

## **PAA 2009 Extended Abstract**

### **Biomarker classification, risk profiles, and mortality in the National Health and Nutrition Examination Survey III**

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#### *Introduction*

Several studies have investigated the relationship of biomarkers to various health outcomes. When considered both independently (e.g., blood pressure alone or triglyceride levels alone) and conjointly (e.g., as in allostatic load), biomarkers have been associated with increasing age (from age 20 to 60) (Crimmins et al., 2003), social relationships (Seeman et al., 2004), disease, and mortality (Karlman, Singer, Seeman, 2006). Hence, allostatic load seems an appropriate indicator of aging or age-related processes.

However, a critique of this framework underlines its simple method of summing the total number of high-risk biomarkers from very different physiological systems. One criticism of allostatic load questions how the variables correlate to one another, which may or may not justify the clumping of individual biomarkers into one composite variable (allostatic load). A second criticism of allostatic load is that all biomarkers are equally weighted in creating an allostatic load score, despite studies indicating that they differentially contribute to a given health outcomes.

The purpose of this study is to empirically test these criticisms by classifying individual biomarkers based on their relationship to one another and based on grouping individuals with similar high-risk profiles. Based on this classification, the individual risk-profile classes will be used to determine their relationship to 6-year mortality.

#### *Methods*

Adults age 45 and older from the National Health and Nutrition Examination Survey III (1988-1994) (N=6947) with linked mortality data were examined. Ten commonly investigated biomarkers were considered: diastolic and systolic blood pressure, glycated hemoglobin, body mass index, triglycerides, total/high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, albumin, C-reactive protein (CRP), and fibrinogen. Table 1 shows the clinical cut points used for these biological markers. Additionally, factor analysis and latent class analysis were used, and logistic regression models examined the relationship of the resultant latent classes to 6-year mortality.

#### *Results*

Table 2 summarizes the characteristics of the study sample. The mean age of the study population was 60 years, with males comprising less than half of the population (45.7%). Overall, 68.3% were married, and the mean years of education were 11.7 years.

Additionally, more than half reported having either very good or excellent health (25.6% and 26.0%, respectively).

Using factor analysis, three factor groupings for the 10 biomarkers were found (Table 3). Factor 1 includes BMI, total/HDL cholesterol, LDL cholesterol, fasting triglycerides, and glycated hemoglobin; this has been named the Metabolic factor (variance explained is 1.76). Factor 2, termed the Inflammation factor, includes albumin, CRP, and fibrinogen (variance explained is 1.40). Lastly, Factor 3 (the Cardiovascular factor) includes systolic and diastolic blood pressure, and it explains 1.26 of the variance.

To determine the latent class profiles that group individuals based on their high-risk biomarker profiles, we first examined all potential baseline models for the entire study sample. Table 4 indicates that the model with 4 latent classes is the best baseline model because the decrease in the Likelihood-ratio  $G^2$  relative to the decrease in degrees of freedom (df) was substantial with the each additional latent class added. However, when up to 5 classes were added, the Bayesian information criteria (BIC) increased, thereby suggesting that, for this population, the 4-class model is ideal.

Before ultimately selecting this 4-class model, tests of measurement invariance by gender were considered. Consequently, measurement invariance by gender was found and a significant difference in the number of latent class profiles between males and females was determined (Likelihood-ratio difference = 240.02, df = 40). Hence, separate analyses for determining the baseline models for males and females were completed. Table 5 indicates that a 5-class model is optimal for males (Likelihood-ratio  $G^2$  = 713.07, df = 969, Akaike's information criteria [AIC] = 821.07, BIC = 1148.46), while Table 6 shows that a 4-class model is optimal for females (Likelihood ratio  $G^2$  = 821.43, df = 980, AIC = 907.43, BIC = 117.56).

The latent class estimates, which illustrate the probability that an individual in a given latent class will be at high-risk for a given biomarker, are shown for each gender in Table 7. For males, individuals were grouped into 5 classes: high inflammation, high cholesterol and inflammation, high cholesterol, high blood pressure, and no high-risk. For females, individuals were grouped into 4 classes: high inflammation, high cholesterol, high blood pressure, and no high-risk.

Using these latent classes, we determined the odds of mortality 6-years after laboratory testing. After adjusting for age and ethnicity, being in the *high inflammation class* increased the risk of mortality at 6-year follow-up for both males and females (Odds Ratio [OR] = 2.37 and OR = 1.84, respectively) (Table 8). Conversely, there were greater gender differences in the odds ratios predicting mortality among individuals in the *high cholesterol* and *high blood pressure classes* compared to the gender specific *no high-risk class*. While males in the *high cholesterol class* were less likely to die at 6-year follow-up compared to males in the *no high-risk class* (OR = 0.34), females belonging to the *high cholesterol class* were more likely to die compared to females in the *no high-risk class* (OR = 1.73). Additionally, while males in the *high blood pressure class* were also less likely to die at 6-year follow-up compared to the *no high-risk class* for males (OR=0.88), females in this same *high blood pressure class* were more likely to die than females in the *no high-risk class* (OR = 2.42). The fifth latent class group (found for males only), indicated that males belonging to the *high cholesterol and high inflammation class* were 1.23 times as likely to die at 6-year follow-up compared to males in the *no high-risk class*.

## *Conclusions*

This study finds that based on the inter-correlations of the 10 biomarkers examined, these biomarkers can be grouped into three factors: cardiovascular, metabolic, and inflammatory. Further, 4 or 5 classes (for females and males, respectively) can be used to group individuals based on their high-risk biomarker profiles. Aside from gender differences in the number of high-risk profile classes, differences in the relationships among the high-risk profile classes and 6-year mortality also differed by gender. Compared to their respective *no high-risk class*, females in the *high inflammation class* had higher odds of 6-year mortality than males in the same *high inflammation class*. Additionally, when compared to their gender-specific *no high-risk class*, the other high-risk profiles (e.g., the *high blood pressure* and *high cholesterol classes*) were greater predictors of mortality at 6-year follow-up for women than for men.

## *References*

- Crimmins EM, Johnston M, Hayward M, Seeman T. 2003. Age differences in allostatic load: an index of physiological dysregulation. *Exp Gerontology* 38, 731-734.
- Seeman T, Gleib D, Goldman N, Weinstein M, Singer B, Lin Y. 2004. Social relationships and allostatic load in Taiwanese elderly and near elderly. *Social Science & Med* 59, 2245-2257.
- Karlamangla AS, Singer BH, Seeman TE. 2006. Reduction in allostatic load in older adults is associated with lower all-cause mortality risk: MacArthur Studies of Successful Aging. *Psychosomatic Med* 68, 500-507.

**Table 1. Clinical cutoff points for ten biological markers**

Biomarker	High-risk cutoff
Systolic blood pressure	> 90 mmHg
Diastolic blood pressure	> 140 mmHg
Body mass index	> 30 kg/m <sup>2</sup>
Total/HDL cholesterol	≥ 5.92
LDL cholesterol	≥ 160
Fasting triglycerides	≥ 150 mg/dl
Glycated hemoglobin	≥ 5.6%
Albumin	≤ 3.9 g/dl
C-reactive protein	> 0.33 mg/dl
Fibrinogen	> 336 mg/dl

**Table 2. Study sample characteristics (N=6947)**

	Mean(SD) or %
Age	60.1(13.9)
Male (%)	45.7
Ethnicity (%)	
Non-hispanic white	81.9
Non-hispanic black	8.9
Hispanic	6.4
Other	2.8
Years of education	11.7(3.7)
Married (%)	68.3
Self-reported health status (%)	
Excellent	25.6
Very good	26.0
Good	33.0
Fair	13.2
Poor	2.2

**Table 3. Factor analysis of high-risk biological markers**

Biomarker	Factor Analysis		
	<i>Factor 1</i> Metabolic	<i>Factor 2</i> Inflammation	<i>Factor 3</i> Cardiovascular
Systolic blood pressure	0.27	0.29	<b>0.69</b>
Diastolic blood pressure	0.25	0.17	<b>0.75</b>
Body mass index	<b>0.46</b>	0.33	-0.14
Total/HDL cholesterol	<b>0.69</b>	-0.47	-0.05
LDL cholesterol	<b>0.47</b>	-0.44	0.08
Fasting triglycerides	<b>0.58</b>	-0.22	-0.15
Glycated hemoglobin	<b>0.37</b>	0.09	-0.24
Albumin	0.02	<b>0.48</b>	-0.20
C-reactive protein	0.39	<b>0.58</b>	-0.21
Fibrinogen	0.30	<b>0.37</b>	-0.17
<i>Variance explained</i>	1.76	1.40	1.26

N=2595

**Bold >0.35**

HDL = high-density lipoprotein

LDL = low-density lipoprotein

**Table 4. Comparison of baseline models from LCA for entire study sample**

No. of classes	Likelihood Ratio G2	df	AIC	BIC
2	1851.42	1002	1893.42	1893.42
3	1347.53	991	1411.53	1625.59
<b>4</b>	<b>1037.73</b>	<b>980</b>	<b>1123.73</b>	<b>1411.37</b>
5	943.58	969	1051.58	1412.80
6	775.77	958	905.77	1340.57
7	728.24	947	880.24	1388.63

Boldface type indicates the optimal model.

LCA = Latent class analysis

df = Degrees of freedom

AIC = Akaike's Information Criteria

BIC = Bayesian Information Criterion



**Table 5. Comparison of baseline models from LCA among males**

No. of classes	Likelihood Ratio G2	df	AIC	BIC
2	1396.79	1002	1438.69	1566.10
3	1714.79	991	1778.79	1997.87
4	814.45	980	900.45	1161.15
<b>5</b>	<b>713.07</b>	<b>969</b>	<b>821.07</b>	<b>1148.46</b>
6	646.08	958	776.08	1170.16
7	597.58	947	749.58	1210.35

Boldface type indicates the selected model.

LCA = Latent Class Analysis

df = Degrees of freedom

AIC = Akaike's Information Criteria

BIC = Bayesian Information Criterion

**Table 6. Comparison of baseline models from LCA among females**

No. of classes	Likelihood Ratio G2	df	AIC	BIC
2	1301.15	1002	1343.15	1474.1
3	1714.79	991	1778.79	1997.87
<b>4</b>	<b>821.43</b>	<b>980</b>	<b>907.43</b>	<b>117.56</b>
5	706.57	969	814.57	1151.29
6	655.2	958	785.2	1190.52
7	616.5	947	768.5	1242.41

Boldface type indicates the selected model.

LCA = Latent Class Analysis

df = Degrees of freedom

AIC = Akaike's Information Criteria

BIC = Bayesian Information Criterion

**Table 7. Latent class estimates of high-risk biomarkers by gender**

Biomarker	Males*					Females**			
	Class 1 High inflammation	Class 2 High cholesterol + inflammation	Class 3 High cholesterol	Class 4 High blood pressure	Class 5 No high-risk	Class 1 High inflammation	Class 2 High cholesterol	Class 3 No high-risk	Class 4 High blood pressure
Systolic blood pressure	0.39	0.43	0.22	<b>1.00</b>	0.25	0.33	0.42	0.22	<b>0.86</b>
Diastolic blood pressure	0.08	0.15	0.05	<b>1.00</b>	0.04	0.02	0.07	0.00	0.31
Body mass index	0.33	0.46	0.25	0.28	0.16	<b>0.61</b>	0.35	0.17	0.37
Total/HDL cholesterol	0.00	1.00	<b>0.94</b>	0.21	0.00	0.13	<b>1.00</b>	0.00	0.00
LDL cholesterol	0.14	<b>0.65</b>	<b>0.55</b>	0.20	0.16	0.22	<b>0.82</b>	0.22	0.28
Fasting triglycerides	0.09	<b>0.54</b>	<b>0.50</b>	0.17	0.12	0.28	<b>0.66</b>	0.09	0.16
Glycated hemoglobin	0.24	0.38	0.13	0.14	0.09	0.28	0.21	0.05	0.21
Albumin	0.25	0.19	0.06	0.07	0.05	0.36	0.09	0.11	0.18
C-reactive protein	<b>0.80</b>	<b>0.86</b>	0.18	0.28	0.12	<b>0.90</b>	0.39	0.18	0.45
Fibrinogen	0.39	0.39	0.04	0.07	0.02	0.36	0.11	0.05	0.13
<i>Class probability</i>	0.17		0.17	0.07	0.52	0.25	0.11	0.51	0.13

\*N=3174

\*\*N=3773

**Bold >0.50**

HDL = high-density lipoprotein

LDL = low-density lipoprotein

**Table 8. Parameter estimates and Odds Ratios of latent class profiles predicting 6-year mortality in males and females\***

Latent class profile	Males		Females	
	B	Odds Ratio	B	Odds Ratio
No high-risk		Reference		Reference
Inflammation	0.86	2.37	0.61	1.84
Cholesterol	-1.09	0.34	1.03	1.73
Blood pressure	-0.13	0.88	0.88	2.42
Cholesterol + inflammation	0.20	1.23		

\*Adjusted for age and ethnicity