Multiwave Associations Between Depressive Symptoms and Endothelial Function in Adolescent and Young Adult Females

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Objective: Depression has been linked to endothelial dysfunction, and some research suggests that past depressive episodes are associated with a lasting, negative impact on the endothelium. However, investigations in this area have been predominantly cross-sectional, raising questions about the direction of these associations. Using a multiwave design, we sought to extend previous research in this area by examining whether depressive symptoms have a lasting negative influence on endothelial function. **Methods:** A total of 135 adolescent and young adult females with no known or suspected major health problems were followed for 2½ years. Endothelial function was assessed at three time points throughout the study. The Beck Depression Inventory was administered, and information about health practices was collected every 6 months. **Results:** Self-reported depressive symptoms covaried with endothelial functioning on a within-person basis ($\beta = -0.23$, $p < .05$). As a participant's depression symptoms rose beyond her typical level, her endothelial function declined commensurately. This association persisted after controlling for health practices and adiposity. There was no evidence that depressive symptoms predicted endothelial function at later time points or interacted with time to predict the trajectories of endothelial function over the follow-up period. **Conclusions:** Depressive symptoms were concurrently associated with endothelial function in this cohort of healthy adolescent girls and young women. On visits when participants endorsed depressive symptoms that were higher than their mean level of depression, they tended to have worse endothelial function. We did not observe a lasting negative effect of depression on endothelial function. **Key words:** depression, endothelial function, adolescent, women, atherosclerosis.

BDI = Beck Depression Inventory; **PWA** = pulse-wave amplitude.

INTRODUCTION

Depression is a widespread problem, affecting an estimated 8% to 9% of the North American population each year (1,2). In addition to psychological and societal costs, individuals with depression are 50% to 60% more likely to develop coronary heart disease than their euthymic counterparts and are at an increased risk of lethal and nonlethal coronary incidents (3–6).

Endothelial dysfunction is a potential mechanism linking depressive symptoms and coronary heart disease. The endothelium plays a pivotal role in maintaining vascular homeostasis, exerting its influence through a variety of mechanisms, most notably the secretion of nitric oxide. Endothelial dysfunction, or impairment of nitric oxide–mediated vasodilation, indicates impairment in homeostatic mechanisms (7). It is one of the earliest manifestations of atherosclerosis and is a documented predictor of its progression and adverse cardiovascular events (8–10). An increasing body of literature has linked depression and endothelial function. The association seems to be graded and linear such that even minor increases in depressive symptoms covary with decreased endothelial function (11–18).

Investigations conducted in this area have been predominantly cross-sectional in design, leaving open questions about temporal precedence and whether the impact of depression on endothelial function persists after depressive symptoms have resolved. Two recent studies have addressed whether endothelial dysfunction persists after depression abates in samples of postmenopausal women, reporting an association between more lifetime depressive episodes (assessed via retrospective self-report) and current impairments in flow-mediated vasodilation, a marker of endothelial function. An apparent dose-response relationship exists, whereby the escalating number of lifetime depressive episodes was associated with increasingly worse endothelial function, above and beyond current depressive symptoms (14,19). Although this work suggests that depression leaves a lasting, negative mark on the endothelium, it is limited by the retrospective nature of psychiatric assessments and the absence of baseline measures of flow-mediated vasodilation taken before the onset of symptom. To our knowledge, there have been no multiwave prospective studies that examine how depression and endothelial function change together over time.

The foundations of adult psychiatric problems and cardiovascular health are laid in childhood and adolescence (20,21). Understanding the relationship between depression and markers of vascular function that presage a diseased state helps to guide the search for potentially modifiable risk factors, yet only a limited body of work has examined these associations in younger, healthy individuals. Our group recently published a cross-sectional analysis of females aged 15–20 years, which found that even mild increases in depressive symptoms were associated with decreased endothelial function above and beyond the influence of traditional risk factors (13). This finding was recently replicated in a sample of healthy females aged 12–16 years in Sweden (22).

Objectives

This article reports on follow-up data from our original cohort (13), collected at 6-month increments for a period of 2½ years. The purpose of the article was three-fold. First, we sought to extend previous findings linking depressive states and endothelial function in a study with a more rigorous multiwave design. Second, we tested whether depressive symptoms exert a

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lasting negative influence on endothelial function above and beyond current mood (i.e., is there some kind of scarring effect as other studies suggest). Third, we aimed to examine whether health practices that are often associated with both low mood and vascular health, such as physical inactivity (23–25), alcohol use (26,27), and smoking (28,29), account for the previously observed associations between depressive symptoms and endothelial function.

METHODS

Participants

The data for this project were collected as part of a longitudinal study on depression and atherosclerosis among adolescent girls and young women at high risk of developing affective disorders. Participants were recruited from the larger Vancouver, British Columbia, community through advertisements in schools, newspapers, and magazines. Adolescent girls and young women were eligible for the study if they were a) between the ages of 15 and 19 years, b) fluent in the English language, c) free of acute and chronic medical conditions, d) without a lifetime history of major psychiatric disorders, and e) at high risk of developing the first episode of major depression. *High risk* was defined as having a first-degree relative with a history of depression or as a scoring in the top quartile of the sample distribution on one of two indices of cognitive vulnerability, the Dysfunctional Attitudes Scale (30) or the Adolescent Cognitive Style Questionnaire (31). At a screening interview before enrollment, each participant was administered a lifetime version of the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (32). Anyone who showed evidence of a lifetime history of an Axis I psychiatric disorder was excluded from participation.

A total of 157 participants enrolled in the study between October 2004 and July 2007. The current article focuses on 135 participants who completed at least one examination of endothelial function. Ninety-three participants were enrolled based on cognitive vulnerability to depression, 15 had a family history of depression, and 27 had both a family history and cognitive vulnerability. At the first assessment of endothelial function, the participants were a mean age of 17.0 (standard deviation = 1.3) years. Fifty percent self-identified as white, 33% as Chinese, and the remaining 17% as aboriginal, African, non-Chinese Asian, East Indian, or "other." The participants came from families whose mothers and fathers averaged 14.7 and 15.0 years of education, respectively, and 58% of the participants had at least one parent who had obtained a college degree or higher. Seventy-four percent of participants came from a family whose parents were currently married at the onset of the study.

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 also provided consent.

Procedures

The participants visited our research facility every 6 months over the course of 2½ years (T1–T6) and underwent an assessment of endothelial function at the second (T2), fourth (T4), and sixth visits (T6). Depressive symptoms[1] were assessed at each visit. In addition, information regarding current health practices and measures of body composition were obtained at each visit. Ninety-three percent of the participants completed at least two endothelial function assessments, and 67% completed all three.

[1]The Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition,* Non-Patient Edition, was administered at each time point to obtain data about current depression and the occurrence of major and minor depressive episodes in the time period between participant visits (32). However, fewer women in the study experienced a major depressive episode than was expected, and we were underpowered to investigate relationships between depression as assessed by the Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, Non-Patient Edition, and endothelial function.

Measures

Endothelial Function

Endothelial function was assessed using the EndoPAT2000 (Itamar Medical, Caesarea, Israel). This noninvasive technology captures a beat-to-beat plethysmographic recording of the finger arterial pulse-wave amplitude (PWA) with pneumatic probes (33). The EndoPAT is a well-established measure of finger endothelial function (34–36), and validation studies indicate that it captures nitric oxide–mediated vasodilation (37). Initial findings suggest that the EndoPAT may be able to accurately identify the early stages of atherosclerosis. For example, in a study of patients who were either healthy or experiencing coronary microvascular dysfunction, the EndoPAT demonstrated 80% sensitivity and 85% specificity in detecting the disease (34). EndoPAT results are related to numerous cardiovascular risk factors in addition to being predictive of poor cardiovascular outcomes for 7 years (10,38). The EndoPAT has demonstrated excellent reproducibility when used with healthy adolescents and young adults (intraclass correlation coefficient [ICC] = 0.78) (13,39).

To control for diurnal variations, EndoPAT sessions occurred between 8 AM and 11 AM. The participants arrived at our laboratory after having abstained from food and drink (except for water) overnight. The participants were also asked to refrain from exercise in the morning before testing. The session began with a baseline-recording period where participants were seated in a chair with their arms placed at heart level. A pneumatic probe was then placed on the index finger of each hand, and after the PWA signal had been acquired, the participant rested quietly for a 5-minute period. PWA during this period served as an index of resting vascular tone. To induce reactive hyperemia, a blood pressure cuff was placed around the participant's nondominant arm and was inflated to 60 mm Hg above their systolic blood pressure. After a 5-minute occlusion period, the cuff was rapidly deflated, inducing reactive hyperemia. The PWA signal was recorded for the next 5 minutes on both the occluded and nonoccluded 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 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 postocclusion PWA (from 1.5 to 2.5 minutes after the release of the occlusion) to the average baseline PWA. Baseline PWA was defined as the average of the final 2.5 minutes of resting (excluding the 20 seconds before occlusion). To reduce error from potential systemic changes, the ratio was normalized to the corresponding signal as recorded in the nonoccluded 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.

Depression

The severity of each participant's current depressive symptoms was measured using the 21-item Beck Depression Inventory (BDI). In our sample, the BDI showed high levels of internal consistency (Cronbach α ranged from 0.83 to 0.86 for the six visits) and moderate stability across the entire study (ICC = 0.49). The distribution of depression scores at each visit was significantly positively skewed, with the vast majority of individuals reporting no or mild depression. To better represent the nature of the distribution, we categorized the participants according to clinical cutoffs from the BDI: 0 to 9 = not depressed, 10 to 18 = mild depression, 19 to 28 = moderate depression, and 29 to 63 = severe depression (40). Because of the small percentage of individuals with severe depression (<1% at each visit), we later collapsed the latter two groups into a single moderate/severe category. This three-category indicator (none, mild, and moderate/severe) was used in all analyses. In addition to minimizing the skew of the data and reducing the influence of outliers, this categorization has the advantage of increased clinical interpretability.

Health Practices and Body Composition

A variety of health practices were measured by an inventory used in our previous research on depression and immunity (41). These measures have shown excellent reliability and validity (41–43). The participants were classified as smokers if they reported smoking at least one cigarette, cigar, or pipe on a daily basis in a typical weeklong period. Alcohol consumption was recorded as

TABLE 1. Demographic Characteristics of the Sample

Variable	Time 1 (n = 134)	Time 2 (n = 122)	Time 3 (n = 113)
Age, M (SD)	17.6 (1.3)	18.6 (1.4)	19.7 (1.5)
Percentage of body fat, M (SD)	24.8 (6.1)	24.7 (6.7)	25.1 (6.8)
Smoking (yes/no), %	6.3	9.6	10.5
Alcohol consumption, M (SD)	1.9 (6.0)	3.5 (8.5)	4.9 (9.4)
Exercise, M (SD), h/wk	2.5 (3.3)	1.7 (2.3)	1.4 (1.8)
BDI, current at visit, %			
None	72.7	76.5	82.9
Mild	21.9	20.9	12.4
Moderate/severe	5.5	2.6	4.8
PWA ratio from EndoPAT	1.9 (0.6)	2.0 (0.6)	1.9 (0.5)

BDI = Beck Depression Inventory; M = mean; PWA = pulse-wave amplitude SD = standard deviation.

the number of beverages consumed in a typical weeklong period. A drink was considered as one glass of wine, one 12-oz beer, or one shot of hard liquor. Physical activity was measured with a modified version of the Paffenbarger activity scale that provides an estimate of the number of minutes of brisk physical activity the participant engaged in per week (44). Adiposity[2] was calculated using the Tanita BF-350 Body Composition Analyzer (Tanita Corporation, Arlington Heights, Illinois, USA), a device that estimates the percentage of a person's body that is fat using bioelectrical impudence. At study entry, no participants reported using antidepressant medication, and only two participants reported using an antidepressant at follow-up visits. In both cases, antidepressant medication use was limited to only one visit.

Statistical Analyses

The data were analyzed using Hierarchical Linear Modeling (HLM 6.06; Scientific Software International, Inc, Lincolnwood, IL), a multilevel modeling technique that allowed us to test both within-person and between-person contributions to changes in RH-PAT over time, as well as accommodate for unequal number of visits per participant. In the within-person (or Level 1) models, we estimated RH-PAT as a function of factors that vary over time including time since study entry (coded in months) and self-reported depressive symptoms. In the between-person (or Level 2) models, we estimated person-specific slopes and intercepts as a function of factors that varied across people (i.e., mean depressive symptoms). Level 1 predictor variables were centered on the mean of each participant's depressive symptoms (group-mean centered) at the time points being investigated. We calculated within-person aggregate means for the person-centered Level 1 predictors and entered them on Level 2. Centering Level 1 variables within persons and including each person's aggregated mean at Level 2 ensures that coefficients of the within-person effects are not biased by treating the intercepts as random factors (45–47). This method allowed us to answer the question: At times when a subject's depressive symptoms were higher than usual, did her endothelial function go down in a corresponding manner irregardless of her average depression throughout the study? See Kreft et al. (48) for a discussion of centering choices and rationale for group-mean centering Level 1 variables. Within-person analyses like this are an especially rigorous way to evaluate our hypothesis because they eliminate the possibility that individual difference variables (genetics, personality, and socioeconomic status) underlie any association that is observed between depressive symptoms and endothelial function. Other health-related variables that changed over time and might account for the observed associations (e.g., alcohol, exercise, smoking, and adiposity) were later added to Level 1 models so that their influence could be evaluated.

[2]The substitution of waist-to-hip ratio for the adiposity measure did not substantially change any of the reported findings.

RESULTS

Demographic and Medical Characteristics of the Sample

The characteristics of the sample are presented in Table 1. The participants were in middle to late adolescence at study onset. The average self-reported depressive symptoms were generally mild. PWA ratios ranged from 1.0 to 4.3 across study visits. The mean PWA ratios from the EndoPAT for each visit fell within the healthy range reported by the manufacturer.

Preliminary Analyses

For the 2-year study period, mean RH-PAT ratios did not change significantly with time ($\beta = -0.0016$, standard error [SE] = 0.0029, $p = .49$). The ICC (0.341) indicated that 34.1% of the variance in RH-PAT scores occurred between people and the remaining 65.9% of the variance occurred at an individual level. In other words, more than 65% of the variation in RH-PAT occurred within persons, supporting our examination of specific contextual factors that might predict RH-PAT directly or better account for the effects of depression on RH-PAT.

Do Depression and Endothelial Function Change Together Over Time?

The first model (Table 2) yielded a series of person-specific slopes reflecting the difference in RH-PAT ratios between visits when participants were experiencing more versus less depression than was typical for them. In line with our previous findings (13), self-reported depressive symptoms (BDI) were significantly associated with the RH-PAT ratios, such that, on visits when participants endorsed depressive symptoms that were higher than their mean level of depression, they tended to have worse endothelial function.

Does Depression Have a Lasting Impact on the Endothelium?

Next, we investigated whether depression (BDI) assessed approximately 6-months before each endothelial function assessment was predictive of RH-PAT ratios above and beyond the current depressive (BDI) symptoms. Previous depressive symptoms were not predictive of endothelial function beyond current depressive symptoms ($\beta = -0.0581$, SE = 0.0745, $p = .44$).

TABLE 2. Do Depression and Endothelial Function Change Together Over Time?

Model, Level, Predictor	β	SE	p
Current BDI			
Level 1			
Time	−0.0019	0.0022	.40
Depression (BDI at T2, T4, and T6)	−0.1961	0.0975	.05
Level 2			
Depression (mean BDI across T2, T4, and T6)	−0.0939	0.0811	.25

BDI = Beck Depression Inventory; SE = standard error; T = time.

TABLE 3. Do Health Practices Account for Significant Associations?

Current BDI	β	SE	*p*
Level 1			
Time	−0.0012	0.0021	.58
Percentage of body fat	0.0018	0.0013	.14
Smoking (yes/no)	0.0868	0.0042	.45
Alcohol	0.0001	0.0042	.98
Brisk exercise, h/wk	0.0299	0.0170	.08
Depression (BDI at T2, T4, and T6)	−0.2348	0.1004	.02
Level 2			
BDI (cumulative T2, T4, and T6)	−0.1038	0.0710	.27

BDI = Beck Depression Inventory; SE = standard error; T = time.

Does Depression Predict the Trajectory of Endothelial Function Slopes?

We next investigated whether depression was associated with the trajectory of endothelial function over follow-up. A cumulative depressive symptom index was developed by taking the mean of the participants' categorized BDI scores over the course of the study. When this variable was added to the HLM model as a Level 2 predictor, it did not significantly interact with time to predict RH-PAT slopes ($\beta = 0.0072$, SE = 0.0053, $t_{342} = 1.344$, $p = .18$). These findings indicate that depressive symptoms were not associated with the 2-year trajectory of endothelial function in our sample.

Do Health Practices Account for the Observed Association?

We then examined whether health practices or adiposity accounted for the concurrent relationship between depressive symptoms and endothelial function reported previously. To investigate, we included smoking, alcohol use, exercise, and adiposity into the models as additional Level 1 variables. The addition of these variables did not significantly attenuate the relationships between depression and RH-PAT ratios. The results are presented in Table 3.

DISCUSSION

There were several aims of the current study. First, we investigated in a multiwave longitudinal fashion the association between depression and endothelial function. We found that self-reported depressive symptoms covaried with endothelial function over time. While depressive symptoms increased beyond an individual's average level of depression, endothelial function worsened; while depression abated, endothelial function improved. These findings replicate previous research showing concurrent associations between depressive symptoms and endothelial function in youth (13,22) and extend them by using a more powerful and rigorous multiwave design, which shows that the process covaries on a within-person basis. This design eliminates the possibility that the observed association is due to between-person confounds (genetic liability, socioeconomic status, and ethnicity) that commonly pose threats to the interpretation of previous work. We also found that the association persisted after controlling for self-reported physical activity, smoking, alcohol consumption, and adiposity. Of course, the findings were cross-sectional in nature; thus, we still cannot ascertain temporal precedence. In future research, it will be important to resolve this in randomized controlled trials that ameliorate depression and look at changes in endothelial function.

We also investigated whether past depression exerts a residual, negative impact on current endothelial function. Prior research has found that recurrent episodes of depression throughout the life span are associated with impaired endothelial function in postmenopausal women, even when depression is in full remission (14,19). We did not find evidence of such residual effects. This could mean that the scarring findings in previous research are an artifact of the designs they used; studies of remitted depressed patients have methodological features that can bias them toward such conclusions (49). Alternatively, features of our sample or design may have biased it toward null findings.

The fact that a residual influence of depressive symptoms on endothelial function did not emerge in analyses could be because of methodological features like the relatively short duration of follow-up. Participant attrition resulting from the development of new-onset depressive symptoms (and associated reductions in motivation to participate) also may have limited our ability to detect significant temporal relationships. Alternatively, the young age of our participants may have been protective against the development of lasting endothelial damage. Age-related declines in endothelial function do not emerge in women until menopause, in large part because of the protective effect that estrogens confer on the arterial walls (50). In healthy adolescent females and young women, the protective effects of estrogens may encourage the reestablishment of normal endothelial function after a depressive episode. Finally, symptoms of depression alone, especially in the mild range that we observed, may not initiate the types of biologic changes that would support a lingering impact of depression on endothelial function.

The underlying mechanisms linking concurrent depression and endothelial function remain unclear, and several biologically plausible mechanisms have been proposed. For example, depressive mood is linked to dysregulation of the autonomic nervous system and hypothalamic-pituitary-adrenal axis (51,52), both of which are associated with worse endothelial functioning (53,54). In addition, oxidative damage may play a part in the relationship. Our group has shown that depression is associated with higher levels of 8-hydroxy-2′-deoxyguanosine and 8-isoprostaglandin-$F_{2\alpha}$, which are the biomarkers of oxidative damage to deoxyribonucleic acid and lipids, respectively (55,56). In turn, oxidative damage reduces the bioavailability of nitric oxide, blunting normal vasodilatory responses (57,58). It is likely that oxidative damage, hypothalamic-pituitary-adrenal axis activation, and other factors associated with depression combine to disrupt normal homeostatic mechanisms in the endothelium. Another possibility is that depression serves as a moderator of the effects of health practices, adiposity, or other

factors that may promote endothelial dysfunction in adolescents and young adults. For example, depression may have little effect on healthy arteries but could accelerate the development of atherosclerosis in arteries that are showing early signs of disease because of exposure to cigarette smoke, obesity, or other reasons (59). Given the restricted range of regular exercise, smoking, and adiposity, we were unable to investigate this question in our sample; however, it is an interesting question that could be addressed in samples with a larger range in health practices.

The findings must be interpreted in light of limitations. First, the data about health practices were obtained via self-report. We have found excellent validity and reliability using these self-reported measures in previous work, yet we acknowledge that ideally objective information about physical fitness and other health behaviours (i.e., via maximum oxygen consumption or tobacco metabolites) would be obtained to track changes in health practices over time. Inclusion of objectively assessed health practices in future studies may allow for identifying potential mediators, or even moderators, of the depression–endothelial function relationship. Finally, recent work suggests that correcting for shear stress may facilitate the detection of endothelial dysfunction. The EndoPAT does not provide a measure of shear stress, and it is possible that accounting for this factor may have revealed additional relationships (60).

In summary, our results show that depressive symptoms and endothelial function are associated. Previous investigations in this area have demonstrated between-person associations between endothelial function and both clinical depression and depressive symptoms. Our findings extend this work showing associations between within-person changes in depressive symptoms and changes in endothelial function. On visits when participants reported higher than normal levels of depression, they also had worse endothelial function, but when their mood returned to normal, so did their endothelial function. We did not detect scarring or a long-term negative mark on the endothelium associated with past depression, nor did we see that depressive symptoms exerted an influence on the trajectory of endothelial function in this cohort of healthy, adolescent girls and young women.

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