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## Periodontitis is associated with cognitive impairment among older adults: analysis of NHANES-III

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### Abstract

**Background**—Periodontitis is ubiquitous and associated with serological evidence of exposure to periodontal organisms, systemic inflammation and vascular disease. Dementia is a major public health problem likely related to a complex interaction between genetics and diseases associated with systemic inflammation, including diabetes, smoking and stroke.

**Methods**—To assess relationships between systemic exposure to periodontal pathogens and cognitive test outcomes, data were analysed from the Third National Health and Nutrition Examination Survey (NHANES-III), a nationally representative cross sectional observational study among older adults. We included 2355 participants  $\geq 60$  years who completed measures of cognition and *Poryphyromonas gingivalis* IgG. Using SUDAAN, logistic regression models examined the association of *P gingivalis* IgG with cognitive test performance.

**Results**—Poor immediate verbal memory ( $< 5/9$  points) was prevalent in 5.7% of patients, and 6.5% overall had impaired delayed recall ( $< 4/9$ ); 22.1% had difficulty with serial subtractions ( $< 5/5$  trials correct). Individuals with the highest *P gingivalis* IgG ( $> 119$  ELISA Units (EU)) were more likely to have poor delayed verbal recall (OR 2.89, 95% CI 1.14 to 7.29) and impaired subtraction (OR 1.95, 95% CI 1.22 to 3.11) than those with the lowest ( $\leq 57$  EU), with dose–

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response relationships for both ( $p$  trend, delayed memory=0.045, subtraction=0.04). After adjusting for socioeconomic and vascular variables, these relationships remained robust for the highest *P. gingivalis* IgG group (delayed verbal memory OR 3.01 (95% CI 1.06 to 8.53); subtraction OR 2.00 (95% CI 1.19 to 3.36)). In contrast, immediate verbal memory was not significantly associated with *P. gingivalis*.

**Conclusion**—A serological marker of periodontitis is associated with impaired delayed memory and calculation. Further exploration of relationships between oral health and cognition is warranted.

Oral health problems, including periodontal disease, caries, edentulism and infrequent preventative care, become more prevalent with increasing age.<sup>1 2</sup> Periodontitis and caries are the two predominant causes of tooth loss and reflect similar risk factors, including inattention to care; periodontitis is more common than caries among adults.<sup>3 4</sup> Estimates of adult prevalence of clinical periodontitis vary from 20% to greater than 80%,<sup>5</sup> and differences in prevalence estimates likely depend on clinical markers used for disease definition.

Periodontitis is a chronic, potentially transmissible oral biofilm infection.<sup>6 7</sup> Exposure to periodontal pathogens is ubiquitous in older adults,<sup>8</sup> with a large proportion exposed by adolescence.<sup>9</sup> A systemic host response to periodontitis is evidenced by serum antibodies to common periodontal bacteria,<sup>8</sup> such as *Porphyromonas gingivalis* (a pathogen causally associated with periodontitis),<sup>6</sup> plus elevations in serum inflammatory markers interleukin 6 and C reactive protein.<sup>11</sup> In addition to epidemiological associations, treatment of periodontal disease decreases serum levels of interleukin 6 and C reactive protein.<sup>11</sup>

Epidemiological evidence supports an association between stroke and serum antibody measures to *P. gingivalis*.<sup>12</sup> *P. gingivalis* is associated with accelerated aortic atherogenesis<sup>13</sup> and increased carotid artery intimal–medial thickness.<sup>14</sup> Risk factors for stroke and dementia, including diabetes, obesity and smoking, have a similar systemic inflammatory profile to periodontitis<sup>15 16</sup> and suggest that they could play similar roles in a final common pathway of atherogenesis related to systemic inflammation.<sup>15</sup>

Despite the association of periodontitis with stroke and shared risk factors between stroke and dementia,<sup>17</sup> to our knowledge, no epidemiological studies have investigated periodontitis relative to cognition. We hypothesised that periodontal disease is a risk factor for poor cognition. Thus we investigated whether periodontitis, as defined by a serological marker, is independently associated with cognitive test performance in older adults in a nationally representative US sample, before and after controlling for potential socioeconomic and vascular confounders.

## METHODS

### Source of data

The Third National Health and Nutrition Examination Survey (NHANES-III) was a cross sectional nationwide health survey of the USA, performed between 1988 and 1994 by the National Center for Health Statistics. NHANES-III enrolled 33 994 persons aged 2 months and older using a stratified multistage probability sampling design.

### Inclusion criteria

During the second phase of enrolment (1991–1994), 9371 persons had serum analysis for immunoglobulin levels of *P. gingivalis*,<sup>18</sup> with 2531  $\geq 60$  years of age. Of these, persons with

both cognitive evaluations and serum analysis for these pathogens (n=2355) were included in this analysis.

### Study variables

Serum *P. gingivalis* IgG was chosen for study to capture evidence of systemic exposure to a common periodontal disease causing pathogenic bacterium with well described pathogenicity<sup>8</sup> and associations with systemic disease and stroke. Antibody measurements were reported in ELISA units of IgG (EU). To examine for possible dose-response relationships of *P. gingivalis* and cognition, we created four ranges of *P. gingivalis* IgG based on the only known report relating periodontitis severity to *P. gingivalis* IgG.<sup>8</sup> That report from the Atherosclerosis Risk in Communities Study (ARIC, n=1673) had similar demographics to the NHANES-III subjects studied here and reported mean *P. gingivalis* IgG for healthy individuals of 53.8 EU (SD 9.1), mild periodontitis 60.9 EU (SD 8.4), moderate periodontitis 69.4 EU (SD 5.5) and severe periodontitis 168.4 (SD 9.5) (p<0.0001, determined by non-parametric rank scores from general linear models for overall significance after having p<0.05 for the Hotelling T<sup>2</sup> statistic for multiple comparisons of 17 periodontal bacteria serum titres).<sup>8</sup> To capture the relationship of increasing *P. gingivalis* IgG associated with increasing periodontitis severity, we used the midpoint between each of these *P. gingivalis* IgG means to create cut-off points for four *P. gingivalis* IgG groups: ≤57 EU (referent), 58–65 EU, 66–119 EU and > 119 EU (highest).

Three cognitive tests were measured in NHANES-III: an immediate and delayed logical verbal memory test from the East Boston Memory Test,<sup>19</sup> a three word registration/memory task (“apple,” “table” and “ penny”) and five serial subtractions by intervals of three. Consistent with previous NHANES-III reports,<sup>20 21</sup> a summary score of less than 4 out of a possible 9 points in total (0–6 points from paragraph/story memory, plus 0–3 points from three word recall) was considered impaired. For immediate memory (registration), again using a summary score of logical memory and three word task, we considered less than 5 out of 9 points (10th percentile) to be impaired. For the test of serial subtractions, any miscalculation during the five trials was considered impaired. We also initially explored a clinical definition of periodontitis<sup>22</sup> relative to delayed memory but found no association (data not shown).

A comprehensive history was taken, including medical history, medication use and self-reported sociodemographic factors. Race-ethnicity included data from the three major groups, as collected in the survey: non-Hispanic White, non-Hispanic Black and Mexican-American. Annual individual income was categorised into three groups: ≤\$14 999, \$15 000–24 999 and >\$25 000. Health insurance status was defined by active health insurance within the last month (private company, Medicare, Medicaid or military). Years of education were categorised as <12 years (less than high school education), 12 years (equivalent to completion of high school) and >12 years of (at least some education beyond high school). Smoking status was specified as never, current or former smokers.

Coronary artery disease (CAD) was defined by history of myocardial infarction or anginal symptoms (pain or discomfort in the chest while walking uphill that abates with rest). Congestive heart failure (CHF) was based on a history of a physician informing the patient of CHF. Stroke was defined as a self-reported history of stroke or if the subject had been informed by a physician of stroke. Diabetes mellitus was defined by self-report of diabetes; women with only a history of gestational diabetes were not considered diabetic. Hypertension was defined as present if the participant self-reported hypertension, used anti-hypertensive medications or had measured systolic blood pressure > 130 mm Hg or diastolic blood pressure >85 mm Hg. This more liberal assessment of blood pressure is consistent

with that of the metabolic syndrome<sup>23</sup> and was used in order to minimise the potential effect of this possible confounder.

### Statistical methods

Descriptive statistics for selected characteristics and prevalence of the outcomes of interest were estimated. To determine significance of differences, t tests for comparison of means of continuous variables were used. To determine the strength of the association between *P gingivalis* IgG and cognitive test performance before and after controlling for selected covariates, logistic regression models were fitted. All data management was done using SAS v9.1 (SAS/STAT 9.1 User's Guide, 2004; SAS Institute Inc, Cary, North Carolina, USA). All analyses were performed with SUDAAN (SUDAAN Language Manual, Release 9.0, 2004; Research Triangle Institute, North Carolina, USA), which takes into account the complex sampling design used in NHANES-III yielding unbiased standard error estimates.

## RESULTS

Mean age of the study participants was 70.8 years (95% CI 70.0 to 1.6); 57% were women (table 1). Overall, the mean *P gingivalis* IgG level was 117.2 EU (95% CI 103.6 to 131.1). Mean *P gingivalis* IgG significantly differed by sex, race, income, smoking history, dental health status, CAD and hypertension (table 2).

Poor immediate verbal memory (registration) was prevalent in 5.7% of patients, and overall 6.5% had impaired verbal memory; 22.1% had some difficulty with serial subtractions. Mean *P gingivalis* IgG was higher among those with impaired performance for each of the three cognitive tests (table 3). Immediate verbal memory (registration) was not significantly associated with high *P gingivalis* IgG in any model (table 4). In unadjusted models, individuals in the highest *P gingivalis* IgG group (> 119 EU) were more likely to have poor delayed verbal memory (OR 2.89, 95% CI 1.14 to 7.29) and impaired subtraction (OR 1.95, 95% CI 1.22 to 3.11) than those in the lowest group (≤57 EU), with apparent dose–response relationships for both (p trend, delayed memory=0.045; p trend, subtraction=0.04) (tables 5, 6).

We then explored potential effects on the relationship between *P gingivalis* IgG and cognitive tests, initially by age, sex and education, which did not appreciably affect the relationship between *P gingivalis* IgG and delayed memory or subtraction (model 1, tables 5, 6). Additionally adjusting for other socioeconomic confounders (insurance status, race and income) led to marked attenuation of the relationship between the highest *P gingivalis* IgG group and delayed memory (OR 1.81, 95% CI 0.56 to 5.85, p trend=0.45) but did not affect the relationship with the subtraction test (model 2, tables 5, 6). Finally, we explored a model additionally including potential vascular confounders hypertension, CAD, CHF, diabetes mellitus, smoking and stroke. Inclusion of vascular variables strengthened the relationship between the highest *P gingivalis* IgG group and delayed verbal memory (OR 3.01, 95% CI 1.06 to 8.53) but had minimal effect on the test of subtraction (OR 2.00, 95% CI 1.19 to 3.36). Taken together, these findings suggest that vascular factors are a negative confounder in the relationship of *P gingivalis* and delayed memory in a model adjusting for socioeconomic factors. Moreover, neither vascular nor socioeconomic factors played an appreciable role in the relationship of *P gingivalis* IgG and subtraction test performance.

We also explored potential effect modification of the relationship between *P gingivalis* IgG and cognitive tests by age (dichotomised at a median age of 72 years), stroke history and race (given its apparent role as a confounder in the relationship with delayed memory). None of these potential effect modifiers were statistically significant in crude or fully adjusted models for any of the cognitive tests (data not shown).

## DISCUSSION

We identified a cross sectional association between a serological marker of a common periodontitis pathogen and poor cognitive test performance in a large nationally representative sample. Individuals with high levels of *P gingivalis* IgG had significantly greater odds of impaired verbal memory and subtraction test performance and this finding remained robust when adjusting for potential sociodemographic and vascular confounders. Furthermore, we identified a statistically significant dose–response relationship between subtraction test performance and increasing *P gingivalis* IgG and a similar but non-significant trend regarding delayed verbal memory and *P gingivalis* IgG. Given these findings, we performed post hoc analyses of *A actinomycetemcomitans* IgG (the only other periodontal pathogen evaluated in NHANES-III) and clinical periodontitis<sup>22</sup> relative to all cognitive test outcomes but found no relationship in any models (data not shown), perhaps related to weak associations of *A actinomycetemcomitans* with systemic disease<sup>12</sup> and imprecise clinical periodontal measurements in NHANES-III.<sup>24</sup> Notably, an NHANES-III study found that among those aged 20–59 years, markers of periodontitis (gingival bleeding, loss of periodontal attachment and tooth loss) were associated with poor symbol digit substitution test and serial digit learning test performance. However, these same individual clinical measures of periodontitis were not associated with story recall in adjusted models among those aged 70 years and older.<sup>25</sup>

These cross sectional analyses do not allow inferences regarding the directionality of the association of cognition and dental health. A relatively straightforward argument can be made for cognitive impairment leading to poor dental health: persons with impaired cognition could be inattentive to oral hygiene or oral health maintenance as impairment in cognition progresses.<sup>26</sup> Conversely, worth considering is whether poor oral health could contribute to subsequent cognitive impairment.

Although results presented here are preliminary and inconclusive, a growing body of evidence supports exploration of a possible association between poor oral health and incident dementia. Poor dentition, a late-life marker of earlier oral health conditions such as periodontitis, is associated with both prevalent cognitive impairment<sup>25 27 28</sup> and incident dementia.<sup>29–31</sup> In addition, at least one randomised trial demonstrated that more intensive dental care was associated to a 1.5 point significantly slower decline in Folstein Mini-Mental Status Examination score after 2 years.<sup>32</sup>

Despite association of stroke with periodontitis,<sup>17 33</sup> stroke did not appear to be a confounder or effect modifier in the relationship between *P gingivalis* IgG and cognitive test performance. This could reflect an imprecise assessment of stroke based on self-report, or that the relationship between stroke, periodontitis and memory is masked within a cross-sectional study. Alternatively, periodontitis could be related to cognition independent of clinical stroke. Similar to diabetes, hypertension and smoking,<sup>34</sup> periodontitis is associated with impaired systemic arterial endothelial function,<sup>35</sup> and the latter has been associated with cerebral white matter hyperintensities,<sup>36</sup> vascular dementia and Alzheimer's disease.<sup>37 38</sup> Alternatively, systemic inflammation has been hypothesised to directly influence expression of neurodegenerative disorders such as Alzheimer's disease.<sup>39</sup>

This study has several limitations other than the constraints of cross sectional analysis. Measurable socioeconomic covariates provide a restricted scope of lifelong socioeconomic status and periodontitis could be or lead, at least in part, to residual confounder; indeed, low socioeconomic status is strongly associated with periodontitis in NHANES-III.<sup>22</sup> Moreover, persons with low socioeconomic status may have low cognitive reserve,<sup>40</sup> or relatively

worse memory test performance despite similar brain pathology compared with other groups.

Available NHANES-III cognitive tests are another limitation. The cognitive measurements reported here are crude assessments of cognitive test performance and may reflect individual or group differences in test understanding, rather than a true assessment of cognition. The limited scope of these tests also does not clearly inform a potential neuroanatomical basis for impaired test performance, given likely overlapping cognitive domains involved with each task. Furthermore, the precise aetiology of impaired cognitive test performance cannot be known from these data. Nonetheless, the components of the outcome used here have been validated as rigorous tools for screening memory in epidemiological studies.<sup>19</sup>

In an attempt to capture a dose–response relationship between *P gingivalis* IgG and cognitive test performance, we created *P gingivalis* IgG groups based on a report from another large multicentre population based American study (ARIC),<sup>8</sup> which found a strong association between escalating levels of *P gingivalis* IgG and clinical periodontitis severity. Use of this schema for creating *P gingivalis* IgG groups appears plausible but requires validation in other studies. Serum antibodies to periodontal pathogens are strongly associated with worse states of oral health<sup>8</sup> and remain persistently elevated despite clinical treatment.<sup>41</sup> Taken together, these findings suggest that serum antibody levels reflect chronic, intermittent exposures of clinical periodontitis, but it is uncertain whether to state that a higher periodontal titre implies higher burden of acute exposures, more recent exposure or more intense response to periodontal pathogens.

Periodontitis is a lifelong, highly prevalent, chronic inflammatory disease associated with stroke, systemic inflammation and endothelial dysfunction. Although our results are preliminary, they suggest that further exploration of relationships between oral health and cognition is warranted.

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**Table 1**

Distribution and prevalence of selected characteristics in NHANES-III adults included in the analyses (unweighted n=2355)

Characteristic	Overall (%)
Sex	
Women	57.3
Men	42.7
Race-ethnicity	
Non-Hispanic White	89.2
Non-Hispanic Black	8.3
Mexican-American	2.5
Active health insurance	
Yes	98.7
No	1.3
Education	
<12 years	38.5
12 years	32.5
>12 years	28.9
Annual income	
≤\$14 999	31.4
\$15 000–24 999	26.2
>\$25 000	42.4
Smoking history	
Non-smokers	45.8
Former smokers	40.3
Active smokers	13.8
CAD	
Yes	15.4
No	84.6
CHF	
Yes	6.5
No	93.5
Prior stroke	
Yes	7.1
No	92.9
Diabetes	
Yes	11.9
No	88.1
Hypertension	
Yes	74.5
No	25.5
Dentate status	

Characteristic	Overall (%)
Completely edentulous	29.3
Edentulous in 1 arch	14.5
Some natural teeth present	56.2
<i>P gingivalis</i> IgG (EU)	
( $\leq 57$ )	7.9
(58–65)	18.9
(66–119)	54.1
(>119)	19.1

CAD, coronary artery disease; CHF, congestive heart failure.

**Table 2**Mean *P. gingivalis* IgG level for selected population characteristics: NHANES III

Characteristic	Mean <i>P. gingivalis</i> IgG (EU) (95% CI)	p Value *		
Overall	117.2 (103.6–131.1)			
Age				
≤72 years	117.0 (103.3–130.6)	0.62		
>72 years	121.3 (102.6–139.9)			
Sex				
Men	127.1 (111.2–143.1)	0.03		
Women	112.1 (97.8–126.3)			
Race-ethnicity		W vs B	W vs M	B vs M
Non-Hispanic White (W)	105.7 (96.3–115.0)	<0.01	0.05	0.89
Non-Hispanic Black (B)	220.8 (152.7–288.9)			
Mexican–American (M)	212.1 (104.9–319.2)			
Active health insurance				
Yes	118.0 (104.6–131.5)	0.15		
No	150.5 (103.4–197.6)			
Education		E vs HS	E vs C	HS vs C
<12 years (E)	121.1 (101.0–141.3)	0.49	0.61	0.88
12 years (HS)	113.3 (96.7–129.9)			
>12 years (C)	114.8 (97.7–131.8)			
Annual income		L vs M	L vs Hi	M vs Hi
≤\$14 999 (L)	138.2 (114.1–162.4)	0.01	0.01	0.56
\$15 000–24 999 (M)	111.5 (93.6–129.5)			
>\$25 000 (Hi)	106.5 (95.1–117.8)			
Smoking history		A vs F	A vs N	F vs N
Active smokers (A)	99.1 (87.7–110.5)	0.01	<0.01	0.29
Former smokers (F)	116.4 (101.1–131.7)			
Non-smokers (N)	126.1 (108.1–144.1)			
CAD				
Yes	104.1 (91.4–116.8)	0.02		
No	121.0 (106.5–135.6)			
CHF				
Yes	124.3 (98.9–149.7)	0.59		
No	118.1 (104.8–131.4)			
Prior stroke				
Yes	143.0 (98.9–187.2)	0.23		
No	116.7 (103.6–129.9)			
Diabetes				
Yes	139.4 (101.6–177.3)	0.66		
No	115.7 (103.0–128.4)			
Hypertension				

Characteristic	Mean <i>P. gingivalis</i> IgG (EU) (95% CI)	p Value*		
Yes	125.4 (108.8–142.0)	<0.01		
No	99.4 (88.0–110.8)			
Dentate status		EA vs E1	EA vs T	E1 vs T
Edentulous (EA)	80.7 (73.2–88.2)	0.02	<0.01	0.01
Edentulous in 1 arch (E1)	105.9 (85.8–125.9)			
At least some natural teeth present (T)	143.6 (122.3–164.8)			

\* p values derived from t test comparison of means of *P. gingivalis* IgG by population characteristic.

CAD, coronary artery disease; CHF, congestive heart failure; EU, ELISA unit.

**Table 3**Cognitive test performance relative to *P gingivalis* IgG

Test	Overall (%)	<i>P gingivalis</i> IgG (EU) (95% CI)	p Value*
Immediate verbal memory/registration (9 possible points)			
Low (0–4 points)	5.7	164.3 (78.3–250.3)	0.24
High (5–9 points)		113.6 (100.7–126.5)	
Delayed verbal memory (9 possible points)			
Low (0–3 points)	6.9	155.3 (87.4–223.2)	0.23
High (4–9 points)		114.6 (101.6–127.7)	
Serial 3 subtraction test (5 possible points)			
Low (0–4 points)	22.1	132.3 (114.3–150.4)	0.046
High (5 points)		114.8 (100.6–129.0)	

\* p values derived from t test comparison of means of *P gingivalis* IgG by population characteristic.

**Table 4**

Crude and adjusted odds ratios for *P gingivalis* IgG and memory tests. Immediate verbal memory/registration (impaired <5/9 possible points)

<i>P gingivalis</i> IgG (EU)	Models for immediate verbal memory OR (95% CI)			
	Crude	Model 1	Model 2	Model 3
(≤57) [reference]	1	1	1	1
(58–65)	0.99 (0.34–2.86)	0.90 (0.29–2.80)	0.57 (0.18–1.83)	1.01 (0.38–2.67)
(66–119)	1.63 (0.48–5.54)	1.44 (0.38–5.42)	1.17 (0.29–4.73)	1.99 (0.57–6.98)
(>119)	2.14 (0.62–7.39)	2.02 (0.54–7.63)	1.62 (0.39–6.80)	2.57 (0.75–8.85)
p Trend	0.11	0.21	0.04	0.07

Crude, association of *P gingivalis* IgG and cognitive test; Model 1, additionally adjusted for age, sex and education; Model 2, additionally adjusted for race, insurance and income; Model 3, additionally adjusted for history of diabetes mellitus, hypertension, smoking, congestive heart failure, coronary artery disease, stroke and C reactive protein.

**Table 5**

Crude and adjusted odds ratios for *P gingivalis* IgG and memory tests. Delayed verbal memory (impaired <4/9 possible points)

<i>P gingivalis</i> IgG (EU)	Models for delayed verbal memory OR (95% CI)			
	Crude	Model 1	Model 2	Model 3
(≤57) [reference]	1	1	1	1
(58–65)	1.43 (0.67–3.03)	1.40 (0.64–3.09)	1.04 (0.43–2.50)	1.82 (0.88–3.75)
(66–119)	2.03 (0.80–5.18)	1.94 (0.69–5.41)	1.54 (0.49–4.81)	2.60 (0.91–7.46)
(>119)	2.89 (1.14–7.29)	3.23 (1.19–8.79)	1.81 (0.56–5.85)	3.01 (1.06–8.53)
p Trend	0.045	0.01	0.45	0.22

Crude, association of *P gingivalis* IgG and cognitive test; Model 1, additionally adjusted for age, sex and education; Model 2, additionally adjusted for race, insurance and income; Model 3, additionally adjusted for history of diabetes mellitus, hypertension, smoking, congestive heart failure, coronary artery disease, stroke and C reactive protein.

**Table 6**

Crude and adjusted odds ratios (OR) for *P gingivalis* IgG and memory tests. Serial subtraction (impaired <5/5 possible points)

<i>P gingivalis</i> IgG (EU)	Models for calculation/attention OR (95% CI)			
	Crude	Model 1	Model 2	Model 3
(≤57) [reference]	1	1	1	1
(58–65)	1.49 (0.86–2.59)	1.54 (0.86–2.76)	1.48 (0.69–3.18)	1.57 (0.74–3.31)
(66–119)	1.42 (0.97–2.08)	1.37 (0.94–1.98)	1.34 (0.77–2.34)	1.36 (0.80–2.29)
(>119)	1.95 (1.22–3.11)	2.02 (1.31–3.10)	1.98 (1.14–3.42)	2.00 (1.19–3.36)
p Trend	0.04	0.01	0.06	0.0498

Crude, association of *P gingivalis* IgG and cognitive test; Model 1, additionally adjusted for age, sex and education; Model 2, additionally adjusted for race, insurance and income; Model 3, additionally adjusted for history of diabetes mellitus, hypertension, smoking, congestive heart failure, coronary artery disease, stroke and C reactive protein.