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## Gender differences in the relationships of cardiovascular symptoms and somatosensory amplification to mortality

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### Abstract

Symptoms of angina and dyspnea predict coronary artery disease and death less well in women than in men. Greater somatosensory amplification – a psychosocial propensity to report symptoms of physical discomfort – may lead women to report relatively high levels of angina and dyspnea for reasons unrelated to coronary disease, reducing their associations with mortality. We assessed this hypothesis in a nationally representative survey of U.S. adults. When stratified by gender, angina and dyspnea significantly predicted mortality among men, but predicted it less well among women. After adjusting for amplification, cardiovascular symptoms did not predict mortality among women, but amplification was positively associated with mortality among older women.

### Introduction

As the other articles in this issue attest, Bert Brim is an incredibly intelligent, insightful, and generative individual and scholar; indeed an icon to those of us who had the privilege and pleasure of working with him. As David Featherman and Deborah Phillips describe so well in their article (pp ), Bert has had a profound impact on how social scientists think about the ways in which biological and sociocultural factors influence individuals over the life course. Although Bert has not studied primarily health outcomes, he is acutely aware of the complex ways in which multiple factors affect health and that view of life span development is manifest in the richness of variables included in the MIDUS study, a highly original combination of psychological, sociocultural and health measures in a national longitudinal study. That richness allowed us to delve into the complex relationships among gender, psychological characteristics such as somatosensory amplification that are related to gender, and the manifestations and consequences of a major health condition, cardiovascular disease. Although Bert definitely did not envision this type of analysis as he and colleagues in the MacArthur Foundation Research Network on Successful Midlife Development developed the MIDUS study, his intellectual perspective, openness to ideas, and general approach to studying human development led to a unique and path-breaking study mid-life development.

## Background

Coronary artery disease (CAD) is the leading cause of death for both women and men in the United States,<sup>1, 2</sup> but its epidemiology differs by gender. Initial manifestations of CAD occur ten years earlier, on average, in men than women, and initial myocardial infarctions occur as many as 20 years earlier in men.<sup>2, 3</sup> Major symptoms of CAD include angina pectoris and dyspnea, both of which significantly predict death.<sup>4–7</sup> These symptoms, however, do not predict mortality in women as well as in men.

An estimated 6.5 million Americans suffer from angina—chest pain that occurs when the heart muscle does not get enough oxygen-enriched blood,<sup>2</sup> and this estimate may be conservative.<sup>8</sup> About half of all patients who are admitted to a hospital with a myocardial infarction report angina prior to admission.<sup>9</sup> Angina often negatively impacts functional status and is associated with serious disease and death.<sup>10</sup>

Dyspnea—difficult breathing—is a nonspecific symptom that can be activated during exercise or at rest by many underlying conditions, including myocardial ischemia, heart failure, pulmonary problems, obesity, and other medical conditions. Recent studies report that the risk of cardiac-related death is four times greater in patients with dyspnea than asymptomatic patients, and twice that in patients with angina alone.<sup>6, 7</sup>

Many studies assessing the predictive value of these symptoms, including the landmark study by Rose,<sup>11</sup> examined only men, assuming that the presentation and predictive value of these symptoms would be similar in men and women. Increasing evidence, however, indicates that the presentation and prognostic significance of angina and dyspnea differ between men and women, as does the pathophysiology of CAD itself.<sup>1, 6, 7, 12</sup> Both angina and dyspnea are more common in women, but more predictive of heart disease among men.<sup>1, 6, 7, 12</sup> Moreover, the correlations between angina and dyspnea and other clinical indicators of disease differ by sex. For example, stress tests, coronary angiograms, and other clinical measures are less likely to detect cardiac pathology in women than in men who report high levels of angina.<sup>1, 12</sup>

Surveys commonly measure angina and dyspnea using scales developed by Rose.<sup>11</sup> Many patients who report these symptoms remain symptomatic and disabled over long periods of time.<sup>13</sup> Somatic complaints such as angina and dyspnea are major reasons for outpatient medical visits,<sup>14</sup> costing considerable money and time. Yet frequently they do not lead to an organic diagnosis,<sup>15</sup> contributing to dissatisfaction for both patients and clinicians, and possibly poor quality of care.<sup>16</sup>

Several hypotheses about gender differences in the associations between CAD symptoms and other clinical measures have been put forward. Some suggest that sex differences in physiology, such as smaller lumens of coronary arteries and less collateral circulation among women, might lead to greater ischemia during stressful events.<sup>17</sup> Other biological sex differences include the expression of estrogen, which may protect younger women but contribute to the development of vascular disease after menopause as estrogen levels decline.<sup>1</sup>

Alternate hypotheses point to differences in the ways men and women perceive, interpret, and respond to symptoms. If, for example, some women are more likely to report angina because they generally tend to report more symptoms of all kinds, their symptom reports may not indicate underlying physiological states as well as do reports by other women.

This article examines the latter possibility. The research literature suggests that the self-appraisal of cardiovascular symptoms using Rose's angina and dyspnea scales has

significant clinical and mortality implications. Our objectives were to assess whether these scales predict CAD and mortality less well among women than among men and to evaluate whether these associations are related to sex differences in certain psychosocial characteristics, particularly somatosensory amplification.

## Somatosensory Amplification

Somatosensory amplification is sensitivity to or discomfort with a variety of non-pathological somatic or visceral sensations. It is considered important in how people detect, interpret, and respond to physiological sensations.<sup>18–20</sup> Initially used in clinical studies to understand symptom reporting in hypochondriasis,<sup>20–22</sup> amplification predicts the persistence of hypochondriachal symptoms in transiently hypochondriachal patients.<sup>23</sup> More generally, it may be related to symptom reports and health appraisals.<sup>22, 24</sup>

Barsky, *et al.* have proposed that patients, especially hypochondriachal patients, may selectively focus on a background level of somatic sensation.<sup>25</sup> Barsky, *et al.* used concepts of signal detection theory to explain hypochondriachal responses, reasoning that “hypochondriachal complaints may result more from background noise than from unusually sensitive detection of weak signals.”<sup>26</sup> The experience of high amplifiers may be similar.

High amplification, measured using the Somatosensory Amplification Scale (SSAS),<sup>20</sup> could indicate greater neural ability, a capacity to detect more subtle sensations. Alternatively, they may represent a general tendency to express bodily distress. To test these competing hypotheses, studies have used the Brener-Kluytse procedure to detect resting heartbeat,<sup>13, 26</sup> Holter monitor tests to detect cardiac arrhythmias,<sup>27</sup> and the Method of Constant Stimuli to detect heartbeat,<sup>28</sup> and then compared these measures of physiological phenomena to symptom reports. These studies found that persons scoring high on amplification scales were no more sensitive to cardiac functioning than those with low scores; in fact, high amplifiers were often less aware of arrhythmias than low amplifiers.<sup>27, 28</sup> This led to the conclusion that amplification may represent a “global proclivity to feel uncomfortable” (313).<sup>27</sup> Studies on reports of the severity of upper respiratory infection (URI) found that amplification was a better predictor of somatic symptoms and overall discomfort than were objective clinical symptom measures.<sup>18, 20</sup> Finally, Simon, *et al.* found that amplification predicted the chronicity of symptoms in workers who experienced an occupational chemical exposure.<sup>29</sup>

Cleary, *et al.*, conducted the first population-based examination of gender differences in somatosensory amplification.<sup>19</sup> They found that amplification is more prevalent among women than men, and that controlling for amplification reduced gender differences in many reported chronic conditions.

Overall, this literature on somatosensory amplification raises several provocative issues. Experts generally agree that somatosensory amplification is related to a general tendency to report symptoms and distress.<sup>19, 26, 27, 30–32</sup> If so, then among persons with given objective symptom levels, symptom reports by high amplifiers may be higher and less closely related to mortality than those reported by low amplifiers. Thus, controlling for amplification might provide more accurate estimates of disease states and functional ability. In particular, because somatosensory amplification differs by gender, adjusting for it may affect the association between cardiovascular symptoms and mortality differentially among men and women.

To investigate these issues, we analyzed how somatosensory amplification modifies the relationship of angina and dyspnea to mortality for men and women over a nine-year period using data from a nationally representative cohort of U.S. adults. We hypothesized that after

controlling for amplification, the relation between symptom reports and subsequent mortality would strengthen, and that this effect would be greater for women than men.

## Methods

### Data Sources

This research combined two data sources. The first—the Midlife Development in the United States, or MIDUS, survey—was designed to measure factors influencing the course of midlife development, including mental and physical health, life stresses, and work and family interactions.<sup>33</sup> In 1995, a nationally representative sample of non-institutionalized, English-speaking adults, ages 25 to 74, was selected by random-digit-dialing. Subjects provided information about their demographic characteristics, health status, use of health services, and psychosocial factors that influence well-being during a 45-minute telephone interview and on a mailed questionnaire. The surveys were completed by 3,032 respondents; a 61% response rate.<sup>34</sup> Two respondents who did not report their age were dropped for these analyses, yielding a final analysis sample size of 3,030.

We determined whether MIDUS respondents were still alive at the end of 2004 using reports by household members during a second wave of MIDUS data collection in 2004. We linked the MIDUS records to the National Death Index (NDI) from 1995 to 2004 to identify participants who had died and obtain their dates of death. We identified 187 MIDUS respondents (6.2%) who were deceased by the end of 2004.

### Measures

The MIDUS survey assessed several health status variables, including general health and well-being, being informed of diagnoses by a provider, major and minor symptoms, medication use, and health beliefs and attitudes. All survey measures in this analysis were derived from the initial survey in 1995.

A somatosensory amplification score was developed from responses to the SSAS, a five-item scale that assesses sensitivity to visceral sensations not usually related to disease. Questions asked about sensations such as ‘hunger contractions’, ‘being too hot or cold’, and ‘having a low tolerance for pain’ (Box 1). Studies show that this scale has test-retest reliability of 0.79 over a median interval of 74 days and a Cronbach’s  $\alpha$  of 0.82.<sup>13, 24, 27, 30</sup> Scale scores are higher in hypochondriacs than in non-hypochondriacs, correlated with somatization, and predict symptom reporting in patients with upper respiratory tract infections.<sup>13, 20, 31</sup>

#### Box 1

##### Items that comprise the Somatosensory Amplification Scale

- I am often aware of various things happening within my body.
- Sudden loud noises really bother me.
- I hate to be too hot or too cold.
- I am quick to sense hunger contractions in my stomach.
- I have a low tolerance for pain.

Responses include: *not at all true*, *a little true*, *moderately true*, and *extremely true*.

Angina was measured using the Rose scale, which includes questions like “Do you ever get chest pain or discomfort when you walk uphill or hurry?” (Box 2). Follow-up questions probe the severity of the pain, and whether or not it causes behavior change. Scores of 0 indicate that respondents do not report chest pains when uphill or hurrying. Respondents reporting chest pains when walking uphill, but not when walking at an ordinary pace on a level surface, are scored 1, those reporting chest pains when walking at an ordinary pace on a level surface but no subsequent behavior change are scored 2, and those reporting chest pains when walking at an ordinary pace on a level surface and subsequent behavior change are scored 3. Dyspnea was measured asking “Do you get short of breath in the following situations?” and listing four activities, including “When hurrying on ground level or walking up a short hill” (Box 3).

### Box 2

#### Items that comprise the Rose angina scale

- Do you ever get chest pain or discomfort when you walk uphill or hurry?
- Do you ever get chest pain or discomfort when you walk at an ordinary pace on a level surface, not uphill?

If they answer ‘yes’ to either, they are then asked:

- When you get pain or discomfort in your chest while you are walking, do you stop, slow down, or continue walking at the same pace?
- Does it go away when you stand still?
- How soon?
- Where do you get this pain or discomfort – in the center of your chest, in the left side of your chest ONLY, in the left side of your chest AND your left arm, or elsewhere?

### Box 3

#### Items that comprise the dyspnea scale

Do you get shortness of breath in the following situations?

- When hurrying on ground level or walking up a slight hill;
- When walking with other people your age on level ground;
- When walking your own pace on level ground;
- When washing or dressing.

Age was a continuous variable ranging from 25 to 74; the median age was 46. MIDUS measured race by self-identification; we created a variable indicating whether the respondent was white or nonwhite. Income was based on total reported household income, in quartiles as follows: (1) <\$25,000; (2) \$25,001 – \$42,300; (3) \$42,301–\$65,998; and (4) >\$65,998. Educational attainment had four levels: did not graduate from high school, high school graduate or G.E.D. recipient, some college, and college graduate. We created a measure of health insurance coverage that distinguished between persons who were privately covered, publicly insured (including Medicare, Medicaid, or government insurance for military personnel or veterans), or uninsured. Overall self-reported health status was dichotomized as excellent/very good/good health versus fair/poor health.

## Analyses

Figure 1 depicts the hypothesized relationships among the study variables. We predicted that cardiovascular symptoms are related to an increased rate of mortality, because they may indicate underlying CAD, or some other pathology that might result in death. Covariates may be associated with several other variables. For example, gender could be associated with amplification, reporting various symptoms, CAD, and mortality rates. Finally, amplification may be independently associated with death: negatively, if it represents exaggerated symptom reports, but positively if it is related to pathology not reflected in reports of angina and dyspnea.

We assessed bivariate associations between patient characteristics and subsequent mortality using the chi-square test or Fisher's exact test. Since few deaths occurred in certain categories, cell sizes were sometimes small, so we retained all predictors with significance levels of  $p < 0.10$  in bivariate analyses. We estimated Cox proportional hazards models to determine predictors of the hazard of death.

All analyses accounted for the complex sample design. The technical report on MIDUS survey methodology gives details on the weights used.<sup>34</sup> All analyses were conducted using Stata statistical software, version 8.2.<sup>35</sup>

## Results

Over half of the respondents were women (56.5%) (Table 1), and 84% were white. Approximately one-quarter of the sample had an income of \$25,000 or less, while the median income was slightly over \$42,000. Nearly 84% of subjects reported being in good or better health. Nearly 9% reported symptoms of dyspnea while 5% reported symptoms of angina. Slightly over 1% of the sample reported being diagnosed with CAD and over 5% reported being diagnosed with diabetes. Nearly 80% of the sample was under 60 in 1995, while the mean age was 47; the average SSAS was 2.55 out of 4 (data not shown). Overall, 6.2% of respondents died between 1995 and 2004. Figure 2 depicts the independent associations of key covariates with mortality.

In bivariate analyses, angina and dyspnea were both significantly associated with mortality (Table 1, columns 3–4;  $p < 0.001$ ). Other significant predictors of mortality included age (average of 62.2 compared with 47.0;  $p < 0.001$ ), income, education, type of health insurance coverage, overall health status, and having been diagnosed with CAD or diabetes. The average SSAS among the subsequently deceased was 2.58, slightly higher ( $p = 0.051$ ) than that among those who were alive in 2004. Overall health status had a significant bivariate association with mortality but was not included in the multivariate models, because it was strongly associated with the more specific reports of angina and dyspnea. Only income, education, a diagnosis of CAD, and amplification score differ significantly between deceased women and men (Table 1, columns 5–7). The average SSAS reported for subsequently deceased women was 2.72, compared with 2.42 among subsequently deceased men ( $p < 0.001$ ).

Angina and dyspnea had significant bivariate associations with mortality (angina: unadjusted hazard ratio 2.54,  $p < 0.001$ ; dyspnea: unadjusted hazard ratio 3.29,  $p < 0.001$ , results not shown). Table 2 presents hazard ratios stratified by gender and age, adjusting for significant covariates. We stratified the sample by age as well as gender because age is associated with both CAD and mortality. We stratified the sample at age 60, the mean age in 1995 among those who died over the ensuing 9 years. All models adjusted for income, education, and health insurance status, as well as a diagnosis of CAD or diabetes.



Angina was a significant predictor of mortality only for younger men and close to significant for older men ( $p=0.061$ ) and younger women ( $p=0.079$ ). There was weak evidence that the Rose dyspnea score predicted a greater risk of mortality for younger women ( $p=0.066$ ), but not older women, while a higher dyspnea score was a significant predictor of mortality for both younger and older men in adjusted models.

When amplification was included in the model (Table 3), hazard ratios for angina and dyspnea as predictors of mortality among younger and older men did not change appreciably. For women, however, the pattern changed somewhat. For younger women, the hazard ratio for angina decreased and became insignificant, while the hazard ratio for dyspnea remained roughly the same. Among older women, while the angina and dyspnea coefficients remained insignificant. Amplification was a significant predictor of mortality in both models for older women (adjusted hazard ratio of 1.91 for the model with angina and 1.97 for the model with dyspnea;  $p=0.008$  and  $p=0.007$ , respectively). We also estimated models that included depression and anxiety, but in neither case did the sign or magnitude of the angina and dyspnea coefficients in this population change (data not shown).

## Discussion

This study yielded several important results. Rose's dyspnea scales significantly predicted all-cause mortality in men and younger women, and the angina scale was predictive for men of all ages. Neither scale predicted all-cause mortality in older women – a finding which held even after controlling for somatosensory amplification. Surprisingly, the amplification score itself was a highly significant predictor of increased risk mortality among older women but not among other groups in the sample. Greater somatosensory amplification among older women may reflect awareness of other conditions or other symptoms of heart disease, such as fatigue, that predict mortality, rather than a reporting style that leads to over-reporting of symptoms.

Earlier research identified an association between symptoms, such as shortness of breath and chest discomfort, and CAD. Further research on these symptoms found elevated CAD-related mortality among both men and women who reported angina and dyspnea, though studies yield different results regarding the strength of the associations.<sup>4–7</sup> Although published studies report that most patients with CAD experience prodromal symptoms,<sup>1, 36</sup> a recent article reported that few symptomatic patients with acute coronary syndrome sought medical attention for their prodromal symptoms.<sup>37</sup> The study also found that women who sought care for symptoms had improved survival than men with symptoms, perhaps due to a greater readiness to seek care or more aggressive treatment by physicians. We found that neither angina nor dyspnea scores were significantly associated with all-cause mortality among older women, consistent with that study. Both were significant predictors of mortality for younger men and were marginally predictive of mortality for younger women. Finally, for older men, dyspnea was significantly associated with mortality, while angina was marginally associated.

In bivariate analyses, women who died between waves of the MIDUS survey had significantly higher reports of amplification. We hypothesized that amplification would alter the association between symptom report and mortality, by reducing the “noisiness” of the self-reported angina and dyspnea scores – the over-report of physical symptoms. Adjusting for amplification scores had little effect on the relation of angina or dyspnea scores to mortality. Instead, amplification itself was positively associated with mortality among older women. This is surprising, given the general understanding in the literature of amplification as a reporting style. Perhaps amplification reflects prodromal stages of diseases that were not tested in the earlier studies.

The literature suggests that Rose's angina and dyspnea scores may not have the same predictive values for CAD among men and women.<sup>1</sup> In this study, this was partially true: Rose's dyspnea scores were marginally predictive of all-cause mortality in younger women as well as in all men, whereas the angina scores better predicted all-cause mortality in men. Some of this difference may be due to the different pathophysiology of CAD among women and men.

Although our study had sufficient power to detect the hypothesized differences, only a small fraction of MIDUS respondents died between 1995 and 2004. In addition, we did not have information on cause of death for the MIDUS sample, but because the sample is generally comparable to the US population, it can be assumed that a significant proportion of the deaths were due to CAD. The Rose's angina and dyspnea scores were developed to detect angina and dyspnea in population-based surveys like MIDUS. Other scales that measure the frequency of symptoms, such as the Seattle Angina Questionnaire, might be more sensitive to differences associated with somatosensory amplification. Finally, there is some discussion in the literature that amplifiers do not have a characteristic response style, depending on the stimuli.<sup>31, 32, 38</sup> However, they do not dispute the interpretation of the SSAS as reflecting a reporting style.

Although earlier studies by Barsky and colleagues indicated that persons with high amplification scores were less accurate at detecting specific symptoms, they did not test the hypothesis that reporting tendencies may be learned as the result of illness experiences.<sup>20, 27</sup> Individuals who have experienced earlier symptoms that are indicators of cardiovascular health or other conditions may become more attuned to all sensations. In older women, somatosensory amplification may reflect greater awareness of other current cardiac symptoms, such as fatigue, that may predict mortality.

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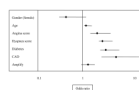


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**Figure 1.**  
Relationships between cardiovascular symptoms, mortality, and somatosensory amplification.



**Figure 2.**  
Unadjusted odds ratios predicting the risk of mortality for selected risk factors

**Table 1**

Weighted bivariate associations with mortality (unweighted n=3,030; weighted n=151,900,000)

Subject characteristics	Percent of total sample with characteristic	Percent deceased	p-value	Female	Male	p-value
Deceased	6.2					
Gender						
Female	56.5	6.7	0.272			
Male	43.5	5.7				
Race						
White	83.8	6.5	0.498	88.1	88.4	0.946
Other	16.2	5.4		11.9	11.6	
Income						
1 <sup>st</sup> quartile	27.0	8.4	0.003	49.4	22.4	<0.001
2 <sup>nd</sup> quartile	25.5	5.7		27.0	18.4	
3 <sup>rd</sup> quartile	24.9	4.8		14.6	28.6	
4 <sup>th</sup> quartile	22.7	3.6		9.0	30.6	
Education						
Grade school	13.2	13.4	<0.001	28.1	14.3	0.009
High school, GED	38.3	5.5		33.7	26.5	
Some college	25.5	4.6		27.0	31.6	
College graduate	23.0	2.9		11.2	27.5	
Health insurance type						
Private	73.8	4.5	<0.001	57.3	68.4	0.208
Public	12.3	14.1		29.2	24.5	
No insurance	13.9	4.5		13.5	7.1	
Overall health						
Excellent/very good/good	83.3	3.6	<0.001	59.1	60.2	0.877
Fair/poor	16.7	16.0		40.9	39.8	
Angina score						

Subject characteristics	Percent of total sample with characteristic	Percent deceased	p-value	Percent of deceased		p-value
				Female	Male	
Angina score of 0	95.1	5.8	<0.001	88.8	87.8	0.831
Angina score (1–3)	4.9	14.1		11.2	12.2	
Dyspnea score						
Dyspnea score (0, 1)	91.1	4.6	<0.001	75.6	79.4	0.538
Dyspnea score (2–4)	8.9	14.5		24.4	20.6	
Coronary artery disease (CAD)						
Not diagnosed	98.7	5.8	<0.001	97.7	89.8	0.027
Diagnosed	1.3	29.3		2.3	10.2	
Diabetes						
Not diagnosed	94.5	5.3	<0.001	82.0	80.6	0.805
Diagnosed	5.5	20.8		18.0	19.4	



Table 2

Cox proportional hazard analysis of the effect of angina and dyspnea score on subsequent mortality, stratified by age and gender\*

	Adjusted model for women					Adjusted model for men				
	25–59 (n=1,221)		60+ (n=338)			25–59 (n=1,177)		60+ (n=290)		
Predictor	Hazard Ratio	95% Confidence Interval	p- value	Hazard Ratio	95% Confidence Interval	p- value	Hazard Ratio	95% Confidence Interval	p- value	
Angina	2.41	0.90, 4.63	0.079	1.39	0.55, 3.50	0.488	3.46	1.43, 8.35	0.006	
CAD	-	-	-	1.37	0.32, 5.85	0.671	4.46	0.99, 20.14	0.052	
Diabetes	4.42	1.75, 11.15	0.002	1.941	0.96, 3.81	0.066	2.48	0.94, 6.54	0.066	
Dyspnea	2.20	0.95, 5.08	0.066	1.41	0.74, 2.69	0.299	4.38	1.96, 9.81	<0.001	
CAD	-	-	-	1.22	0.28, 5.25	0.793	4.02	0.87, 18.57	0.075	
Diabetes	4.28	1.68, 10.91	0.002	1.91	0.95, 3.82	0.068	2.64	1.01, 6.90	0.047	
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\* Models adjusted for income, educational attainment, and health insurance coverage.

