mean ADMA levels by 0.9 SD (which corresponds to about 20%–25%) with a statistical power of 80% at a type I error rate of 0.05. A *P*-value below 0.05 was considered significant.

RESULTS Characteristics of the 2 groups were similar, except for insignificant tendencies towards higher total cholesterol, LDL cholesterol, and eGFR in the group with a positive family history (TABLE 1). Carotid plaques were detected in 2 of 20 offspring of patients with premature CAD (10%) and in none of those without evidence of CAD in their parents (*P* = 0.49).

Compared with individuals with a negative family history, subjects with documented premature parental CAD had significantly elevated carotid IMT and similar plasma levels of ADMA and SDMA (TABLE 2, FIGURE 2).

We found no interaction effects between parental history and sex on IMT (*P* = 0.26 for interaction by a two-way ANOVA), ADMA (*P* = 0.49), and SDMA (*P* = 0.98). The results did not substantially change after exclusion of 9 smokers (intergroup *P* by two-tailed *t* test: IMT [*P* = 0.02]; ADMA [*P* = 0.29]; SDMA [*P* = 0.55]) or after adjustment for LDL cholesterol and eGFR (intergroup *P* by ANCOVA: IMT [*P* = 0.006]; ADMA [*P* = 0.44]; SDMA [*P* = 0.41]).

TABLE 2 Plasma dimethylarginines and carotid intima-media thickness by parental history of coronary artery disease

Characteristic		Parental history		P
		premature CAD (n = 20)	no CAD (n = 20)	
plasma dimethylarginines	ADMA, $\mu\text{mol/l}$	0.66 ± 0.17	0.74 ± 0.15	0.14
	SDMA, $\mu\text{mol/l}$	0.49 ± 0.07	0.50 ± 0.07	0.61
carotid IMT, mm		0.54 ± 0.05	0.48 ± 0.05	<0.001

Values are expressed as means $\pm$ standard deviation.

Abbreviations: ADMA – asymmetric dimethylarginine, CAD – coronary artery disease, IMT – intima-media thickness, SDMA – symmetric dimethylarginine

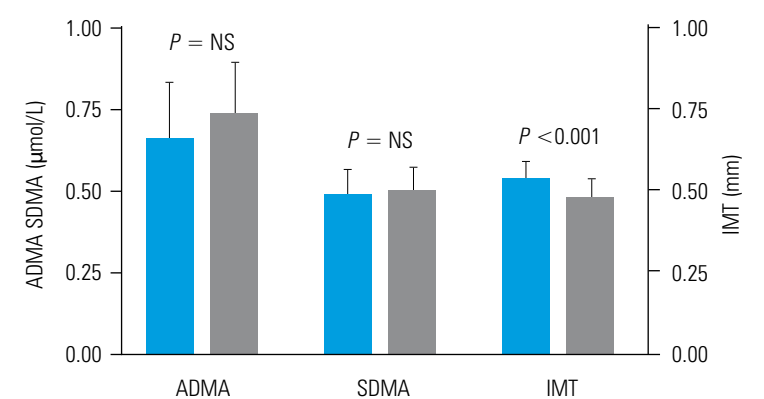


FIGURE 2 Similar plasma levels of asymmetric dimethylarginine (ADMA) and symmetric dimethylarginine (SDMA), and increased carotid intima-media thickness (IMT) in the offspring of patients with premature coronary artery disease (CAD) (blue bars) compared with subjects with a negative parental history of CAD (grey bars); values are shown as means and standard deviation
Abbreviations: NS – nonsignificant

By a multivariate analysis, only positive family history was an independent significant predictor of IMT (non-standardized regression coefficient [β], mean $\pm$ standard error of the mean, 0.049 ± 0.017 , $P = 0.005$) and a respective insignificant tendency was observed for LDL cholesterol ($\beta = 0.021 \pm 0.010$, $P = 0.06$) (adjusted coefficient of multiple determination: $R^2 = 0.29$, $P < 0.001$).

DISCUSSION Our salient observation was no effect of a parental history of premature CAD on ADMA levels in young asymptomatic subjects. In addition, premature parental CAD by itself, but not ADMA, was independently related to an elevated carotid IMT in the offspring.

Satılmışoğlu et al.²² have recently described a borderline tendency towards higher ADMA levels ($P = 0.06$) in young adults with premature MI in their first-degree relatives. However, as they also exhibited significantly higher glucose, triglycerides and diastolic blood pressure, and lower HDL cholesterol levels compared with subjects with a negative family history, a pure effect of familial predisposition to CAD could not be estimated, all the more because a multivariate analysis was not performed. In sharp contrast, our data support no independent effect of parental CAD history on plasma ADMA, at least taking into consideration possible interferences of subjects' characteristics known to be associated with higher ADMA concentrations, such as increased blood pressure,¹⁴ abnormal lipid profile,^{12,16} hyperglycemia,^{13,15} hyperhomocysteinemia,¹⁷ even mild renal insufficiency,^{11,28} and the degree of inflammation.^{19,20}

The present study was based on the assumption that familial predisposition to early CAD might be accompanied by higher ADMA, even in the absence of other major CV risk factors. Even if such hypothetical association would not necessarily imply a causative role of ADMA, increased ADMA concentrations could also be the marker of early steps in atherogenesis, i.e., enhanced endothelial apoptosis and accelerated endothelial cell turnover, and/or intracellular oxidative stress.²⁹⁻³¹ The former might be linked with free ADMA levels via potentiated breakdown of proteins containing dimethylarginine residues,¹¹ whereas the latter via overexpression of type I protein-arginine N-methyltransferases governing ADMA formation³² and/or down-regulation of dimethylarginine dimethylaminohydrolase, a redox-sensitive enzyme degrading over 80% of ADMA.^{11,31}

Nevertheless, our data suggest that excessive ADMA accumulation does not accompany increased carotid IMT, a well-recognized feature of the young-to-middle-aged offspring of patients with premature CAD.^{5,8-10} This finding appears unexpected because elevated ADMA has been reported to be associated with CV risk factors, endothelial dysfunction, subclinical atherosclerosis,^{11-20,28,31} and IMT progression.³³ Furthermore, peripheral endothelial dysfunction has been demonstrated in some studies performed in asymptomatic subjects with the family history of premature CAD.^{7,8} In a seminal study by Clarkson et al.,⁷ impaired endothelium-dependent flow-mediated dilation (FMD) of the brachial artery in 50 healthy subjects aged from 15 to 40 years (mean, 25 ± 8 years) with a positive family history of premature CAD was largely due to an over 2-fold FMD reduction in a subgroup of 16 subjects without additional major conventional CV risk factors either in the subjects themselves or in their affected first-degree relatives. Since in that subgroup, some shared environmental factors, such as passive exposure to tobacco smoke, were also unlikely to considerably decrease FMD, the authors suggested an inherited early abnormality of the vessel wall as a mechanism underlying the independent effect of family history on endothelial function.⁷

On the other hand, the evidence for the notion of endothelial dysfunction in subjects with a positive family history is not unequivocal. Juonala et al.¹⁰ reported no differences in FMD between 291 young adults aged from 24 to 39 years with a parental history of premature CAD and 1974 participants of the Cardiovascular Risk in Young Finns Study with a negative family history, despite elevated carotid IMT in the former. As in nearly the same cohort, an inverse correlation between FMD and IMT had earlier been described,³⁴ the investigators put forward the hypothesis that intact endothelial function was insufficient to protect against atherosclerosis in individuals with familial predisposition to CAD.¹⁰ Accordingly, in our study, similar ADMA levels in the offspring of patients with premature CAD compared with subjects with

a negative parental history might possibly reflect unaltered endothelial function that does not offer protection against enhanced atherogenesis, mirrored by increased IMT.

Additionally, in the present study, the association of family history and elevated IMT was only slightly attenuated after controlling for LDL cholesterol, which is in agreement with Juonala et al.¹⁰ who observed similar effects of family history on IMT after adjustment for present and even childhood risk factors measured earlier in 12- to 18-year-old adolescents. They linked higher IMT not with a more abnormal risk profile but with stronger correlations of IMT with individual metabolic risk factors, including HDL cholesterol, glucose, and triglycerides, and their clustering in subjects with a positive family history,¹⁰ which could not be tested in our small study groups.

Irrespective of the contribution of endothelial dysfunction, adverse risk profile, and arterial vulnerability to some of the risk factors or their coincidence, an increase in carotid IMT (of whose variability about 30% is attributable to genetic factors)³⁵ represents an early abnormality in subjects with a positive family history, being reported not only in young adults,⁸⁻¹⁰ but also in adolescents^{8,9} and even prepubertal children.^{9,36} In the Bogalusa Heart Study, the familial aggregation of coexisting risk factors and parental CAD started at 11 years of age and was amplified thereafter.³⁷ Therefore, it might be postulated that the hypothetical relationship between ADMA and family history per se, if present, could be evident already before puberty, being at that time not obscured by an interfering risk profile. However, ADMA and premature parental CAD in 8-year-old children influenced carotid IMT presumably largely independently of each other because the 2 variables entered the final stepwise regression equation for predicting IMT, although the effect of parental CAD on ADMA was not directly addressed in that study.³⁶

In conclusion, our preliminary data suggest that elevated ADMA is not a part of the proatherogenic milieu in the young offspring of patients with early-onset CAD. Further studies of the emerging risk factors in asymptomatic subjects with a positive parental history of premature CAD are justified.

Study limitations First, a relatively low number of the study subjects limits the conclusions based on a single measurement of ADMA and SDMA. Second, we did not measure plasma L-arginine, and the L-arginine-to-ADMA ratio could not be estimated. Additionally, although comparable selected groups of young healthy adults free of co-existent diseases and with normal standard biochemical characteristics were investigated, we are not able to exclude significant intergroup differences in nontraditional atherosclerotic risk factors, which have not been assessed in our study design.

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Obciążający wywiad rodzinny w kierunku wczesnej manifestacji choroby wieńcowej nie wpływa na poziom asymetrycznej dwumetyloargininy w osoczu krwi u młodych zdrowych osób dorosłych

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SŁOWA KLUCZOWE

asymetryczna
dwumetyloarginina,
choroba wieńcowa,
grubość kompleksu
błony wewnętrznej
i środkowej tętnic
szyjnych, obciążający
wywiad rodzinny

STRESZCZENIE

WPROWADZENIE Wczesna manifestacja choroby wieńcowej (*coronary artery disease* – CAD) w wywiadzie rodzinnym jest czynnikiem ryzyka rozwoju miażdżycy i wystąpienia niekorzystnych zdarzeń wieńcowych.

CELE Celem badania było ustalenie, czy u pacjentów bezobjawowych z dodatnim wywiadem rodzinnym w kierunku CAD poziom asymetrycznej dwumetyloargininy (ADMA), endogennego inhibitora syntezy tlenu azotu, może być podwyższony oraz czy może się przyczynić do rozwoju subklinicznej miażdżycy.

PACJENCI I METODY Badaniem objęto 20 osób (10 mężczyzn i 10 kobiet) w wieku 19–30 lat z udokumentowaną manifestacją kliniczną CAD u rodziców <60. rż. oraz 20-osobową grupę kontrolną z ujemnym wywiadem rodzinnym w tym kierunku. Stężenie ADMA i jej izomeru, symetrycznej dwumetyloargininy (SDMA), zmierzono metodą immunoenzymatyczną. Ultrasonograficznie techniką *B-mode* wyznaczono uśrednioną grubość kompleksu błony wewnętrznej i środkowej (*intima-media thickness* – IMT) tętnic szyjnych wspólnych.

WYNIKI Badane grupy nie różniły się istotnie z wyjątkiem nieznamiennych tendencji do wyższego poziomu cholesterolu frakcji lipoprotein o małej gęstości (*low-density lipoprotein* – LDL) ($p = 0,07$) i oszacowanej wielkości przesączania kłębuszkowego (*estimated glomerular filtration rate* – eGFR) ($p = 0,06$) u osób z dodatnim wywiadem rodzinnym. W porównaniu z grupą kontrolną, u osób z dodatnim wywiadem rodzinnym zaobserwowano zwiększenie grubości IMT tętnic szyjnych ($0,54 \pm 0,05$ vs $0,48 \pm 0,05$ mm, $p < 0,001$) przy niezmiennych stężeniach ADMA ($0,66 \pm 0,17$ vs $0,74 \pm 0,15$ $\mu\text{mol/l}$, $p = 0,14$) i SDMA ($0,49 \pm 0,07$ vs $0,50 \pm 0,07$ $\mu\text{mol/l}$, $p = 0,61$). Wyniki nie uległy istotnym zmianom po uwzględnieniu poprawek na cholesterol LDL i eGFR. W analizie wieloczynnikowej wywiad rodzinny ($p = 0,005$) i cholesterol LDL ($p = 0,06$), a nie poziom ADMA, okazały się zmiennymi powiązanymi w sposób niezależny z IMT.

WNIOSKI Wstępne wyniki badań sugerują, że u młodych osób dorosłych z obciążającym wywiadem rodzinnym w kierunku przedwczesnego występowania CAD u rodziców ryzyko przyspieszonego rozwoju miażdżycy nie jest związane z podwyższonym poziomem ADMA.

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