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Associations of Pentraxin 3 with Cardiovascular Disease: The Multi-Ethnic Study of Atherosclerosis

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Abstract

Objective—Pentraxin 3 (PTX3) is likely a specific marker of vascular inflammation. However, associations of PTX3 with cardiovascular disease (CVD) risk have not been well studied in healthy adults or multi-ethnic populations. We examined associations of PTX3 with CVD risk factors, measures of subclinical CVD, coronary artery calcification (CAC) and CVD events in the Multi-Ethnic Study of Atherosclerosis (MESA).

Approach and Results—2838 participants free of prevalent CVD with measurements of PTX3 were included in the present study. Adjusting for age, sex and ethnicity, PTX3 was positively associated with age, obesity, insulin, systolic blood pressure, C-reactive protein (CRP) and carotid intima media thickness (all $p<0.045$). A one standard deviation increase in PTX3 (1.62 ng/ml) was associated with the presence of CAC in fully adjusted models including multiple CVD risk factors (relative risk; 95% confidence interval 1.05; 1-01-1.08). In fully adjusted models, a standard deviation higher level of PTX3 was associated with an increased risk of myocardial infarction (hazard ratio; 95% confidence interval 1.51; 1.16-1.97), combined CVD events (1.23; 1.05-1.45) and combined CHD events (1.33; 1.10-1.60) but not stroke, CVD-related mortality or all cause death.

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Conclusions—In these apparently healthy adults, PTX3 was associated with CVD risk factors, subclinical CVD, CAC and incident coronary heart disease events independent of CRP and CVD risk factors. These results support the hypothesis that PTX3 reflects different aspects of inflammation than CRP and may provide additional insight into the development and progression of atherosclerosis.

Keywords

Atherosclerosis; Cardiovascular Diseases; Epidemiology; Inflammation; Pentraxin 3

Introduction

Pentraxin 3 (PTX3), a long pentraxin, is thought to be a specific marker of localized vascular inflammation. Unlike the related short pentraxin C-reactive protein (CRP), which is produced primarily in the liver, PTX3 is produced at sites of inflammation by cells such as vascular endothelial cells, smooth muscle cells and macrophages; cells that are directly involved in atherosclerosis. PTX3 has been identified in atherosclerotic lesions and levels appear to be higher in patients with later stages of atherosclerosis such as foam cell formation than in patients with early lesions such as fatty streaks.

Because PTX3 release is likely a specific response to vascular damage and PTX3 levels may be more strongly related to later stages of atherosclerosis, PTX3 levels may provide more explicit information on progression of atherosclerosis in middle-aged and older adults than non-specific markers such as CRP. In primarily white older adults in the Cardiovascular Health Study (CHS), PTX3 was associated with some cardiovascular disease (CVD) risk factors, the presence of subclinical CVD and CVD-related and all cause death. Similarly, in a cohort of older adults with coronary heart disease, PTX3 was associated with cardiovascular events, incident heart failure and all cause death. However, associations of PTX3 with CVD risk factors as well as measures of subclinical CVD and clinical CVD events have not been well studied in younger apparently healthy populations or in non-white ethnic groups. We therefore examined these associations in apparently healthy men and women free of clinical CVD from the Multi-Ethnic Study of Atherosclerosis (MESA).

Methods

Multi-Ethnic Study of Atherosclerosis (MESA)

MESA is a cohort study designed to investigate the prevalence, correlates and progression of subclinical CVD (http://www.mesa-nhlbi.org). The cohort consists of 6,814 men and women, 38.6% white, 27.6% black, 11.8% Chinese and 22.0% Hispanic, who were 45-84 years of age and free of clinical CVD at baseline, July 2000–August 2002. Baseline exams included anthropometry, medical and lifestyle histories, ankle brachial blood pressure index, carotid ultrasound and fasting blood collection. All subjects gave informed consent for participation in the study and all procedures were conducted under institutionally approved protocols for human subjects research. For this study of PTX3, we selected MESA sub-cohort of 2,880 participants; 720 in each of the four ethnic groups, matched for age and sex.

Cardiac Computed Tomography (CT)

At baseline, CT scanning of the chest was performed by an ECG-triggered (at 80% of the RR interval) electron-beam CT scanner or by prospectively ECG-triggered scan acquisition at 50% of the RR interval with a multi-detector CT system. Each participant was scanned twice. Scans were read centrally and calcium scores among field centers and between participants were adjusted with a standard calcium phantom scanned simultaneously with the participant. The average Agatston score for the two scans was used for analyses.

Definitions

At baseline, smoking was defined as never, former (no cigarettes within the past 30 days) or current. Hypertension was defined as seated systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or history of hypertension and use of antihypertensive medication. Dyslipidemia was total/HDL cholesterol ratio >5 or taking lipid-lowering medication. Diabetes (fasting glucose ≥126 mg/dl) and impaired fasting glucose (fasting glucose 110-125 mg/dl) were classified by 1997 American Diabetes Association guidelines.

Laboratory Methods

Fasting blood was drawn, processed and stored using standardized procedures. Total and HDL cholesterol, triglycerides and glucose were measured. Analytical coefficients of variation (CVs) were ≤ 4% for all. LDL cholesterol levels were calculated. High sensitivity CRP and IL-6 were determined as previously described. PTX3 was measured by PTX3 (human) Detection Set from Alexis Biochemicals (Axxora, LLC; San Diego, CA); analytical coefficient of variation 10.2%.

CVD Events and Mortality

At 9-12 month intervals, participants or proxies were contacted regarding interim hospital admissions, outpatient diagnoses of CVD and deaths. Follow-up for this analysis extended through 2011; the median follow-up time for this subgroup was 8.5 years. To verify self-reported diagnoses, data from hospital records was abstracted by trained personnel. Next of kin and physicians were contacted for participants with out-of-hospital cardiovascular deaths. Events were independently classified by at least two physician members of the MESA mortality and morbidity review committee.

Events were classified as due to CVD or coronary heart disease (CHD). CVD events included nonfatal myocardial infarction (MI), resuscitated cardiac arrest, CVD death, definite angina and probable angina associated with revascularization, and ischemic stroke. CHD events included nonfatal MI, resuscitated cardiac arrest, CHD death, definite angina and probable angina associated with revascularization. Revascularizations not preceded by a diagnosis of angina were not included in the CVD endpoint. A death was considered related to CHD if it occurred within 28 days after an MI, if the participant had had chest pain within 72 hours before death, or if the participant had a history of CHD and there was no known nonatherosclerotic, non-cardiac cause of death.

Reviewers classified resuscitated cardiac arrest when a patient successfully recovered from full cardiac arrest through cardiopulmonary resuscitation (including cardioversion). A

classification of definite or probable angina required clear and definite documentation of symptoms distinct from the diagnosis of MI. Classification of definite angina also required objective evidence of reversible myocardial ischemia or obstructive coronary artery disease. Stroke was classified as present or absent and consisted of rapid onset of a documented focal neurologic deficit lasting 24 hours or until death, or, if < 24 hours, there was a clinically relevant lesion on brain imaging. Patients with focal neurologic deficits secondary to brain trauma, tumor, infection, or other non-vascular cause were excluded. A more detailed description of the MESA follow-up methods is available at http://www.mesa-nhlbi.org/followup.aspx.

Statistical Analyses

Data were analyzed using STATA (version 12.0, Stata Corporation). PTX3 measurements were available for 2,838 of the 2,880 participants. Missing measurements were due to insufficient sample availability (n=42). Of the 2,838 participants with PTX3 data, three participants with PTX3 levels > 19 ng/ml were excluded from analyses. 2,821 and 2,770 of the remaining 2,835 participants had measurements of CRP and IL-6, respectively.

PTX3, CRP and IL-6 were natural log (ln)-transformed to achieve normal distributions. Unadjusted means (standard deviations) or proportions (percentages) were calculated for demographic variables, CHD risk factors and inflammatory markers by mean PTX3 level. Differences between groups were assessed by analysis of variance.

Associations of PTX3 with continuous variables were determined by adjusted linear regression. The continuous variable of interest was entered first, followed by age, sex and ethnicity.

CAC status was defined as no detectable CAC (Agatston score = 0) or presence of CAC (Agatston score > 0). Relative risk regression models with robust standard errors, adjusted for age, ethnicity and sex, were used to determine the probability of CAC presence. Additional adjustments were smoking, diabetes, systolic blood pressure, dyslipidemia and body mass index (BMI). Linear regression was used to model associations of continuous Agatston score with inflammatory markers (one standard deviation change in marker level) in those with a positive Agatston score. We used ln-transformed Agatston score; regression coefficients were exponentiated for presentation. Models were adjusted as above.

Cox regression was used to determine hazard ratios (HRs) and 95% confidence intervals (95% CIs) for PTX3 alone and in models containing PTX3 and CRP. Those with an event were compared to all remaining participants. Participants were followed until the event of interest, death or the end of follow-up, at which time they were censored. Models were adjusted as above. The predictive value of PTX3 was evaluated by comparing the full models (age, ethnicity, sex, smoking, diabetes, systolic blood pressure, dyslipidemia and BMI) with and without PTX3 (standard deviation change in PTX3 level) using the differences in Harrell's C-statistic. The proportional hazards assumption was verified using Schoenfeld's residuals. Net Reclassification Improvement (NRI) and) was calculated using risk cut points of 3% and 10% at 10 years translating into 2.6% and 8.5% at a mean follow-

up of 8.5 years. Integrated Discrimination Improvement (IDI was calculated separately for cases and non-cases for each event.

We did not adjust for use of hormone replacement therapy, aspirin or non-steroidal anti-inflammatory agents as including their use in models adjusted for age, sex and ethnicity did not significantly change effect estimates. Although similar results were obtained for statin use, statin use was included in the adjustment for dyslipidemia.

Results

Baseline Characteristics of the MESA Subcohort

PTX3 distribution was skewed; geometric mean ± standard deviation (from ln-transformed PTX3) 1.89 ± 1.61, range 0.31 – 11.95 ng/ml. Baseline characteristics of the MESA participants in this study, stratified into two groups by mean PTX3 level, are shown in Table 1. Those with higher PTX3 were older (p=0.001), more likely to be diabetic (p=0.004), be a current smoker (p=0.028), have detectable CAC (p=0.003), have higher common carotid intima media thickness (IMT; p=0.001), CRP (p=0.003) and IL-6 (p=0.001) and have higher rates of MI (P<0.001), combined CVD and CHD (p<0.001) and CVD/CHD death (p=0.038). Other factors were similar between groups (all p>0.05). Mean (standard deviation) PTX3 levels were similar in Whites and Hispanics, 2.04 (1.57) and 2.09 (1.56) ng/ml (p=0.23), respectively. Compared to Whites, PTX3 levels were lower in Chinese, 1.63 (1.65) ng/ml and Blacks, 1.85 (1.61) ng/ml (both p<0.001). PTX3 levels were similar in men, 1.90 (1.62) ng/ml, and women, 1.89 (1.59) ng/ml (p=0.07).

Cross-Sectional Associations of PTX3 with CVD Risk Factors

Associations of PTX3 with CVD risk factors in the whole group are shown in Table 2. PTX3 was positively associated with age, fasting insulin, systolic blood pressure, CRP and IL-6. There was no association of PTX3 with BMI or lipids.

Mean (standard deviation) PTX3 levels were higher in diabetics, 2.06 (1.64) ng/ml, compared to those with normal glucose levels, 1.87 (1.60) ng/ml (p<0.001). PTX3 levels also varied by smoking; 1.83 (1.63) in never smokers and 1.97 (1.59) ng/ml in ever smokers (p<0.001). Levels were 2.03 (1.57) ng/ml in current smokers (p<0.001 compared to never smokers). While not associated with BMI as a continuous measure, PTX3 levels were associated with BMI categories. Mean PTX3 levels were 1.87 (1.69) ng/ml in 915 participants with BMI <25 kg/m^2, 1.90 (1.58) ng/ml in 1096 participants with BMI ≥25 and <30 kg/m^2, 1.90 (1.57) ng/ml in 734 participants with BMI ≥ 30 and < 40 kg/m^2 and 1.99 (1.62) ng/ml in 90 participants with BMI ≥40 kg/m^2 (p<0.001). Trends were similar across all ethnicities.

Cross-Sectional Associations of PTX3 with Subclinical CVD Measures

There were no associations of PTX with common or internal carotid IMT or ABI as continuous variables in models adjusted for age, sex and ethnicity (Table 2). However, higher mean (standard deviation) PTX3 levels were observed for those with a common carotid IMT ≥ 80^{th} percentile (1.01 mm, n = 564) than for those with a lower IMT, 1.96

(1.60) ng/ml versus 1.88 (1.62) ng/ml, respectively (p<0.001). Similarly, PTX3 levels in those with an internal carotid IMT ≥ 80th percentile (1.37 mm, n = 554) were higher, 1.95 (1.60) ng/ml, than in those with a lower IMT (< 80th percentile), 1.88 (1.62) ng/ml (p<0.001). PTX3 levels were 1.93 (1.62) ng/ml for those in the lowest 20th percentile of ABI (≤ 1.04, n = 562) compared to 1.88 (1.61) ng/ml for those with a higher ABI (p<0.001). All comparisons remained significant (all p <0.001) when additional covariates, dyslipidemia, diabetes, hypertension, body mass index and smoking status, were added to models. Trends were similar across ethnicities.

Cross-Sectional Associations of PTX3 with CAC

Adjusting for age, sex and ethnicity, the relative risk (95% confidence interval) for the presence of CAC (Agatston score > 0) for a one standard deviation increase in ln-transformed PTX3 (0.48) was 1.04 (1.01 – 1.07). The prevalence ratio (95% hazard ratio) remained unchanged with additional adjustments for dyslipidemia, diabetes, hypertension, body mass index and smoking. For comparison, the prevalence ratio for the presence of CAC for a one standard deviation increase in ln-transformed CRP (1.18) was 1.06 (1.03 – 1.09) in minimally adjusted models and 1.05 (1.01 – 1.08) in fully adjusted models.

Examining the linear relationship between ln-transformed PTX3 and ln-transformed Agatston score in those with a positive Agatston score, the regression coefficient was 0.007, p = 0.35. In fully adjusted models, the coefficient was 0.004, p = 0.58. Limiting analyses to those with an Agatston score ≥ 100 produced similar results. Trends were similar across ethnicities.

Associations of PTX3 with Clinical Events

A one standard deviation increase in ln-transformed PTX3 was associated with increased risk of MI, combined CVD events and combined CHD events in minimally and fully adjusted models (Table 3). PTX3 was not associated with risk of stroke, CVD/CHD death or non-cardiovascular death. In this MESA subgroup, a one standard deviation increase in ln-transformed CRP was not associated with any events in fully adjusted models. Adding CRP or alcohol use (never, former or current alcohol use) to the fully adjusted model had trivial effects on the PTX3 associations (data not shown). We did not stratify on ethnicity due to lack of power.

Results for further evaluation of PTX3 in risk prediction were inconsistent. PTX3 was associated with a significant increase in the C-statistic when added to the full model for MI events only (C-statistic 0.0326; p=0.04). The C-statistic did not change significantly when PTX3 was added to the full model for CVD (C-statistic 0.0054; p=0.3) or CHD events (0.0090; p=0.2). The overall NRI was significant for CHD events (NRI 0.0610; p=0.003) but not for MI alone (0.0316; p=0.5) or CVD events (0.251; p=0.1). The IDI was borderline significant for MI events (IDI 0.0084, p=0.05) but not significant for CVD (0.0042; p=0.3) or CHD (0.0086; p=0.6) events.

Discussion

In this study examining associations of circulating PTX3 with CVD risk factors, measures of subclinical CVD and CHD and clinical events in a multi-ethnic cohort of apparently healthy adults, PTX3 was positively associated in cross-sectional studies with risk factors (age, obesity, fasting insulin, systolic blood pressure, CRP and IL-6), measures of subclinical CVD (common and internal carotid IMT ≥ 80th percentile and ABI ≤ 20th percentile) and the presence of CAC. While high sensitivity CRP was not associated with any events in this MESA subcohort, PTX3 was associated with risk of MI and combined CHD events.

The association of PTX3 with a limited number of CVD risk factors in our apparently healthy population is consistent with previous studies. Likewise, the association of PTX3 with the presence of CAC was similar to associations of the inflammatory markers CRP, IL-6 and fibrinogen with CAC in the full MESA cohort.

The lack of association between PTX3 and BMI as a continuous variable in the MESA participants in this study is similar to that seen previously in the Cardiovascular Health Study and the Heart and Soul Study. However, PTX3 levels did vary significantly by BMI category in our MESA sample. PTX3 expression by adipose tissue and circulating levels are reported to be higher in obese subjects compared to normal weight subjects. Conversely, in a small study of men under conditions of caloric restriction and bed rest, Bosutti et al reported inverse associations of PTX3 with fat mass. Knoflach et al likewise found an inverse association of PTX3 levels with obesity in the Brunek Study. Conflicting results may be due to differences in fat mass and distribution between the cohorts. In support of this, PTX3 expression was reported to be higher in visceral adipose tissue from men with a BMI >25 kg/m^2 compared to leaner men while there were no differences in expression in subcutaneous adipose tissue.

PTX3 levels are reported to increase as atherosclerotic lesions progress from early stage fatty streaks to more advanced lesions and PTX3 may also be a more specific marker of plaque vulnerability than CRP. In terms of clinical events, we found associations of PTX3 with risk of MI and combined CHD events. In subjects with stable CHD, PTX3 was associated with risk of all cause death and CVD events. In older adults free of clinical CVD in the Cardiovascular Health Study, PTX3 was associated with risk of CVD-related and all cause death. We did not find an association with fatal events in MESA which is a younger cohort with fewer fatal events. Interestingly, PTX3 was more strongly associated with subclinical CVD measures and was also weakly associated with non-fatal events (angina) in the younger age stratum (<70 years of age) in the Cardiovascular Health Study.

PTX3 may have a role as a specific biomarker of vascular inflammation/damage reflecting risk of clinical events. However, the role of PTX3 in atherosclerosis is not clear. PTX3 is a soluble pattern recognition receptor and is localized in atherosclerotic lesions, potentially promoting lesion progression through the innate immune response. PTX3 has been reported to induce tissue factor expression in monocytes and endothelial cells and may contribute to thrombosis through this mechanism. In contrast, PTX3 has been reported to have athero-protective effects in mice. In mice, PTX3 deficiency is linked to an increased burden of

vascular lesions and increased macrophage accumulation within the lesions. Similarly, in humans, Matsuura et al reported that PTX3 distribution in lesions mirrors that of CD163-positive macrophages. CD163, a haemoglobin scavenger receptor, is believed to have anti-inflammatory properties. Conversely, CRP in human lesions is correlated with the presence of the inflammatory immune cells T-lymphocytes. While PTX3 is clearly associated with the presence and progression of atherosclerosis, further studies are needed to define its precise role.

This study has a number of important strengths: availability of measures of subclinical CVD, multiple risk factors, CAC assessment and clinical events in a large population-based multi-ethnic sample of apparently healthy adults. Limitations of this study should also be noted. PTX3 was measured once and we cannot account for intra-individual variation. However, assay variability would be expected to bias findings towards the null so the observed associations are potentially underestimations. We also had a relatively low number of events and most events were grouped for analyses. In addition, analyses evaluating the potential utility of PTX3 as a risk marker for cardiovascular events were inconclusive. PTX3 was associated with a significant increase in the C-statistic for MI events but not CVD or CHD events. The overall NRI was significant for CHD but not MI or combined CVD events and the IDI was borderline significant for MI events but not CHD or CVD events. However, as these analyses are limited in their ability to evaluate predictive utility of new biomarkers and the results should be interpreted with caution, the inconsistency of the results does not preclude a role for PTX3 in risk prediction models. Future studies with additional events may be able to identify other associations of PTX3 with clinical CVD and refine the benefit of PTX3 in risk prediction models.

In summary, we report that in a population-based study of men and women from four ethnic groups who were free of clinical CVD, PTX3 was associated with CVD risk factors, subclinical CVD, CAC and clinical CHD events. These associations were independent of CRP and notably, CRP was not associated with clinical events in this MESA subcohort supporting the hypothesis that PTX3 reflects different aspects of atherosclerosis-related inflammation than CRP and may provide additional insight into atherosclerosis development and progression. Future population-based and immunologic studies will continue to shed light on roles for this novel inflammation biomarker.

Acknowledgments

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Appendix

Table 4

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Reported on page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-7
Bias	9	Describe any efforts to address potential sources of bias	15
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-9
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	NA
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers	5,7,8

	Item No	Recommendation	Reported on page
		potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	5,7,8
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	22
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	6
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	22
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	NA
		Cross-sectional study—Report numbers of outcome events or summary measures	22
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	24
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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Table 1

Demographics, CVD risk factors, subclinical CVD measures, inflammation biomarkers and events by mean PTX level (ln-transformed) at baseline (MESA 2000 – 2002)

Variable	PTX3 ≤ 1.9 ng/ml n = 1418	PTX3 > 1.90 ng/ml n = 1417
Demographics		
Men (n, %)	655 (50.1)	653 (49.9)
Age, years	60.9 (10.1)	62.2 (10.3)
White (n, %)	318 (44.5)	397 (55.5)
Black (n, %)	367 (52.2)	336 (47.8)
Chinese (n, %)	436 (61.4)	274 (38.6)
Hispanic (n, %)	297 (42.0)	410 (58.0)
CVD Risk Factors		
Body mass index, kg/m^2	27.9 (5.4)	27.8 (5.5)
Total cholesterol, mg/dl	195 (36)	194 (35)
LDL cholesterol, mg/dl	118 (30)	117 (32)
HDL cholesterol, mg/dl	50 (14)	51 (14)
Hypertension (n, %)	590 (48.0)	638 (52.0)
Diabetes (n, %)	160 (42.8)	214 (57.2)
Dyslipidemia (n, %)	480 (50.2)	477 (49.8)
Current smoking (n, %)	172 (44.8)	212 (55.2)
Subclinical CVD Measures		
Common carotid IMT[#], mm	0.85 (0.19)	0.88 (0.20)
Internal carotid IMT[#], mm	1.00 (0.56)	1.11 (0.57)
ABI	1.12 (0.11)	1.11 (0.13)
CAC (n, %)	638 (47.1)	718 (50.6)
Agatston score[*]	67 (6)	73 (6)
Inflammation Biomarkers		
CRP, mg/l[**]	1.66 (3.08)	1.89 (3.41)
IL-6, ng/ml[**]	1.13 (1.94)	1.23 (1.99)
Events		
MI (n, %)	6 (11.8)	45 (88.2)
Combined CVD (n, %)	50 (33.1)	101 (66.9)
Combined CHD (n, %)	28 (26.2)	79 (73.8)
Stroke (n, %)	14 (36.8)	24 (63.2)
CVD Death (n, %)	11 (32.4)	23 (67.7)
Non-CVD Death (n, %)	52 (46.4)	60 (53.6)

Mean (standard deviation) presented unless otherwise noted.

[#]IMT, intima media thickness.

[*]Average Agatston score in those with a positive score, from ln-transformed data.

** From ln-transformed data.

Table 2

Regression coefficients for CVD risk factors in separate linear models of ln-transformed PTX3

Variable (SD)	Coefficient	p-value
CVD Risk Factors		
Age (10.2 years)	**0.046**	<**0.001**
Body mass index (5.5 kg/m^2)	0.007	0.46
Fasting glucose (31 mg/dl)	0.017	0.055
Fasting insulin (5.8 mU/l)	**0.024**	**0.009**
Systolic blood pressure (21 mm Hg)	**0.019**	**0.045**
Diastolic blood pressure (10 mm Hg)	0.007	0.44
Lipids		
Total cholesterol (35 mg/dl)	−0.008	0.34
HDL cholesterol (14 mg/dl)	0.008	0.42
LDL cholesterol (31 mg/dl)	−0.009	0.30
Subclinical CVD Measures		
Common carotid IMT* (0.19 mm)	0.003	0.73
Internal carotid IMT* (0.56 mm)	0.017	0.07
ABI (0.12)	0.004	0.66
Inflammatory Markers		
lnCRP (l.18)	**0.038**	<**0.001**
lnIL-6 (0.67)	**0.042**	<**0.001**

Variables were divided by their standard deviations (SD) shown in parentheses. Models adjusted for age, sex, ethnicity.

*IMT = intima media thickness. Bold values significant at p≤0.05.

Table 3

Hazard ratios (HR) and 95% Confidence Intervals (CI) for CVD and CHD Events and Non-cardiovascular Death for a Standard Deviation Increase in PTX3 Level

Event	Model 1 - HR (95% CI)	Model 2 - HR (95% CI)
MI	**1.47 (1.13 - 1.93)**	**1.51 (1.16 - 1.97)**
Stroke	1.16 (0.84 - 1.59)	1.09 (0.78- 1.52)
Combined CVD	**1.23 (1.05 - 1.45)**	**1.23 (1.05 - 1.45)**
Combined CHD	**1.29 (1.07 - 1.61)**	**1.33 (1.10 - 1.60)**
CVD/CHD Death	1.22 (0.88 - 1.69)	1.19 (0.85 - 1.66)
Other Death*	1.01 (0.84 - 1.21)	0.98 (0.81 - 1.19)

Model 1 adjustments: age, sex, ethnicity. Model 2: Model 1, dyslipidemia, diabetes, hypertension, body mass index, smoking.

*Non CVD/CHD-related death.