Apparently "low" serum asymmetric dimethylarginine is associated with fasting glucose and tends toward association with type-2 diabetes

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Abstract

Objective: We investigated the association of serum asymmetric dimethylarginine (ADMA) with metabolic syndrome (MetS), type-2 diabetes and coronary heart disease (CHD) in the general population.
Methods: Cross-sectional and, at 2000 person-years' follow-up, prospective analysis. Adults with measured serum ADMA level (n=848) were analyzed using tertiles or dichotomized values. ADMA concentrations were measured by a validated commercial ELISA kit.
Results: Dichotomized subjects of combined sexes with low (≤0.68 μmol/L) ADMA values had significantly higher fasting glucose, total cholesterol, apolipoprotein B and lower diastolic blood pressure. In linear regression analyses comprising age, smoking, triglyceride, HDL-cholesterol, C-reactive protein and waist circumference as well, creatinine was significantly and independently associated with ADMA, further in women glucose (inversely). In logistic regression analyses uniformly adjusted for age, smoking status and waist girth, prevalent MetS tended to positive independent association with ADMA tertiles only in men. Combined prevalent and incident diabetes weakly tended to be associated with the lowest (vs mid- and highest) ADMA tertiles in combined gender; and prevalent and incident CHD was not associated with ADMA tertiles in either sex.
Conclusion: Apparently "low" circulating ADMA is independently associated with fasting glucose and tends to be so with type-2 diabetes. The lack of anticipated positive associations of ADMA with cardiometabolic disorders is likely due to autoimmune responses operating against serum ADMA under oxidative stress, rendering partial failure in immunoassay. *(Anadolu Kardiyol Derg 2014; 14: 26-33)*
Key words: asymmetric dimethylarginine, diabetes type-2, glucose, oxidative stress, sex difference, regression analysis

Introduction

Asymmetric dimethylarginine (ADMA), an endogenous inhibitor of nitric oxide synthase (NOS), is synthesized by the proteolytic activity of protein arginine methyltransferases, releasing free ADMA into the cell and to plasma (1). About one-fifth of ADMA is cleared by the kidney and the remainder is mainly metabolized by dimethylarginine dimethylaminohydrolase (2, 3). Excess dietary saturated fat and carbohydrates promptly enhance ADMA levels in diabetic people (4). Elevated levels of ADMA have been associated in the past two decades with hypertension (3), diabetes mellitus (5, 6), insulin resistance (7), renal failure (1), peripheral artery disease (2, 8), cardiovascular risk factors (9), cardiovascular disease (10) and to atherosclerosis in rheumatoid arthritis (11). These studies were generally cross-sectional in design, but subsequent cardiovascular events and mortality were also predicted by circulating ADMA in patients with coronary heart disease (6, 12) or end-stage renal disease (13). There was general agreement that these associations of ADMA were mediated by impairment of endothelial dysfunction.

However, it was recently found in 298 patients with coronary artery disease that plasma ADMA levels were not correlated with coronary endothelial function, nor with coronary vascular function at 6-months' follow-up (14), raising the question of the mechanism of ADMA-associated cardiovascular risk. In regard to the relevance of circulating ADMA in the population at large, a significant association between elevated ADMA levels and cardiovascular events and mortality was found in two

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small-sized studies in non-smoking men (15, 16). Yet at a 24-year follow-up of the 3320 subjects of the Framingham Offspring study, while all-cause mortality was significantly associated with ADMA levels, cardiovascular disease (CVD) events were not (17).

Whereas ADMA levels and their relevance to CVD and mortality have been published in a variety of studies on diabetic patients, studies on the prediction of diabetes by circulating ADMA hardly exist, to our knowledge. Evidence is available that endothelial dysfunction may precede the development of diabetes (18).

We, therefore, explored in part prospectively whether ADMA levels have predictive value for type-2 diabetes in a sample of the Turkish general population in whom this metabolic disease is highly prevalent secondary to obesity and associated enhanced inflammation (19). As a secondary aim, we simultaneously undertook to analyze the relationship of circulating ADMA also with the development of metabolic syndrome (MetS) and coronary heart disease (CHD). Moreover, we contribute herein to the association of circulating ADMA with glycemic status and smoking status (6, 16), major confounders to have caused apparent discrepant results.

Methods

Sample population

The study sample was recruited from the longitudinal Turkish Adult Risk Factor Study, a prospective population-based study on the prevalence of cardiac disease and risk factors, the sampling details of which were described previously (20). The study was approved by the Ethics Committee of the İstanbul University Medical Faculty. Written informed consent for participation was obtained. Partial logistic support was provided by the Turkish Ministry of Health. Data were obtained by history of the past years via a questionnaire, physical examination of the cardiovascular system, sampling of blood and recording of a resting 12-lead electrocardiogram. Serum concentrations of ADMA were assayed in randomly selected 472 men and women of the 2004/06 follow up surveys (21). In further 376 participants of the current sample measurements were made on randomly selected fasting sera of the survey 2011/2012. No participants had serum creatinine concentrations >180 μmol/L to consider exclusion.

Measurement of risk factors

Blood pressure (BP) was measured with an aneroid sphygmomanometer (Erka, Bad Tölz, Germany) in the sitting position on the right arm, and the mean of two recordings 3 min apart was recorded. Waist circumference was measured at the level midway between the lower rib margin and the iliac crest. Body mass index was computed as weight divided by height squared (kg/m^2). Cigarette smoking status was categorized into never, former and current smokers.

Blood samples were collected, spun at 1000 g, shipped to Istanbul and stored in deep-freeze at -75°C, until analyzed. ADMA levels were assayed in fasting sera by a validated ELISA kit (DLD -Gesellschaft für Diagnostika und medizinische Geraete -Diagnostika GMBH, Hamburg, Germany). Day-to-day CV was 4.48%.

Serum concentrations of total cholesterol, fasting triglycerides, glucose, creatinine and high-density lipoprotein (HDL)-cholesterol (without precipitation) were determined by using enzymatic kits from Roche Diagnostics with a Hitachi 902 autoanalyzer. Low-density lipoportein (LDL)-cholesterol values were measured directly in the majority of participants (Roche Diagnostics), or computed according to the Friedewald formula in the remainder. Serum concentrations of C-reactive protein (CRP), apolipoprotein (apo) B, apo A-I and lipoprotein (Lp)(a) were measured by Behring kits and nephelometry (BN Prospec, Behring Diagnostics, Westwood, MA). Concentrations of insulin were determined by the chemiluminescent immunometric method using Roche kits and Elecsys 1010 immunautoanalyzer (Roche Diagnostics, Mannheim, Germany, or Westwood, MA). Concentrations of acylation stimulating protein (ASP) and platelet activating factor (PAF) were determined by kits based on the ELISA method, purchased from Biotechist Co. (Beijing, China), and Novatein Biosciences Inc. (MA, USA), respectively.

Definitions

MetS was identified when 3 out of the 5 criteria of the NCEP ATP-III were met, modified for pre-diabetes [fasting glucose 100-125 mg/dL (22)] and further for abdominal obesity using as cut-point ≥95 cm in men, as assessed in the Turkish Adult Risk Factor study (23). Diabetes was diagnosed with the criteria of the American Diabetes Association (24), namely by self report or when plasma fasting glucose was ≥126 mg/dL or when 2-h postprandial glucose was >200 mg/dL. Cause of death was assigned with the consideration of pre-existing clinical and laboratory findings elicited during biennial surveys. CHD death comprised death from heart failure of coronary origin and fatal coronary event. Nonfatal CHD was identified by presence of angina pectoris, a history of myocardial infarction with or without accompanying Minnesota codes of the electrocardiogram (ECG) (25) or a history of myocardial revascularization. Typical angina and, in women, age >45 years were prerequisite for a diagnosis when the symptom angina was isolated. ECG changes of "ischemic type" of greater than minor degree (Codes 1.1-2, 4.1-2, 5.1-2, 7.1) were considered as myocardial infarct sequelae or myocardial ischemia, respectively.

Statistical analysis

Statistical analyses were performed using SPSS-10 for Windows (SPSS Inc., Chicago, Ill, USA). Numeric variables were shown as mean±standard deviation or in percentages. ADMA values were dichotomized by the median value (0.68 μmol/L). Due to skewed distribution, values derived from log-transformed

(geometric) means were used for ADMA and six other variables. For such variables, an SD value of (for example) 1.7 indicates the factor needed to multiply or divide the mean value to obtain the limits of the SD. ANOVA analyses and pairwise comparisons with post hoc Tukey HSD were made to detect significance between groups. Two-sided t-tests and Pearson's chi-square tests were used to analyze the differences between means and proportions of other groups. Multiple linear regression analyses were performed with continuous parameters. Associations of ADMA tertiles (0.52 and 0.92 μmol/L formed the intermediate tertile) were assessed in logistic regression analyses with prevalent cases of MetS, prevalent and incident cases of diabetes or of CHD. Likelihood estimates (OR) and 95% confidence intervals (CI) were obtained in models that adjusted for sex, age and relevant confounders, expressed in terms of 1-SD increment. A value of $p<0.05$ on the two-tail test was considered statistically significant.

Results

The study sample was composed of 403 men and 445 women aged 34-89 (mean 57.2±11) years. Prevalence of diabetes and MetS at baseline was 12.6% and 47.5%, respectively. In the sample, 404 were followed up over a mean 4.95±1.5 (range 2-6) years; total 2000 person-years). Geometric mean ADMA levels in men (0.687±1.74 μmol/L) and women (0.691±1.79 μmol/L) were virtually identical, median value being 0.68 μmol/L. Normoglycemic never smoking men (0.70±1.71 μmol/L) had ADMA levels by only 3% higher than their female counterparts (0.68±1.86 μmol/L). ADMA levels did not vary significantly with increasing age.

Baseline characteristics of the study sample stratified by high (>0.68 μmol/L) and low ADMA concentrations are shown in Table 1. Whereas the high ADMA group had only significantly higher diastolic BP, the low-ADMA group disclosed significantly higher fasting glucose, total and LDL cholesterol and apoB levels than individuals with elevated ADMA. In addition, significantly higher HDL-cholesterol, apoA-I, ASP, PAF and lower creatinine concentrations were observed in the low-ADMA group.

Table 2 shows distribution of mean ADMA levels in categories of fasting glucose and of smoking status stratified by gender. No significant differences were found across gender and glucose categories, neither by smoking status (ANOVA $p\geq0.3$ in each). Smoking men overall had 12% lower ADMA levels (0.663 vs. 0.752 μmol/L) than never smokers, and smoking women identical levels (0.688 vs. 0.688 μmol/L, $p=0.99$).

Multiple linear regression analyses were performed in a model comprising age, smoking status and fasting glucose, creatinine, triglyceride, HDL-cholesterol, CRP and waist circumference, chosen on the basis of univariate associations and potential determinants of diabetes (Table 3). Serum creatinine emerged as a positive significant covariate of circulating ADMA in each sex and fasting glucose as an independent (inverse) covariate in women.

Associations with metabolic disorders

Findings of logistic regression analyses of ADMA concentrations for MetS, type-2 diabetes and CHD are given in Table 4. In models adjusted for sex, age, smoking status and waist circumference, the upper two tertiles compared with the lowest tertile of ADMA were not associated with prevalent MetS in women, but the mid-tertile was positively associated among men (OR 2.37; 95% CI 1.27; 4.42). In similarly adjusted models, the higher two ADMA tertiles for combined prevalent and incident diabetes disclosed non-significantly lower ORs than the lowest tertile in each sex. The inverse association reached significance in women in the mid-tertile (0.49; 95% CI 0.26; 0.94). Increasing ADMA tertiles were not associated positively also with combined prevalent and incident CHD in either sex. Inclusion of CRP as continuous independent variable in these models changed no more than minimally the existing associations and CRP itself remained invariably far from significance.

Discussion

In this population-based study on circulating ADMA, low levels of dichotomized ADMA exhibited significantly higher glycemia and apoB-containing lipoproteins, as well as of certain variables linked to systemic inflammation such as ASP and PAF. Serum creatinine in both sexes and in women (inversely) fasting glucose were significant independent covariates of ADMA. Positive associations in logistic regression analyses of ADMA tertiles were observed only for MetS in men. The low-ADMA group rather tended to be associated with combined prevalent and incident diabetes, independent of age, smoking status and waist circumference; and ADMA tertiles were not associated with prevalent and incident CHD. Collectively, these findings suggested the operation under oxidative stress of autoimmune responses against circulating ADMA yielding on one hand partial failure in the protein's assayability, tending on the other to reverse anticipated associations with cardiometabolic disorders.

Given the abundance in studies on ADMA levels in patients with a variety of diseases ranging from insulin resistance, type-1 or type-2 diabetes to renal, peripheral arterial and cardiovascular disease, the paucity of studies on predictability of diabetes by circulating ADMA is surprising. This suggests a negative selection bias, i.e. potential lack of relationship, and consequent absence of related publications.

Factors confounding the linearity of the association

Linearity in the association between ADMA concentrations and cardiovascular (and renal) outcomes has not been clarified. In a nested case-control cohort of 850 participants, ADMA levels were positively associated at a relatively brief follow-up with glycemic categories (impaired fasting glucose and diabetes), and elevated ADMA quartiles conferred a two-fold risk of death/

Table 1. Baseline characteristics of the sample, by dichotomized serum ADMA concentrations

Variables	n	ADMA ≤0.68 µmol/L (n=429)		ADMA >0.68 µmol/L (n=419)		*P
		mean	SD	mean	SD	
ADMA¶, µmol/L	848	0.461	1.52	1.10	1.46	<0.001
Sex, female, n, %	848	228	53.1	217	51.8	0.69
Age, years	848	56.5	11.1	57.9	11.4	0.06
Waist circumference, cm	801	95.3	12.1	94.8	11.5	0.51
Body mass index, kg/m^2	785	29.4	5.0	29.6	5.3	0.61
Systolic BP, mmHg	801	124.6	20.7	126.7	21.2	0.15
Diastolic BP, mmHg	801	77.5	11.6	79.3	11.6	0.03
Fasting glucose, mmol/L	797	5.92	3.00	5.57	2.22	0.06
Total cholesterol, mmol/L	799	5.23	1.03	5.03	1.03	0.007
Fast. triglycerides¶, mmol/L	782	1.57	1.66	1.59	1.65	0.70
HDL-cholesterol, mmol/L	799	1.21	0.32	1.16	0.30	0.024
LDL-cholesterol, mmol/L	797	3.21	0.90	3.06	0.87	0.017
Apolipoprotein A-I, g/L	810	1.462	.25	1.41	.24	0.003
Apolipoprotein B, g/L	819	1.089	.35	1.02	.31	0.003
Lipoprotein(a)¶, mg/dL	765	11.6	2.84	12.3	2.87	0.56
Fasting insulin¶, IU/L	820	8.99	2.03	9.07	2.01	0.86
HOMA index¶, u	792	2.34	1.48	2.23	1.59	0.40
Creatinine, µmol/L	804	77.0	23	83.2	52.2	0.041
C-reactive protein¶, mg/L	833	2.14	2.90	2.31	3.02	0.31
ASP¶, nmol/L	516	10.8	2.3	9.21	2.42	0.037
PAF¶, nmol/L	496	25.6	1.74	22.4	1.62	0.005
Current smoking, n, %	845	99	23.1	93	22.3	0.95
Diabetes type-2, n, %	847	81	18.9	66	15.8	0.32

¶Geometric means. Significantly different values are highlighted in bold.
*unpaired t-test and Chi-square test
ADMA - asymmetric dimethylarginine; ASP-acylation stimulating protein; BP - blood pressure; HDL - high-density lipoprotein; HOMA - Homeostatic model assessment; LDL - low-density lipoprotein; PAF - platelet activating factor

myocardial infarction independent of CRP (6). Some studies (2, 17) suggest this risk may not be linear. Indeed, overall mortality tended to be reduced in subjects with diabetes for the intermediate quartiles whereas it increased linearly in the non-diabetic general population in the Framingham Offspring study (17). The concept is emerging that circulating ADMA may influence cardiovascular risk by participating in multiple complex signaling cascades in the cytoplasm and the circulation (26-28). A systematic review of ADMA in chronic kidney disease concluded that, due to wide variability of ADMA values in health and renal disease, ADMA cannot be advocated as a useful clinical laboratory parameter in patients with renal disease (29). Moreover, it has been argued that plasma ADMA concentrations are too low to be an effective inhibitor of NOS (26).

ADMA levels, influenced by enhanced inflammation, affects glycemia

The association of ADMA concentrations with plasma glucose has sparsely been examined previously (6). Our study indicated that ADMA concentrations were inversely related to plasma glucose and diabetes. This is in agreement with the effect modification of ADMA found in the Framingham Offspring study, manifesting surprisingly with a tendency to lower risk in those with diabetes, yet significantly higher risk of death in non-diabetic individuals (17). Our findings are also in line with a report on ADMA concentrations in subjects with normal glucose tolerance being correlated with plasma soluble vascular cell adhesion molecule-1 rather than CRP, contrasted to a lack of both correlations in individuals with impaired glucose

tolerance and a correlation existing with CRP in the diabetic state (30).

A decline in ADMA as a response to inflammation in acute infections was documented by Zoccali et al. (31), an observation with which our findings are in line.

Lack of positive association of ADMA with diabetes: confounding by autoimmunity

That our lacking a positive association of ADMA with diabetes is not a consequence of limited statistical power is evident from eliciting a significant inverse independent linear association with fasting glucose level, as well as the dichotomized lower ADMA concentrations being accompanied by significantly higher serum apoB, LDL and total cholesterol levels. Attenuated or reversed risk of the development of diabetes may be linked to higher glycemia, a mediator of enhanced low-grade inflammation, to be independently associated inversely with circulating ADMA. Subjects with "apparently" low ADMA levels may represent being both harbinger of an autoimmune process and concomitantly reflect partial escape of ADMA protein from immunoassay. In analogy, complexes of β2-glycoprotein I-Lp(a) (or oxidized LDL) have been found associated with stable (32) and acute CHD (33) wherein was pointed out that immunoassay results may be interfered due to failure by capture antibodies to recognize oxidized epitopes (33), in this instance, presumably, of ADMA. An association between serum ADMA and endothelial function was lacking also in patients with rheumatoid arthritis (34). From the distribution of apoB-containing lipoproteins and the positive linear association of serum creatinine with ADMA, it may be considered that both creatinine (35, 36) and lipoprotein(a) (37) may have been further involved in the autoimmune complex formation in this sample, as previously shown by us to confer incident CHD risk.

Two studies in patients with chronic kidney disease provide evidence that may be interpreted to support the notion of paradoxically lower plasma ADMA levels conferring cardiovascular risk. A lower ADMA level was found a significant independent risk factor for cardiovascular events in a heterogeneous group of patients with renal disease at a brief follow-up (38). In another study, the total amount of ADMA removed from the dialysate was markedly lower than expected, and significant protein binding was suspected (39).

Table 2. Geometric mean ADMA levels in subjects stratified by gender, baseline fasting glucose and smoking status

Variables		Men		Women	
	n	Mean	SD	Mean	SD
Normoglycemia	262/303	0.700	1.71	0.681	1.86
Never smokers	298	0.758	1.59	0.683	1.88
Former smokers	114	0.700	1.68	0.659	1.71
Current smokers	153	0.667	1.81	0.675	1.67
Pre-diabetes	49/46	0.689	1.85	0.714	1.61
Never smokers	51	0.737	1.69	0.741	1.62
Former smokers	33	0.613	1.93	0.650	1.51
Current smokers	11	0.888	1.85	0.564	1.97
Diabetes, type-2	64/73	0.642	1.87	0.685	1.55
Never smokers	79	0.746	1.69	0.675	1.67
Former smokers	31	0.603	2.13	0.590	1.40
Current smokers	27	0.557	1.67	0.773	1.80

*unpaired t-test
Differences did not reach significance.
Overall, there were 127 male and 64 female current smokers.

Table 3. Linear regression analysis for baseline covariates of serum ADMA¶ (n=778) baseline fasting glucose and smoking status

Variables	Men (n=369)			Women (n=409)		
	β-coeff.	SE	*P*	β-coeff.	SE	*P*
Creatinine, 25 μmol/L	0.068	0.028	0.016	0.04	0.015	0.015
Fasting glucose, 1.4 mmol/L	-0.011	0.00	0.46	-0.034	0.00	0.03
HDL-cholesterol, 0.3 mmol/L	-0.05	0.028	0.14	-0.041	0.028	0.16
Fasting triglycerides¶, 1.6-fold	0.005	0.023	0.84	0.006	0.024	0.79
Waist circumference, 12 cm	-0.008	0.028	0.82	0.04	0.028	0.21
Current vs never smoking	-0.052	0.086	0.51	-0.056	0.086	0.50
Age, 11 years	0.015	0.026	0.64	-0.019	0.026	0.51
C-reactive protein¶, 3-fold	-0.001	0.021	0.98	0.002	0.02	0.92
Explained variance (r^2)	0.02 (p=0.16)			0.03 (p=0.026)		

Change in serum ADMA is expressed in terms of 1-SD difference in covariates, except for the categorical smoking status.
ADMA - asymmetric dimethylarginine

Table 4. Multiple logistic regression analyses for metabolic syndrome, diabetes and coronary heart disease in men and women

Variables	Total		Men		Women	
	OR	95% CI	OR	95% CI	OR	95% CI
MetS		426/809†		170/372†		258/437†
Sex, female	2.43	1.68; 3.52				
Age, 11 years	1.37	1.15;	1.48	1.10; 1.98	1.41	1.15; 1.75
ADMA¶, mid-tertile 0.69 µmol/L	1.35	0.92; 1.97	2.37	1.27; 4.42	0.98	0.59; 1.16
Highest tertile 1.23 µmol/L	1.26	0.86; 1.84	1.56	0.83; 2.91	1.19	0.73; 1.97
Waist circumference, 12 cm	2.81	1. 81	6.38	4.20; 9.66	1.97	1.58; 2.46
Current vs never smoking	1.08	0.70; 1.68	1.32	0.66; 2.66	1.03	0.56; 1.88
Prevalent & incid.diabetes*	**159/845†**		**81/400†**		**78/445†**	
Age, 11 years	1.34	1.11; 1.61	1.56	1.18; 2.04	1.23	0.95; 1.59
ADMA¶ mid-tertile 0.69 µmol/L	0.65	0.42; 1.01	0.88	0.47; 1.64	0.49	0.26; 0.94
ADMA¶ top-tertile 1.23 µmol/L	0.76	0.50; 1.18	0.73	0.39; 1.39	0.78	0.43; 1.40
Waist circumference, 12 cm	1.92	1.52; 2.33	2.06	1.53; 2.75	1.88	1.44; 2.46
Current vs never smoking	1.03	0.60; 1.77	0.53	0.25; 1.13	1.55	0.72; 3.33
Prevalent & incident CHD.*	**170/802†**		**85/382†**		**85/420†**	
Sex, female	0.94	0.61; 1.45				
Age, 11 years	1.84	1.52; 2.19	1.62	1.24; 2.10	2.00	1.54; 2.58
ADMA¶ mid-tertile 0.69 µmol/L	0.85	0.54; 1.33	0.64	0.34; 1.23	1.03	0.55; 1.94
ADMA¶ top-tertile 1.23 µmol/L	1.01	0.65; 1.56	1.01	0.56; 1.84	0.95	0.50; 1.80
Waist circumference, 12 cm	1.56	1.30; 1.90	1.34	1.04; 1.76	1.84	1.39; 2.41
Current vs never smoking	0.87	0.50; 1.53	0.64	0.30; 1.36	1.34	0.58; 3.13

*Cases with prevalent diabetes but no follow-up at baseline were excluded. Incident diabetes cases numbered 19, incident CHD cases 32. Female sex had a non-significant OR of 0.92 in the model on diabetes.
The referent lowest ADMA tertile was 0.40 µmol/L
¶log-transformed values
ADMA - asymmetric dimethylarginine

Clinical implications

In clinical practice, the physician confronted with a patient susceptible to MetS or impaired glucose tolerance, should not be complacent facing a low-normal serum ADMA, consider that this might represent activated autoimmunity and try to understand its clinical significance by an extensive evaluation of lipid and non-lipid parameters.

Study limitations

The somewhat limited size of the population sample may urge some caution in interpreting findings. A logistic regression rather than a Cox approach was required to combine incident with prevalent diabetes. Potential residual confounding may not have been fully excluded. Having not measured L-arginine and not examined the Arginine/ADMA ratio is a shortcoming not of crucial relevance. Current findings based on a representative population sample of both sexes including an intermediate follow-up and comparative data on glucose categories, smoking status, waist girth and CRP constitute major strengths of this study.

Conclusion

Serum ADMA levels in a middle-aged general population prone to MetS may paradoxically be inversely related to fasting glucose, fail to display positive associations with cardiometabolic disorders and even tend to be inversely associated with type 2 diabetes. This supports the hypothesis that plasma ADMA may not be recognized in specific immunoassays in the setting of prevailing autoimmune processes, reversing the latter's association with diabetes and abolishing associations with CHD. Large-sized prospective studies on apparently healthy people are warranted to elucidate further the factors for the recognized variability of ADMA levels and their influence on cardiometabolic risk in different ethnicities and settings.

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