J Behav Med (2008) 31:137–143
DOI 10.1007/s10865-007-9141-4

Symptoms of depression and impaired endothelial function in healthy adolescent women

Lianne M. Tomfohr · Tara M. Martin · Gregory E. Miller

Accepted: November 21, 2007 / Published online: 29 December 2007

Abstract Depression is related to increased morbidity and mortality from coronary heart disease (CHD), but the underlying mechanisms are unclear. One possibility is that depressive symptoms influence CHD pathogenesis by fostering endothelial dysfunction. To evaluate this possibility, we studied one hundred and two adolescent women with no known or suspected major health problems. Depressive symptoms were assessed using the Beck Depression Inventory (BDI) and endothelial function with a non-invasive beat-to-beat plethysmographic recording of the finger arterial pulse-wave amplitude (PWA) before and after occlusion of the brachial artery. Regression analysis revealed a significant inverse relationship between depressive symptoms and endothelial function. This persisted after controlling for age, ethnicity, health practices and waist circumference. Depression explained 4–6% of the variance in endothelial function above and beyond the effects of covariates. Most patients in our sample had subclinical depressive symptoms, suggesting that even mild affective difficulties are capable of negatively influencing endothelial function in otherwise healthy youngsters.

Keywords Depression · Endothelial function · Adolescent · Females · Atherosclerosis

L. M. Tomfohr (✉) · T. M. Martin · G. E. Miller
Department of Psychology, University of British Columbia, Vancouver, BC, Canada
e-mail: ltomfohr@psych.ubc.ca

Introduction

Depression is related to increased morbidity and mortality from coronary heart disease (CHD) (Frasure-Smith and Lesperance 2005; Hemingway and Marmot 1999). This association is independent of conventional risk factors for CHD, and meta-analyses suggest that it is quite large in magnitude. Depressed individuals are 50–60% more likely to develop CHD than their euthymic counterparts (Rugulies 2002; Wulsin and Singal 2003). This seems to be a graded effect, whereby depressive symptoms increase CHD risk in linear fashion, even when they do not meet formal diagnostic criteria. A similar pattern is also evident among patients with established CHD. Following the onset of acute coronary syndrome, the presence of depressive symptoms is associated with a 2- to 2.5-fold increased risk of adverse cardiovascular outcome (van Melle et al. 2004).

One mechanism through which depressive symptoms may influence the development and progression of CHD is by fostering endothelial dysfunction. In support of this hypothesis a number of studies have shown that depression is associated with attenuated flow-mediated vasodilatory responses (Broadley et al. 2002; Harris et al. 2003; Rajagopalan et al. 2001; Sherwood et al. 2005; Wagner et al. 2006). However, these studies have primarily focused on adults who were 50 years and older, and there is reason to suspect that underlying atherosclerosis may be contributing to these effects, as it is known to alter mental state as well as compromise vascular function (Tiemeier et al. 2004). Previous research also has largely focused on patients suffering from formal affective disorders, or broken samples into artificial groups consisting of low and high levels of symptoms. It thus remains unclear to what extent subsyndromal depressive symptoms are related to endothelial dysfunction, and whether this relationship is

linear and graded, as is the case with the morbidity and mortality outcomes previously associated with depression (Barth et al. 2004).

This article examines whether depressive symptoms are associated with endothelial dysfunction in a cohort of adolescent females. Because these women are in their teenage years they should be free of significant atherosclerosis, which diminishes the plausibility that any association between depressive symptoms and endothelial dysfunction stems from underlying vascular disease. We also examine whether depressive symptoms foster endothelial dysfunction by promoting maladaptive behaviors such as smoking, alcohol consumption, sedentary behavior, and adiposity. These behaviors are more common among depressed individuals (Miller et al. 1999, 2002) and they also are known to compromise endothelial function (Thorand et al. 2006).

Methods

Participants

Data for this article were collected as part of a larger research project on depression and atherosclerosis among young women at high-risk for affective disorders. Adolescent females were recruited from the larger Vancouver, British Columbia community through advertisements in schools, newspapers, and magazines. Young women were eligible for the study if they were (1) between the ages of 15 and 19, (2) fluent in the English language, (3) free of acute and chronic medical conditions, (4) without a lifetime history of major psychiatric disorders, and (5) at high risk for developing an initial episode of major depression. High-risk was defined as having a first-degree relative with a history of depression, or as scoring in the top quartile of the sample distribution on one of two indices of cognitive vulnerability, the Dysfunctional Attitudes Scale (Weissman 1978) or the Adolescent Cognitive Style Questionnaire (Hankin and Abramson 2002).

The current article focuses on 102 young women who completed an endothelial function examination during the second round of data collection. They had a mean age of 17.67 years (SD = 1.39). At the time of the examination 26% of the women were 15 or 16, 37% were 17 or 18, and 36% were 19 or 20. Forty-five percent of the women self-identified as Caucasian, 44% as of East Asian descent, and the remaining, 11% described themselves as East Indian, African, Aboriginal, or other. The majority of women were enrolled based on showing cognitive vulnerability to depression (67%). The others had a positive family history of depression (11%), which in some cases was also accompanied by cognitive vulnerability (22%). Participants came from homes where mothers had an average of 14.8 years of education and fathers had an average of 15.1 years of education, and 53% of parents had at least a college diploma. Eighty-one percent of the participants came from a family in which their parents were currently married or common-law.

This project was approved by the Research Ethics Board of the University of British Columbia. Written consent was obtained from all participants older than 18 years; for those who were younger, a parent or guardian provided consent.

Assessment of depressive symptoms

The severity of each woman's depressive symptoms was measured with the Beck Depression Inventory (BDI; Beck et al. 1961). The BDI is a 21-item self-report measure with excellent psychometric characteristics. In this cohort it showed high levels of internal consistency ($\alpha = .82$) and was moderately stable across a 6-month period ($r_s = .69$).

Assessment of endothelial function

Assessments of the participants' endothelial function were done with the EndoPAT2000 (Itamar Medical, Israel). This non-invasive technology captures a beat-to-beat plethysmographic recording of the finger arterial pulse-wave amplitude (PWA) with pneumatic probes (Rozanski et al. 2001). The EndoPAT has been widely used to measure finger endothelial function (Bonetti et al. 2003, 2004; Itzhaki et al. 2005; Kuvin et al. 2003; Mahmud et al. 2006; Nohria et al. 2006; Schroeter et al. 2006; Yinon et al. 2006), and validation studies indicate that it captures nitric-oxide-mediated vasodilation (Nohria et al. 2006). Work also shows that it accurately identifies the early stages of coronary atherosclerosis (Bonetti et al. 2004). For example, in a study of patients who were healthy or had coronary microvascular dysfunction, the EndoPAT had 80% sensitivity and 85% specificity for detecting the disease. Results derived from the EndoPAT correlate moderately, $r = .55$, with other techniques for measuring endothelial dysfunction, such as ultrasonic imaging of the brachial artery (Kuvin et al. 2003).

EndoPAT sessions occurred between 8:00 and 11:00 am to control for diurnal variations. Participants arrived after having abstained from food and drink (except for water) overnight. The session began with a baseline-recording period. Participants were seated in a chair with their arms placed at heart level. A pneumatic probe was placed on the index finger of each hand, and after the PWA signal had been acquired, the participant rested quietly for a 5 min period. PWA during this period served as an index of resting vascular tone. To induce reactive hyperemia, a blood-pressure cuff placed around the participant's

non-dominant arm was inflated to 60 mmHg above their systolic pressure. After a 5-min occlusion period, the cuff was rapidly deflated, inducing reactive hyperemia. The PWA signal was recorded for the next 5 min on both the occluded and non-occluded arms.

The data were analyzed with a computerized, automated algorithm from Itamar Medical (version 2.3.2) that standardizes artifact detection and computational procedures. The Itamar Medical software was used to compute a measure of endothelial function, the reactive hyperemia peripheral arterial tonometry index (RH-PAT index). The RH-PAT index was calculated as the ratio of the average post-occlusion PWA (from 1.5 to 2.5 min after release of the occlusion) to the average baseline PWA. Baseline PWA was defined as the average of the final 2.5 min of resting (excluding the 20 s before occlusion). In order to reduce error from potential systemic changes, the ratio was normalized to the corresponding signal as recorded in the unoccluded arm. Higher values of the ratio indicate greater dilatation in the finger arteries, which reflects greater nitric-oxide-mediated vasodilation of these vessels and, thus, better local endothelial function.

Reproducibility of EndoPAT

The EndoPAT has not been used with healthy young adults, and there are few data published on the reproducibility of its measurements. Therefore, we first conducted a small pilot study to address these issues. Twelve young adults working in our laboratory underwent repeated EndoPAT examinations. 91.7% of them were female with a mean age of 26.8 years. All were healthy and without medical or psychiatric illness. The interval between exams ranged from 1 day to 1 week. In half of the cases the same technician conducted both assessments. We found the EndoPAT to have a high level of reproducibility. Figure 1 displays the scatterplot of RH-PAT values. The Pearson correlation between examinations was $r = .76$, $P = .00$. Because some of the data points in the plot were outliers, we also computed a Spearman rank-order correlation, RH-PAT values were still quite high in reproducibility, $r_s = .51$ $P = .09$. Finally, we calculated an intraclass correlation coefficient which was .73, $P = .00$, suggesting that the bulk of the variability in EndoPAT measurements is between, rather than within, individuals.

Contribution of health practices and body composition

We assessed a number of processes that could provide explanations for the relationship between depressive symptomology and endothelial dysfunction. Participants were queried as to their age, ethnicity and health practices. Because the majority of the sample (89%) was of Caucasian

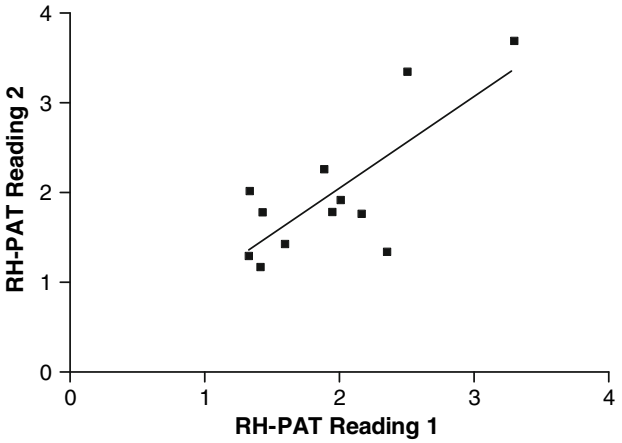

Fig. 1 Scatterplot depicting results from repeat EndoPAT examinations for 12 young adults. The intraclass correlation between readings is .729

or Asian decent, ethnicity was coded dichotomously as either Caucasian or Other. Health practices were measured by an inventory utilized in our previous research on depression and immunity (Miller et al. 1999). These measures have shown excellent reliability and validity (Cohen et al. 1997, 1993; Miller et al. 1999). Participants were classified as smokers if they reported smoking at least one cigarette, cigar or pipe on a daily basis (Cohen et al. 1993). Since only three participants reported daily use of cigarettes, we could not assess the impact of this variable. We also evaluated the role of smoking using a cigarettes/week variable of which six participants endorsed. It was not associated with endothelial function, probably because of the lack of variability. Alcohol consumption was recorded as the number of beverages consumed in a typical week long period. A drink was considered a glass of wine, a 12-ounce beer or a shot of hard liquor (Cohen et al. 1993). Regular physical activity was measured with a modified version of the Paffenbarger Activity Scale. It provides an estimate of the number of minutes of brisk physical activity the participant engaged in per week (Paffenbarger et al. 1993). Waist circumference reflects fat deposited in the abdominal region and was obtained by measuring around the midpoint between the top of the iliac crease (hipbone) and the lowest rib. The use of contraceptive medication was ascertained by self-report of the participant. No participants reported taking any antidepressant medication at the time of their visit.

Results

Demographic and medical characteristics of the sample

The characteristics of the sample are presented in Table 1. Participants were in mid to late adolescence. They reported

Table 1 Characteristics of the sample ($N = 102$)

Demographics and medical characteristics	Mean	SD
Age (years)	17.7	1.4
Contraceptive use (%)	23.8	–
Waist circumference (cm)	71.1	6.2
Daily smoker (%)	2.9	–
Alcoholic drinks weekly	1.8	5.3
Brisk exercise per week (h)	2.7	3.6
Beck Depression Inventory score	7.0	6.1
PWA ratio from EndoPAT	1.9	.5

low levels of smoking and drinking and high levels of weekly exercise. Few participants reported depressive symptomology; of those who did, the severity was typically mild. PWA ratios ranged from 1.1 to 3.9. Respective scores at the 25, 50 and 75th percentile of the sample were 1.5, 1.8 and 2.2. The average PWA ratios from the EndoPAT fell within the healthy range reported by the manufacturer.

Depressive symptoms and endothelial dysfunction

The first statistical analyses examined the relationship between depressive symptoms and endothelial dysfunction in our sample of healthy young women. To investigate this relationship, a hierarchical regression equation was constructed in which RH-PAT ratios were predicted from age, race, and contraceptive use followed on the next step by depressive symptoms. Table 2 displays the results of this analysis. Neither age, ethnicity nor contraception was related to endothelial dysfunction (P's > .31). However, there was an inverse relationship between depressive symptoms and RH-PAT ratios, such that higher scores on the BDI were associated with lower RH-PAT ratios, reflecting dysfunction of the endothelium. The R^2 value for depressive symptoms was .04, indicating that they explained 4% of the variance in RH-PAT values above and beyond the effects of age, race, and contraception use.[1]

Table 2 Hierarchical regression of depressive symptoms predicting PWA ratio

Predictor	B	SE	t	P
Step 1				
Race	.11	.13	.86	.39
Age	–.01	.05	–.22	.83
Contraceptive use	–.15	.14	–1.02	.31
Step 2				
Depressive symptoms	–.02	.01	–1.95	.05

*For step 1 of the equation $\Delta R^2 = .02$, $F = .69$, $P = .56$. For step 2 of the equation $\Delta R^2 = .04$, $F = 3.80$, $P < .05$

Role of health behaviors and body composition

Our second analysis examined whether disparities in health practices and body composition might explain this association. To answer this question, a hierarchical regression equation was constructed in which RH-PAT ratios were predicted from physical activity, alcohol consumption, and waist circumference, followed on the next step by depressive symptoms. Table 3 displays the results of this analysis. Neither exercise, alcohol consumption, nor waist circumference was significantly related to RH-PAT ratios (P's > .36). In total, the health practices explained 2% of the variance in RH-PAT ratios. Above and beyond this, there was a significant inverse relationship between depressive symptoms and RH-PAT ratios, with higher BDI scores predicting a smaller degree of nitric-oxide-mediated vasodilation. The R^2 value indicated that depressive symptoms explained 6% of the variance in endothelial function above and beyond the effects of exercise, alcohol consumption, and waist circumference.

Discussion

Results from this study show that in our sample of healthy, active young women, symptoms of depression are associated with diminished nitric-oxide-mediated vasodilation, which is a reflection of endothelial dysfunction. These findings extend the corpus of research in this area (Broadley et al. 2002; Harris et al. 2003; Rajagopalan et al. 2001; Sherwood et al. 2005; Wagner et al. 2006) into healthy youngsters who are too young to have developed significant atherosclerosis and are without other major risks

[1] Two reviewers of this paper noted that the association between depressive symptoms and endothelial dysfunction could be a result of confounding by menstrual status. Unfortunately, we did not have hormonal samples available to determine exactly where in her cycle each participant was at the time of assessment. However, we did collect self-reports of cycle length, timing, and regularity. Using the methods outlined by Holding and Minkoff (1973), we used these data to categorize participants as currently menstruating versus in the follicular or luteal phases of their cycle. Because some of these data were missing, and other participants reported irregular cycles, these analyses could only be done on about half of the sample ($n = 52$). Nonetheless, among these participants there was no evidence of a relationship between menstrual status and either depressive symptoms ($r = .04$, $P = .79$) or endothelial function ($r = –.01$, $P = .95$). There also were no significant associations between these variables and cycle regularity (r's < .12, P's > .26). This pattern of findings suggests that menstrual status is unlikely to be acting as a confound in our sample. However, we recognize that our approach to these analyses has limitations, and in future research a more rigorous assessment of menstrual status using hormonal data would be valuable.

Table 3 Hierarchical regression of depressive symptoms and health practices predicting PWA ratio

Predictor	B	SE	*t*	*P*
Step 1				
Exercise	.00	.00	.91	.36
Alcohol	.01	.01	.82	.42
Waist circumference	.00	.02	.21	.84
Step 2				
Depressive symptoms	–.02	.01	–2.51	.01

*For step 1 of the equation $\Delta R^2 = .02$, $F = .49$, $P = .69$. For step 2 of the equation $\Delta R^2 = .06$, $F = 6.27$, $P < .01$

for CHD. This is important because it suggests that the previously documented association between depression and endothelial dysfunction emerges in samples with little (or no) underlying vascular disease.

Despite mounting evidence linking depression to CHD morbidity and mortality, little is known about the timing and kinetics of depression's influence. Does it contribute to the slow growth of atherosclerosis? Or does it act later in the disease process, triggering unstable angina and myocardial infarction in vulnerable patients? The answers to these questions have significant theoretical and practical implications, because they can help to narrow the search for underlying mechanisms, and highlight critical periods where interventions could be used to minimize negative outcomes (Carney et al. 2001). Though our project does not provide a definitive answer to these questions, its findings are consistent with the possibility that depression contributes to the progression of the early stages of atherosclerosis, the first sign of which is dysfunction of nitric-oxide signaling in the vascular endothelium. Of course, longitudinal research with repeated evaluations of endothelial function and other indicators of subclinical CHD will be necessary to substantiate this interpretation.

If depression does induce changes in endothelial function, the question that arises next is what mechanisms underlie the process? Our findings indicate that cigarette smoking, physical inactivity, alcohol consumption, and central adiposity are not the proximal mechanisms underlying the association we detected. One intriguing hypothesis is that oxidative damage is the culprit. We have shown that depression is associated with higher levels of 8-hydroxy-2′-deoxyguanosine (8-OHdG), a biomarker of oxidative damage to DNA (Forlenza and Miller 2006). This proved to be a dose–response relationship, such that symptoms of greater severity and duration were related to increased 8-OHdG. Mounting evidence indicates that oxidative damage inhibits the endothelium's capacity to produce nitric oxide, by reducing the presence and activity of an enzyme that catalyzes its synthesis (eNOS) (Landmesser et al. 2004). Future research should evaluate the possibility that oxidative damage is the mechanism through which depressive symptoms "get under the skin" to influence functions of the vascular endothelium.

Importantly, most of our sample was not experiencing serious depressive symptoms. About 74% of the women had BDI scores of less than 10 and, even among relatively distressed women, the severity of symptoms was in the mild range (The BDI score at the 75th percentile of the sample distribution was 13). These findings suggest that even mild symptoms of depression may be sufficient to impair endothelial function. This is an important observation because it is consistent with the dose–response consequences of depression that have been seen in studies of CHD morbidity and mortality (Rugulies 2002; Wulsin and Singal 2003).

This study has a number of limitations: first, its cross-sectional design makes it impossible to determine whether depressive symptoms contribute to endothelial dysfunction or vice-versa. Prospective investigations will be needed to evaluate the directionality of this association; controlled intervention trials that assess endothelial function after easing depressive symptoms would also clarify the causal nature of this association. Secondly, the sample consisted of young women, aged 15–20, who were all free of chronic illness at study entry and were at high risk for developing depression. While these features ensured that underlying atherosclerosis was likely not acting as a confound, they do limit the generalizability of our findings to the broader population. Relatedly, the healthy and active lifestyles of our participants may have limited our ability to detect relationships between health behaviors such as smoking and endothelial function. Another limitation is that we did not repeat the examinations after administering a donor of nitric oxide (NO)—which under normal circumstances, the endothelium must release for dilation to occur. This leaves open the possibility that our findings were related to dysfunction of smooth muscle cells or other mechanical properties of the finger vessels. This seems quite unlikely given that our sample was young and healthy. Moreover, previous research has shown that deficient NO signaling is responsible for the endothelial dysfunction observed in depressed individuals (Broadley et al. 2002; Rajagopalan et al. 2001; Sherwood et al. 2005; Wagner et al. 2006). The final limitation of the study is that endothelial function was measured using plethysmography in the fingers, a less established method than the traditional ultrasound of the brachial artery. However, this method has the advantage of being more adaptable for clinical settings, because it is less technically challenging to perform and analyze, and more portable than ultrasounds of the brachial artery (Kuvin et al. 2003, 2007). Moreover, results derived from these methods are quite strongly correlated (Kuvin et al. 2003). Thus, we suspect that findings similar to ours would

emerge with the more traditional method for assessing endothelial function.

Despite these limitations, our findings reveal that even mild depressive symptoms are related to endothelial dysfunction, and that maladaptive behaviors such as smoking, drinking, inactivity, and central adiposity are not responsible for this association. Future research in this area needs to employ a longitudinal design in order to clarify directionality and identify the mechanisms underlying the association. Answering these questions will provide deeper insights into how depression increases CHD morbidity and mortality, and over the long-term inform the development of efficacious interventions to minimize the impact of depression.

Acknowledgements Supported by the Michael Smith Foundation for Health Research; the Canadian Institutes of Health Research; the Heart & Stroke Foundation of Canada; and the National Alliance for Research on Schizophrenia and Depression. The authors thank Jasmen Sze for coordinating and collecting data in the reliability study. We are also grateful to Ekin Blackwell for her assistance in performing EndoPAT examinations. Finally, we thank Doron Dinstein for his help setting up the EndoPAT and answering innumerable questions.

References

Barth, J., Schumacher, M., & Herrmann-Lingen, C. (2004). Depression as a risk factor for mortality in patients with coronary heart disease: A meta-analysis. *Psychosomatic Medicine, 66*(6), 802–813.

Beck, A. T., Ward, C. H., Mendelson, M., Mock, J., & Erbaugh, J. (1961). An inventory for measuring depression. *Archives of General Psychiatry, 4*, 561–571.

Bonetti, P. O., Barsness, G. W., Keelan, P. C., Schnell, T. I., Pumper, G. M., Kuvin, J. T., et al. (2003). Enhanced external counterpulsation improves endothelial function in patients with symptomatic coronary artery disease. *Journal of the American College of Cardiology, 41*(10), 1761–1768.

Bonetti, P. O., Pumper, G. M., Higano, S. T., Holmes, D. R. Jr., Kuvin, J. T., & Lerman, A. (2004). Noninvasive identification of patients with early coronary atherosclerosis by assessment of digital reactive hyperemia. *Journal of the American College of Cardiology, 44*(11), 2137–2141.

Broadley, A. J., Korszun, A., Jones, C. J., & Frenneaux, M. P. (2002). Arterial endothelial function is impaired in treated depression. *Heart, 88*(5), 521–523.

Carney, R. M., Freedland, K. E., & Jaffe, A. S. (2001). Depression as a risk factor for coronary heart disease mortality. *Archives of General Psychiatry, 58*(3), 229–230.

Cohen, S., Doyle, W., Skoner, D., Rabin, B., & Gwaltney, J. (1997). Social ties and susceptibility to the common cold. *JAMA, 277*, 1940–1944.

Cohen, S., Tyrell, D., Russell, M., Jarvis, M., & Smith, A. (1993). Smoking, alcohol consumption, and susceptibility to the common cold. *Americal Journal of Public Health, 83*, 1277–1283.

Forlenza, M. J., & Miller, G. E. (2006). Increased serum levels of 8-hydroxy-2′-deoxyguanosine in clinical depression. *Psychosomatic Medicine, 68*(1), 1–7.

Frasure-Smith, N., & Lesperance, F. (2005). Reflections on depression as a cardiac risk factor. *Psychosomatic Medicine, 67*(Suppl 1), S19–S25.

Hankin, B. L., & Abramson, L. Y. (2002). Measuring cognitive vulnerability to depression in adolescence: Reliability, validity, and gender differences. *Journal of Clinical Child and Adolescent Psychology, 31*(4), 491–504.

Harris, K. F., Matthews, K. A., Sutton-Tyrrell, K., & Kuller, L. H. (2003). Associations between psychological traits and endothelial function in postmenopausal women. *Psychosomatic Medicine, 65*(3), 402–409.

Hemingway, H., & Marmot, M. (1999). Evidence based cardiology: Psychosocial factors in the aetiology and prognosis of coronary heart disease. Systematic review of prospective cohort studies. *BMJ, 318*(7196), 1460–1467.

Holding, T. A., & Minkoff, K. (1973). Parasuicide and the menstrual cycle. *Journal of Psychosomatic Research, 17*, 365–368.

Itzhaki, S., Lavie, L., Pillar, G., Tal, G., & Lavie, P. (2005). Endothelial dysfunction in obstructive sleep apnea measured by peripheral arterial tone response in the finger to reactive hyperemia. *Sleep, 28*(5), 594–600.

Kuvin, J. T., Mammen, A., Mooney, P., Alsheikh-Ali, A. A., & Karas, R. H. (2007). Assessment of peripheral vascular endothelial function in the ambulatory setting. *Vascular Medicine, 12*(1), 13–16.

Kuvin, J. T., Patel, A. R., Sliney, K. A., Pandian, N. G., Sheffy, J., Schnall, R. P., et al. (2003). Assessment of peripheral vascular endothelial function with finger arterial pulse wave amplitude. *American Heart Journal, 146*(1), 168–174.

Landmesser, U., Hornig, B., & Drexler, H. (2004). Endothelial function: A critical determinant in atherosclerosis? *Circulation, 109*(21 Suppl 1), II27–II33.

Mahmud, F., Earing, M., Lee, R., Lteif, A., Driscoll, D., & Lerman, A. (2006). Altered endothelial function in asymptomatic male adolescents with type I diabetes. *Congenital Heart Disease, 1*(3), 98–103.

Miller, G. E., Cohen, S., & Herbert, T. B. (1999). Pathways linking major depression and immunity in ambulatory female patients. *Psychosomatic Medicine, 61*(6), 850–860.

Miller, G. E., Stetler, C. A., Carney, R. M., Freedland, K. E., & Banks, W. A. (2002). Clinical depression and inflammatory risk markers for coronary heart disease. *American Journal of Cardiology, 90*(12), 1279–1283.

Nohria, A., Gerhard-Herman, M., Creager, M. A., Hurley, S., Mitra, D., & Ganz, P. (2006). Role of nitric oxide in the regulation of digital pulse volume amplitude in humans. *Journal of Applied Physiology, 101*(2), 545–548.

Paffenbarger, R. S. Jr., Blair, S. N., Lee, I. M., & Hyde, R. T. (1993). Measurement of physical activity to assess health effects in free-living populations. *Medicine and Science in Sports and Exercise, 25*(1), 60–70.

Rajagopalan, S., Brook, R., Rubenfire, M., Pitt, E., Young, E., & Pitt, B. (2001). Abnormal brachial artery flow-mediated vasodilation in young adults with major depression. *Americal Journal of Cardiology, 88*(2), 196–198, A197.

Rozanski, A., Qureshi, E., Bauman, M., Reed, G., Pillar, G., & Diamond, G. A. (2001). Peripheral arterial responses to treadmill exercise among healthy subjects and atherosclerotic patients. *Circulation, 103*(16), 2084–2089.

Rugulies, R. (2002). Depression as a predictor for coronary heart disease. a review and meta-analysis. *Americal Journal of Preventive Medicine, 23*(1), 51–61.

Schroeter, H., Heiss, C., Balzer, J., Kleinbongard, P., Keen, C. L., Hollenberg, N. K., et al. (2006). (-)-Epicatechin mediates beneficial effects of flavanol-rich cocoa on vascular function in

humans. *Proceedings of the National Academy of Sciences, 103*(4), 1024–1029.

Sherwood, A., Hinderliter, A. L., Watkins, L. L., Waugh, R. A., & Blumenthal, J. A. (2005). Impaired endothelial function in coronary heart disease patients with depressive symptomatology. *Journal of the American College of Cardiology, 46*(4), 656–659.

Thorand, B., Baumert, J., Doring, A., Schneider, A., Chambless, L., Lowel, H., et al. (2006). Association of cardiovascular risk factors with markers of endothelial dysfunction in middle-aged men and women. Results from the MONICA/KORA Augsburg Study. *Thrombosis and Haemostasis, 95*(1), 134–141.

Tiemeier, H., van Dijck, W., Hofman, A., Witteman, J. C., Stijnen, T., & Breteler, M. M. (2004). Relationship between atherosclerosis and late-life depression: The Rotterdam Study. *Archives of General Psychiatry, 61*(4), 369–376.

van Melle, J. P., de Jonge, P., Spijkerman, T. A., Tijssen, J. G., Ormel, J., van Veldhuisen, D. J., et al. (2004). Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: A meta-analysis. *Psychosomatic Medicine, 66*(6), 814–822.

Wagner, J. A., Tennen, H., Mansoor, G. A., & Abbott, G. (2006). History of major depressive disorder and endothelial function in postmenopausal women. *Psychosomatic Medicine, 68*(1), 80–86.

Weissman, A., & Beck, A. T. (1978). Development and validation of the Dysfunctional Attitudes Scales: A preliminary investigation. Paper presented at the meeting of the American Educational Research Association, Toronto, Ontario, Canada.

Wulsin, L. R., & Singal, B. M. (2003). Do depressive symptoms increase the risk for the onset of coronary disease? A systematic quantitative review. *Psychosomatic Medicine, 65*(2), 201–210.

Yinon, D., Lowenstein, L., Suraya, S., Beloosesky, R., Zmora, O., Malhotra, A., et al. (2006). Pre-eclampsia is associated with sleep-disordered breathing and endothelial dysfunction. *European Respiratory Journal, 27*(2), 328–333.