# The Use of Statins After a Cardiac Intervention Is Associated With Reduced Risk of Subsequent Depression: Proof of Concept for the Inflammatory and Oxidative Hypotheses of Depression?

*Lesley Stafford, PhD, and Michael Berk, MD, PhD*

**ABSTRACT**

***Objective:*** Depression is associated with immune activation as well as oxidative stress. Statins have in vitro and in vivo antiinflammatory and antioxidative properties. We prospectively investigated whether the use of statins was associated with a reduced risk of development of depression in individuals who have had a cardiac event or intervention.

***Method:*** Participants were recruited between May 2005 and March 2006 from the Geelong Hospital, Geelong, Australia, a tertiary hospital in regional Australia that serves a catchment area shown to be representative of the broader Australian community. Patients who were hospitalized for angioplasty, myocardial infarction, or coronary artery bypass graft surgery (N = 193) were followed up prospectively for 9 months to assess development of depression. Depression data were collected 3 months postdischarge (T1) by structured clinical interview (using the Mini International Neuropsychiatric Interview, version 5) and 9 months postdischarge (T2) by self-report (using the Hospital Anxiety and Depression Scale). Major depressive disorder, minor depression, and dysthymia were diagnosed according to *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition criteria. Data on statins were collected from medical records. The association between statin therapy and depression was tested using both linear and logistic regression models controlling for clinical, psychological, and demographic confounders.

***Results:*** At discharge, 157 participants (81.3%) were receiving statin therapy. Adjusting for possible confounders, taking statins at discharge had a protective effect on depression at T1, reducing the likelihood of dysthymia, minor depression, or major depression by 69% (95% CI, 0.097–0.972; $P = .045$). At the T2 end point, statin therapy again had a protective effect and was associated with a 79% reduction in the likelihood of depression (95% CI, 0.052–0.876; $P = .032$). The linear regression model to predict depression at T2 was significantly different from zero ($F_{11,180} = 8.686$, $P < .001$) and explained 36.3% of the variance in depression.

***Conclusions:*** The use of statins was associated with significant reduction in the risk of depression in individuals who have had a cardiac event. This supports the role of oxidative and inflammatory processes in depression and opens the door to rational and novel pathophysiologically based therapies distinct from conventional antidepressants.

*J Clin Psychiatry 2011;72(9):1229–1235*


***Submitted:*** *November 9, 2009; accepted March 15, 2010.*
***Online ahead of print:*** *December 14, 2010 (doi:10.4088/JCP.09m05825blu).*
***Corresponding author:*** *Michael Berk, MD, PhD, Department of Clinical and Biomedical Sciences, Barwon Health, University of Melbourne, PO Box 281, Geelong VIC 3220, Australia (mikebe@barwonhealth.org.au).*

Depression is associated with both increased immune activation and impaired immune function.[1] Evidence of immune dysfunction in depression includes an impaired lymphocyte proliferative response to mitogens, increased monocyte phagocytosis, and increased concentrations of proinflammatory cytokines and positive acute phase proteins.[2–4] In healthy volunteers, administration of exogenous cytokines induced many of the core phenotypes of a depressive illness, including behavioral and cognitive alterations, a depressed mood state, increased stress reactions, cognitive impairment, and difficulties with motivation.[3] These studies are perhaps the best human experimental models of depression. Treatment with established antidepressants reduced inflammatory marker levels in patients with major depressive disorder,[5,6] and treatment nonresponse was associated with elevated inflammatory marker levels.[7] In a 10-year follow-up study, elevated levels of C-reactive protein (CRP) predicted the subsequent risk for de novo depression, suggesting that immune dysregulation is not simply an epiphenomenon of depression but that it contributes to the genesis of the disorder.[8]

Statins have known effects on inflammatory cytokines, and they also reduce markers of oxidative stress. It is possible that this effect is greater in lipophilic than in hydrophilic statins.[9] Statins have reduced markers of oxidative stress and inflammatory markers in spontaneously hypertensive rats.[10] They have been shown to reduce inflammation and oxidative stress in patients with hypertension and dyslipidemia.[11] In patients who have had an acute cardiac event, statins induced a rapid reduction of tumor necrosis factor-alpha and interferon-gamma production in stimulated T-lymphocytes and inhibited the Th-1-immune response.[12] In human hepatocytes, statins reduced interleukin-6–induced expression of CRP,[13] suggesting a hepatic source of its anti-inflammatory effects.

There are also extensive data on the relationship between oxidative stress and depression. Compared with healthy controls, patients with depression have significantly elevated markers of oxidative damage, which includes lipid peroxidation products,[14–17] the oxidized DNA marker 8-hydroxy-2′-deoxyguanosine,[18] and depleted omega-3 fatty acids that indicate oxidative damage of erythrocytic membranes.[19] Altered antioxidant levels have also been found in those persons with depression, including diminished levels of serum vitamins C[15] and E,[20,21] albumin,[22] and alterations in the antioxidative enzymes superoxide dismutase,[14–16,23] glutathione peroxidase, and glutathione reductase.[14] There is a significantly higher oxidative stress index, as determined by the ratio of total plasma peroxide to total plasma antioxidant potential, in medication-free patients with depression,[24] and there are studies showing correlations between depressive severity and

the magnitude of disturbances in their respective oxidative indices.[14,16,18,21] Concordant with these findings, there is preclinical evidence that established antidepressant agents, including venlafaxine, moclobemide, and phenelzine, reduce markers of oxidative stress.[25–29] Lastly, markers of oxidative stress normalize with the resolution of depression.[14,15] In aggregate, these studies provide substantial evidence for the role of oxidative systems in the pathophysiology of depression.

There are now clear data to show that statins additionally reduce oxidative stress. Statins have in vitro antioxidant and DNA protective effects.[30] In spontaneously hypertensive rats, statins reduced reactive oxygen species production in circulating monocytes.[10] Given the data suggesting a dysregulation in glutathione in depression, the fact that statins may reverse oxidative stress by up-regulation of glutathione synthesis is of considerable interest.[31] Statins decrease lipid peroxidation, reducing oxidized low-density lipoprotein accumulation by increasing the expression of the free radical scavenging enzyme SOD1.[32] These data suggest that in vivo statin treatment reduces oxidative stress and that this mechanism may be additive in its potential efficacy profile. Principally exploring the finding that there may be a relationship between cholesterol and mood, a couple of earlier studies examined the relationship between statin use and depression and found a protective effect.[33,34] In a 10-year, community-based prospective study, the hazard ratio for the emergence of de novo major depression was 0.20 (95% Cl, 0.04–0.85, $P = .03$) among women taking statins.[35]

The aims of this study were therefore to examine the effects of statin treatment on the development of depression in patients who were hospitalized for myocardial infarction (MI), percutaneous transluminal coronary angioplasty (PTCA), or coronary artery bypass graft surgery (CABG). Given the nexus between inflammatory and oxidative stress in depression and the effects of statins on those parameters, we hypothesized that those individuals taking statins would have a lower risk of developing depression. We hypothesized that there would be a significant association between statin therapy and depression, even when potentially confounding clinical (ie, disease severity,[36] functional cardiac status,[37,38] smoking,[39,40] diabetes,[41] body mass index [BMI][42]), psychological (ie, history of depression,[40,43] neuroticism[44,45]), and demographic (ie, sex,[46] age[47]) factors were statistically controlled a priori.

## METHOD

### Sample

Participants were recruited between May 2005 and March 2006 from the Geelong Hospital, Geelong, Australia, a tertiary hospital in regional Australia that serves a catchment area shown to be representative of the broader Australian community.[48] All English-speaking, consenting patients who were hospitalized for PTCA, MI, or CABG during this time were eligible for participation. According to discharge diagnoses, 528 patients were treated for these presentations during the study period. Patients with different coronary artery disease (CAD) presentations were regarded as a homogenous group on the basis of evidence that the association between depression and CAD is found across all subgroups of CAD patients, with similar prognostic effects for cardiac[49,50] and quality of life[51,52] outcomes. Participants were recruited by postal invitation and follow-up phone calls 6 weeks postdischarge. Reasons for nonparticipation were death (n = 13), lack of facility in English (n = 16), inability to consent (n = 9), medical illness (n = 9), depression (n = 3), and no given reason (n = 249). Agreement to participate was obtained from 229 patients. The study received ethics approval from the Barwon Health and University of Melbourne institutional review committees. After complete description of the study to participants, written informed consent was obtained.

### Procedures

Self-report data were collected at 3 months (T1) and 9 months (T2) after hospital discharge. Baseline assessment was undertaken 3 months postdischarge, rather than during admission, to avoid potential confounding of the effects of acute illness and stress associated with hospitalization with the assessment of predictor variables and to minimize the burden on participants. Other studies[39,40,53] have highlighted difficulties in reliably identifying patients in whom depression will emerge, persist, or worsen solely on the basis of level of depressive symptomatology present during hospitalization. Structured clinical interviews were administered by telephone at T1. Telephonic administration of structured clinical interviews has been found to be valid and reliable.[54,55] For analyses, participants were assigned to the diagnostic group *major depressive disorder* (MDD) or to a broader group *any depressive disorder* (ADD). The latter comprised, in addition to participants with MDD, participants with minor depression and dysthymia.

Participants were mailed self-report questionnaires at T1 and T2. T1 questionnaires assessed neuroticism and functional disability. The depression self-report measure was administered at T2. Relevant clinical and sociodemographic data were collected by T1 self-report and from medical records at T1. Additional details regarding the study methodology have been published elsewhere.[56]

### Measures

Clinical data such as disease severity, presence of diabetes, and discharge medications such as aspirin and statins were obtained from medical records. Disease severity was measured with left ventricular ejection fraction (LVEF). An LVEF ≤ 30% was considered poor. Body mass index was computed based on self-reported height and weight ($kg/m^2$) at the time of the index event. Sociodemographic data, prior history of depression, and tobacco use at the index event were gathered by self-report.

Clinical depression was assessed at T1 using the Mini International Neuropsychiatric Interview version 5 (MINI),[57,58] a diagnostic structured interview compatible with the *International Statistical Classification of Diseases and Related*

 © Copyright 2010 Physicians Postgraduate Press, Inc.

*Health Problems, Tenth Revision* (*ICD-10)* and the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV)* criteria and similar to the Structured Clinical Interview for *DSM-IV* Disorders (SCID)[59] in operation and principle. The MINI has excellent psychometric properties and has been validated against the SCID-Patient Version[60] and the Composite International Diagnostic Interview (CIDI).[57,58,61,62] The MINI modules for depression and dysthymia were administered. Major depressive disorder was diagnosed if participants fulfilled at least 1 *DSM-IV* core criterion (depressed mood or anhedonia) and at least 4 additional *DSM-IV* criteria within a 2-week duration. With the use of the MINI depression module, minor depression was diagnosed if participants fulfilled at least 1 *DSM-IV* core criterion and 1 to 3 additional *DSM-IV* criteria within a 2-week period.

Depressive symptomatology was measured at T2 with the 7-item depression subscale of the Hospital Anxiety and Depression Scale (HADS).[63] The HADS has well-established psychometric properties[64,65] and is widely used in studies with cardiac patients.[66–68] Possible scores range from 0 to 21. Higher scores denote greater depressive symptomatology. Cronbach α at T2 was 0.84. In accordance with previous data,[65,69–71] a score ≥ 8 was considered to indicate depression.

Neuroticism was measured with a 10-item scale from the self-report version of the Revised NEO Personality Inventory (NEO PI-R),[72] the International Personality Item Pool Representation of the NEO PI-R (IPIP-NEO).[73] Scores range from 10 to 50, with higher scores indicating greater neuroticism. The IPIP-NEO has been shown to be reliable[74] and valid[72,75] and its factor structure has been confirmed[76,77] (Cronbach α = 0.88).

Functional status (effort tolerance) was measured using the 10 items from the Short Form-36 (SF-36)[78] that assess physical functioning. Items include activities such as walking 1 block and climbing a flight of stairs. In the original context, these items assess limitations on physical activities. Here, the response format was altered to assess the severity of symptoms experienced when performing these physical tasks. The items are similar to measures like the Canadian Cardiovascular Society grading scale for angina severity[79] and the New York Heart Association classification criteria for the prescription of physical activity for cardiac patients.[80] Responses include *I do not experience symptoms*, *I experience mild symptoms*, *I experience severe symptoms*, and *I am not able to perform this activity*. Scores range from 0 to 30, with lower scores indicating greater functional disability.

### Analysis

Data were analyzed using SPSS version 16.0 (SPSS Inc, Chicago, Illinois). All tests were 2-tailed, and α was set at .05. Multivariate analyses to predict the association between statins and depression at T1 comprised predicting MDD and ADD, as defined above. At T2, multivariate analyses comprised both linear (HADS as a continuous variable) and logistic regression (HADS with a cutoff ≥ 8). All predictor variables were entered in 1 block. Multivariate analyses were adjusted for age, sex, functional status (effort tolerance), neuroticism, history of depression, smoking, diabetes, BMI, disease severity, and aspirin therapy. Scores for effort tolerance at T1 were transformed by cubing the original scores. T2 HADS scores were transformed using the square root of the original scores.

**Table 1. Characteristics of Patients Recovering From a Cardiac Event (N = 193) at T1**

| Variable | N | % | |
|---|---|---|---|
| Male | 156 | 80.8 | |
| Income ≤ A$ 20,000 | 63 | 32.6 | |
| Married | 146 | 75.5 | |
| Aspirin therapy | 178 | 93.2 | |
| Statin therapy | 157 | 81.3 | |
| Smoker | 27 | 14.0 | |
| Diabetes | 45 | 23.3 | |
| Left ventricular ejection fraction ≤ 30% | 11 | 5.7 | |
| Major depressive disorder | 35 | 18.1 | |
| Any depressive disorder | 54 | 28.0 | |
| History of depression | 67 | 34.7 | |
| | Mean | SD | Range |
| Body mass index, kg/m$^2$ | 28.00 | 4.22 | 20–40 |
| Functional status* | 24.09 | 6.11 | 0–30 |
| Age, y | 64.14 | 10.37 | 38–91 |
| Neuroticism | 27.32 | 9.02 | 10–50 |

*Untransformed data.

## RESULTS

### Characteristics of the Sample

T1 questionnaires were completed by 193 of the 229 recruited patients (84%; or 37% of all patients treated during the study period, including those deceased and ineligible). Compared to nonparticipants, participants were significantly more likely to be male ($\chi^2_1 = 5.93$, N = 528, $P = .02$) and were, on average, younger ($t_{526} = 3.12$, $P < .01$). The mean (SD) age for participants versus nonparticipants was 64.14 (10.37) versus 67.31 (11.70) years, respectively. Twenty-eight participants did not return their questionnaires for an unspecified reason, 3 withdrew due to physical illness, and 4 withdrew due to depression. There were no significant sex differences between those who completed T1 questionnaires and those who did not ($\chi^2_1 = 0.64$, N = 229, $P = .42$), but nonrespondents were, on average, significantly younger than respondents ($t_{227} = -2.13$, $P < .03$). The mean (SD) age of nonresponders was 59.94 (13.22) years. At T2, 184 of the 193 T1 participants remained (95%; or 35% of the original patient group [184 of 528]). One participant had formally withdrawn due to depressive illness, and 8 participants did not return their questionnaires for unspecified reasons. Complete data were available for 180 participants. There were no sex or age differences between participants who completed T2 questionnaires and those who did not. Baseline clinical, sociodemographic, and psychological data for the sample are described in Table 1.

### Association Between Statin Therapy and Depression

The statins used were pravastatin (n = 14), simvastatin (n = 29), and atorvastatin (n = 114). A total of 157 patients

**Table 2. Logistic Regression to Predict Any Depressive Disorder in Patients Recovering From a Cardiac Event (N = 193) at T1**

| | | | | | | | 95% CI for EXP(B) | |
|---|---|---|---|---|---|---|---|---|
| Variable | B | SE | Wald | *df* | *P* | Exp(B) | Lower Bound | Upper Bound |
| Statin therapy | −1.178 | 0.587 | 4.031 | 1 | .045 | 0.308 | 0.097 | 0.972 |
| Aspirin therapy | 1.813 | 1.068 | 2.884 | 1 | .089 | 6.130 | 0.756 | 49.686 |
| Neuroticism | 0.125 | 0.029 | 18.096 | 1 | .000 | 1.133 | 1.070 | 1.201 |
| Age | −0.022 | 0.025 | 0.781 | 1 | .377 | 0.978 | 0.932 | 1.027 |
| LVEF ≤ 30% | −0.747 | 1.156 | 0.418 | 1 | .518 | 0.474 | 0.049 | 4.561 |
| Male | 0.062 | 0.570 | 0.012 | 1 | .914 | 1.064 | 0.348 | 3.250 |
| Smoker | 2.332 | 0.642 | 13.205 | 1 | .000 | 10.302 | 2.928 | 36.248 |
| History of depression | 0.332 | 0.465 | 0.510 | 1 | .475 | 1.394 | 0.560 | 3.471 |
| Diabetes | −0.790 | 0.545 | 2.105 | 1 | .147 | 0.454 | 0.156 | 1.320 |
| Body mass index | 0.071 | 0.050 | 2.048 | 1 | .152 | 1.074 | 0.974 | 1.185 |
| Functional status | 0.000 | 0.000 | 4.281 | 1 | .039 | 1.000 | 1.000 | 1.000 |
| Constant | −5.290 | 3.089 | 2.932 | 1 | .087 | 0.005 | | |

Abbreviations: LVEF = left ventricular ejection fraction, T1 = 3 months postdischarge.

**Table 3. Logistic Regression to Predict Depression in Patients Recovering From a Cardiac Event (N = 184) at T2**

| | | | | | | | 95% CI for EXP(B) | |
|---|---|---|---|---|---|---|---|---|
| Variable | B | SE | Wald | *df* | *P* | Exp(B) | Lower Bound | Upper Bound |
| Statin therapy | −1.543 | 0.720 | 4.597 | 1 | .032 | 0.214 | 0.052 | 0.876 |
| Aspirin therapy | 3.218 | 1.771 | 3.300 | 1 | .069 | 24.969 | 0.776 | 803.686 |
| Neuroticism | 0.110 | 0.036 | 9.638 | 1 | .002 | 1.117 | 1.041 | 1.197 |
| Age | −0.077 | 0.031 | 6.357 | 1 | .012 | 0.926 | 0.871 | 0.983 |
| LVEF ≤ 30% | −18.704 | 11,400.674 | 0.000 | 1 | .999 | 0.000 | 0.000 | 0.000 |
| Male | 0.717 | 0.654 | 1.204 | 1 | .273 | 2.049 | 0.569 | 7.379 |
| Smoker | −0.181 | 0.769 | 0.055 | 1 | .814 | 0.835 | 0.185 | 3.770 |
| History of depression | 0.330 | 0.558 | 0.350 | 1 | .554 | 1.391 | 0.466 | 4.151 |
| Diabetes | 0.705 | 0.572 | 1.520 | 1 | .218 | 2.024 | 0.660 | 6.212 |
| Body mass index | 0.186 | 0.065 | 8.075 | 1 | .004 | 1.204 | 1.059 | 1.368 |
| Functional status | 0.000 | 0.000 | 6.895 | 1 | .009 | 1.000 | 1.000 | 1.000 |
| Constant | −6.818 | 3.883 | 3.083 | 1 | .079 | 0.001 | | |

Abbreviations: LVEF = left ventricular ejection fraction, T2 = 9 months postdischarge.

**Table 4. Linear Regression to Predict Depression in Patients Recovering From a Cardiac Event (N = 184) at T2**

| | | | | | | 95% CI for B | |
|---|---|---|---|---|---|---|---|
| Variable | B | SE | β | *t* | *P* | Lower Bound | Upper Bound |
| (Constant) | −0.396 | 0.872 | | −0.454 | .650 | −2.118 | 1.326 |
| Statin therapy | −0.340 | 0.171 | −0.130 | −1.985 | .049 | −0.678 | −0.002 |
| Aspirin therapy | 0.220 | 0.244 | 0.056 | 0.903 | .368 | −0.261 | 0.702 |
| Neuroticism | 0.038 | 0.008 | 0.351 | 4.971 | .000 | 0.023 | 0.053 |
| Age | 0.001 | 0.007 | 0.012 | 0.167 | .868 | −0.013 | 0.015 |
| LVEF ≤ 30% | −0.047 | 0.257 | −0.012 | −0.184 | .854 | −0.555 | 0.461 |
| Male | 0.230 | 0.156 | 0.094 | 1.471 | .143 | −0.079 | 0.538 |
| Smoker | 0.372 | 0.190 | 0.129 | 1.960 | .052 | −0.003 | 0.747 |
| History of depression | 0.115 | 0.140 | 0.056 | 0.825 | .411 | −0.161 | 0.392 |
| Diabetes | 0.059 | 0.144 | 0.026 | 0.407 | .685 | −0.226 | 0.343 |
| Body mass index | 0.047 | 0.015 | 0.202 | 3.130 | .002 | 0.017 | 0.076 |
| Functional status | −3.481 | 0.000 | −0.279 | −3.778 | .000 | 0.000 | 0.000 |

Abbreviations: LVEF = left ventricular ejection fraction, T2 = 9 months postdischarge.

were taking statins. There was insufficient power to test the effect of individual agents. The logistic regression model to test the association between statin therapy prescribed at time of hospital discharge and ADD 3 months later (T1) was significant ($\chi^2_{11} = 78.08$, N = 189, $P < .001$). Inspection of the odds ratios (Table 2) showed that taking statins at discharge had a protective effect, reducing the likelihood of dysthymia, minor depression, or major depression at T1 by 69% (95% CI, 0.097–0.972; $P = .045$). The model to predict MDD was significant ($\chi^2_{11} = 64.41$, N = 180, $P < .001$), but statin therapy was not a reliable predictor of MDD ($P = .486$; analyses not shown).

At T2, 29 (16.1%) participants scored ≥ 8 on the HADS, and they were classified as depressed. The mean (SD) score on the HADS was 3.70 (3.60). Multivariate analyses to predict depression 9 months after hospital discharge are shown in Table 3 (logistic regression) and Table 4 (linear regression). The logistic regression model was significant ($\chi^2_{11} = 53.08$, N = 180, $P < .001$). Inspection of the odds ratios in Table 3 showed that statin therapy at discharge had a protective effect, reducing the likelihood of depression at T2 by 79% (95% CI, 0.052–0.876; $P = .032$). The linear regression model to predict depression was significantly different from zero ($F_{11,180} = 8.686$, $P < .001$), and it explained 36.3% of the variance in depression at T2. The results of the linear regression analysis confirm the negative association between statin therapy and depression ($\beta = -0.340$; $P = .049$). Inspection of the partial and semipartial correlations showed that statin therapy contributed 2.28% of the unique variance and 1.5% of the total variance in depression.

The 2 measures of depression were significantly correlated. The correlations between the HADS and the variables MDD and ADD were 0.41 ($P < .001$) and 0.54 ($P < .001$), respectively. Other data based on this patient group[81] have shown that, relative to the structured clinical interview as the referent standard, the operating characteristics of the HADS are acceptable for detecting depression.

## DISCUSSION

The results of this study suggest that statin therapy at time of discharge following cardiac event is associated with a 79% reduction in the likelihood of developing depression 9 months later. This is an unexpectedly large clinical effect; however, it is concordant with the ability of statins to reduce inflammatory cytokines, which appear to play an etiological role in the genesis of depression. In addition, the antioxidant

properties of statins are concordant with the data showing increased oxidative stress in depression. Conventional antidepressants have been shown to reduce both oxidative stress and cytokines.

A number of the methodological characteristics of this study merit discussion. Strengths of the study include its prospective nature and the low attrition rate. We were able to include a diverse array of cardiac, lifestyle, and psychological factors that have been shown to predict depression, and we were able to adjust for these in the multivariate models; however, confounding by additional variables remains possible. The results of the study may have been influenced by variables present before the onset of the study assessments. We acknowledge limitations in the generalizability of the study. The compliance rate was low, and it is possible that patients with depression were less likely to participate, possibly resulting in an underestimation of the effects of statins. Statins were not randomly assigned, and individual statins were not examined. There is evidence that statins differ in efficacy.[82] The percentage of patients remaining on statin therapy at T2 is not known. Respondents were more likely to be male and were on average older than nonrespondents. The study was restricted to individuals who have had a cardiac event, and while this group is at higher risk of developing depression,[83] it is unclear if all the risk factors for this group, and hence the results of this study in their entirety, can be extended to the general population. As the age range of the sample was relatively old, it is also unclear if these findings would apply to younger patients. While we had data for a range of cardiac medications, including aspirin, we did not have data on other agents, such as nonsteroidal anti-inflammatory drugs, that may impact inflammatory processes and impact the model. It would have been of value to have blood levels of such inflammatory markers. Future studies of statins and depression may wish to examine whether changes in symptoms are indeed correlated with altered inflammatory markers.

One possible confounding explanation for the effect of statins is via cholesterol. Low serum cholesterol was associated with increased depressive symptoms in cross-sectional population studies.[84,85] There are prospective reports of an association between low serum cholesterol and the risk of depression.[86–90] There are 2 intervention studies that show conflicting results in terms of the relationship between cholesterol-reducing diets and mood and hostility,[91,92] which do not allow definitive conclusions to be made.

Nevertheless, these data suggest that the use of statins is associated with a substantially reduced risk of depression in individuals who have had a cardiac event. The known effects of statins on oxidative and inflammatory processes support the role of oxidative and inflammatory processes in depression. Although there are limitations on the generalizability of these findings, these preliminary data open the door to rational and novel pathophysiologically based therapies distinct from conventional antidepressants, which have a limited range of efficacy in the treatment and prevention of depression.

***Drug names:*** atorvastatin (Lipitor), phenelzine (Nardil), pravastatin (Pravachol and others), simvastatin (Zocor and others), venlafaxine (Effexor and others)

***Author affiliations:*** Centre for Women's Mental Health, Royal Women's Hospital, Parkville (Dr Stafford); Departments of Psychology and Psychiatry (Dr Stafford) and Clinical and Biomedical Sciences, Barwon Health (Dr Berk), University of Melbourne; Australia Orygen Research Centre, Parkville (Dr Berk); and the Mental Health Research Institute, Parkville (Dr Berk), Victoria, Australia.

***Potential conflicts of interest:*** **Dr Stafford** has received grant/research support from the University of Melbourne. **Dr Berk** has received grant/research support from the Stanley Medical Research Foundation, the Medical Benefits Fund, the National Health and Medical Research Council, Beyond Blue, the Geelong Medical Research Foundation, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Organon, Novartis, Mayne Pharma, and Servier; is a member of the speakers/advisory boards for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Lundbeck, Pfizer, sanofi synthelabo, Servier, Solvay, and Wyeth; and is a consultant for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Lundbeck, and Servier.
***Funding/support:*** None reported.

## REFERENCES

1. Leonard BE. Immunological aspects of depressive illness. In: Leonard BE, Miller K, eds. *Stress, the Immune System and Psychiatry*. Chichester, United Kingdom: Wiley; 1995:113–136.
2. Leonard BE. The immune system, depression and the action of antidepressants. *Prog Neuropsychopharmacol Biol Psychiatry*. 2001; 25(4):767–780.
3. Connor TJ, Leonard BE. Depression, stress and immunological activation: the role of cytokines in depressive disorders. *Life Sci*. 1998;62(7): 583–606.
4. McAdams C, Leonard BE. Neutrophil and monocyte phagocytosis in depressed patients. *Prog Neuropsychopharmacol Biol Psychiatry*. 1993; 17(6):971–984.
5. O'Brien SM, Scott LV, Dinan TG. Antidepressant therapy and C-reactive protein levels. *Br J Psychiatry*. 2006;188(5):449–452.
6. Basterzi AD, Aydemir C, Kisa C, et al. IL-6 levels decrease with SSRI treatment in patients with major depression. *Hum Psychopharmacol*. 2005;20(7):473–476.
7. Eller T, Vasar V, Shlik J, et al. Pro-inflammatory cytokines and treatment response to escitalopram in major depressive disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 2008;32(2):445–450.
8. Pasco JA, Nicholson GC, Williams LJ, et al. Association of high-sensitivity C-reactive protein with *de novo* major depression. *Br J Psychiatry*. 2010;197(11):372–377.
9. Sironi L, Gianazza E, Gelosa P, et al. Rosuvastatin, but not simvastatin, provides end-organ protection in stroke-prone rats by antiinflammatory effects. *Arterioscler Thromb Vasc Biol*. 2005;25(3):598–603.
10. Sicard P, Delemasure S, Korandji C, et al. Anti-hypertensive effects of Rosuvastatin are associated with decreased inflammation and oxidative stress markers in hypertensive rats. *Free Radic Res*. 2008;42(3):226–236.
11. Gómez-García A, Martínez Torres G, Ortega-Pierres LE, et al. Rosuvastatin and metformin decrease inflammation and oxidative stress in patients with hypertension and dyslipidemia. *Rev Esp Cardiol*. 2007; 60(12):1242–1249.
12. Link A, Ayadhi T, Böhm M, et al. Rapid immunomodulation by rosuvastatin in patients with acute coronary syndrome. *Eur Heart J*. 2006;27(24): 2945–2955.
13. Mayer C, Gruber HJ, Landl EM, et al. Rosuvastatin reduces interleukin-6-induced expression of C-reactive protein in human hepatocytes in a STAT3- and C/EBP-dependent fashion. *Int J Clin Pharmacol Ther*. 2007; 45(6):319–327.
14. Bilici M, Efe H, Köroğlu MA, et al. Antioxidative enzyme activities and lipid peroxidation in major depression: alterations by antidepressant treatments. *J Affect Disord*. 2001;64(1):43–51.
15. Khanzode SD, Dakhale GN, Khanzode SS, et al. Oxidative damage and major depression: the potential antioxidant action of selective serotonin re-uptake inhibitors. *Redox Rep*. 2003;8(6):365–370.
16. Sarandol A, Sarandol E, Eker SS, et al. Major depressive disorder is accompanied with oxidative stress: short-term antidepressant treatment does not alter oxidative-antioxidative systems. *Hum Psychopharmacol*. 2007;22(2):67–73.
17. Selley ML. Increased (E)-4-hydroxy-2-nonenal and asymmetric

dimethylarginine concentrations and decreased nitric oxide concentrations in the plasma of patients with major depression. *J Affect Disord*. 2004;80(2–3):249–256.
18. Forlenza MJ, Miller GE. Increased serum levels of 8-hydroxy-2′-deoxyguanosine in clinical depression. *Psychosom Med*. 2006;68(1):1–7.
19. Peet M, Murphy B, Shay J, et al. Depletion of omega-3 fatty acid levels in red blood cell membranes of depressive patients. *Biol Psychiatry*. 1998; 43(5):315–319.
20. Maes M, De Vos N, Pioli R, et al. Lower serum vitamin E concentrations in major depression. Another marker of lowered antioxidant defenses in that illness. *J Affect Disord*. 2000;58(3):241–246.
21. Owen AJ, Batterham MJ, Probst YC, et al. Low plasma vitamin E levels in major depression: diet or disease? *Eur J Clin Nutr*. 2005;59(2):304–306.
22. Van Hunsel F, Wauters A, Vandoolaeghe E, et al. Lower total serum protein, albumin, and beta- and gamma-globulin in major and treatment-resistant depression: effects of antidepressant treatments. *Psychiatry Res*. 1996;65(3):159–169.
23. Herken H, Gurel A, Selek S, et al. Adenosine deaminase, nitric oxide, superoxide dismutase, and xanthine oxidase in patients with major depression: impact of antidepressant treatment. *Arch Med Res*. 2007; 38(2):247–252.
24. Yanik M, Erel O, Kati M. The relationship between potency of oxidative stress and severity of depression. *Acta Neuropsychiatr*. 2004;16(4): 200–203.
25. Pal SN, Dandiya PC. Glutathione as a cerebral substrate in depressive behavior. *Pharmacol Biochem Behav*. 1994;48(4):845–851.
26. Eren I, Naziroğlu M, Demirdaş A, et al. Venlafaxine modulates depression-induced oxidative stress in brain and medulla of rat. *Neurochem Res*. 2007;32(3):497–505.
27. Lee CS, Han ES, Lee WB. Antioxidant effect of phenelzine on MPP+-induced cell viability loss in differentiated PC12 cells. *Neurochem Res*. 2003;28(12):1833–1841.
28. Khawaja X, Xu J, Liang JJ, et al. Proteomic analysis of protein changes developing in rat hippocampus after chronic antidepressant treatment: implications for depressive disorders and future therapies. *J Neurosci Res*. 2004;75(4):451–460.
29. Verleye M, Steinschneider R, Bernard FX, et al. Moclobemide attenuates anoxia and glutamate-induced neuronal damage in vitro independently of interaction with glutamate receptor subtypes. *Brain Res*. 2007;1138: 30–38.
30. Ajith TA, Riji T, Anu V. In vitro anti-oxidant and DNA protective effects of the novel 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor rosuvastatin. *Clin Exp Pharmacol Physiol*. 2008;35(5–6):625–629.
31. Schupp N, Schmid U, Heidland A, et al. Rosuvastatin protects against oxidative stress and DNA damage in vitro via upregulation of glutathione synthesis. *Atherosclerosis*. 2008;199(2):278–287.
32. Holvoet P, Verh K. Relations between metabolic syndrome, oxidative stress and inflammation and cardiovascular disease. *Acad Geneeskd Belg*. 2008;70(3):193–219.
33. Young-Xu Y, Chan KA, Liao JK, et al. Long-term statin use and psychological well-being. *J Am Coll Cardiol*. 2003;42(4):690–697.
34. Yang CC, Jick SS, Jick H. Lipid-lowering drugs and the risk of depression and suicidal behavior. *Arch Intern Med*. 2003;163(16):1926–1932.
35. Pasco JA, Jacka FN, Williams LJ, et al. Clinical implications of the cytokine hypothesis of depression: the association between use of statins and aspirin, and the risk of major depression. *Psychother Psychosom*. 2009;
78(1):16–25.
36. van Melle JP, de Jonge P, Ormel J, et al; MIND-IT Investigators. Relationship between left ventricular dysfunction and depression following myocardial infarction: data from the MIND-IT. *Eur Heart J*. 2005;26(24):2650–2656.
37. Dunlop DD, Lyons JS, Manheim LM, et al. Arthritis and heart disease as risk factors for major depression: the role of functional limitation. *Med Care*. 2004;42(6):502–511.
38. Surtees PG, Wainwright NW, Khaw KT, et al. Functional health status, chronic medical conditions and disorders of mood. *Br J Psychiatry*. 2003; 183(4):299–303.
39. Schrader G, Cheok F, Hordacre AL, et al. Predictors of depression three months after cardiac hospitalization. *Psychosom Med*. 2004;66(4): 514–520.
40. Schrader G, Cheok F, Hordacre A-L, et al. Predictors of depression 12 months after cardiac hospitalization: the Identifying Depression as a Comorbid Condition study. *Aust N Z J Psychiatry*. 2006;40(11-12): 1025–1030.
41. Lustman PJ, Penckofer SM, Clouse RE. Recent advances in understanding depression in adults with diabetes. *Curr Psychiatry Rep*. 2008;10(6): 495–502.
42. Markowitz S, Friedman MA, Arent SM. Understanding the relation between obesity and depression: causal mechanisms and implications for treatment. *Clin Psychol Sci Pract*. 2008;15(1):1–20.
43. Lesperance F, Frasure-Smith N, Talajic M. Major depression before and after myocardial infarction: its nature and consequences. *Psychosom Med*. 1996;58(2):99–110.
44. Hirschfeld RM, Klerman GL, Lavori P, et al. Premorbid personality assessments of first onset of major depression. *Arch Gen Psychiatry*. 1989;46(4):345–350.
45. Krueger RF, Caspi A, Moffitt TE, et al. Personality traits are differentially linked to mental disorders: a multitrait-multidiagnosis study of an adolescent birth cohort. *J Abnorm Psychol*. 1996;105(3):299–312.
46. Kessler RC, McGonagle KA, Swartz M, et al. Sex and depression in the National Comorbidity Survey, I: lifetime prevalence, chronicity and recurrence. *J Affect Disord*. 1993;29(2-3):85–96.
47. Weissman MM, Bland RC, Canino GJ, et al. Cross-national epidemiology of major depression and bipolar disorder. *JAMA*. 1996;276(4):293–299.
48. Henry MJ, Pasco JA, Nicholson GC, et al. Prevalence of osteoporosis in Australian women: Geelong Osteoporosis Study. *J Clin Densitom*. 2000; 3(3):261–268.
49. Barth J, Schumacher M, Herrmann-Lingen C. Depression as a risk factor for mortality in patients with coronary heart disease: a meta-analysis. *Psychosom Med*. 2004;66(6):802–813.
50. Nicholson A, Kuper H, Hemingway H. Depression as an aetiologic and prognostic factor in coronary heart disease: a meta-analysis of 6362 events among 146 538 participants in 54 observational studies. *Eur Heart J*. 2006;27(23):2763–2774.
51. Burg MM, Benedetto MC, Rosenberg R, et al. Presurgical depression predicts medical morbidity 6 months after coronary artery bypass graft surgery. *Psychosom Med*. 2003;65(1):111–118.
52. Sullivan MD, LaCroix AZ, Russo JE, et al. Depression and self-reported physical health in patients with coronary disease: mediating and moderating factors. *Psychosom Med*. 2001;63(2):248–256.
53. Kaptein KI, de Jonge P, van den Brink RHS, et al. Course of depressive symptoms after myocardial infarction and cardiac prognosis: a latent class analysis. *Psychosom Med*. 2006;68(5):662–668.
54. Potts MK, Daniels M, Burnam MA, et al. A structured interview version of the Hamilton Depression Rating Scale: evidence of reliability and versatility of administration. *J Psychiatr Res*. 1990;24(4):335–350.
55. Simon GE, Revicki D, VonKorff M. Telephone assessment of depression severity. *J Psychiatr Res*. 1993;27(3):247–252.
56. Stafford L, Jackson HJ, Berk M. Illness beliefs about heart disease and adherence to secondary prevention regimens. *Psychosom Med*. 2008; 70(8):942–948.
57. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The validity of the Mini International Neuropsychiatric Interview (MINI) according to the SCID-P and its reliability. *Eur Psychiatry*. 1997;12(5):232–241.
58. Lecrubier Y, Sheehan DV, Weiller E, et al. The Mini International Neuropsychiatric Interview (MINI.): a short diagnostic structured interview: Reliability and validity according to the CIDI. *Eur Psychiatry*. 1997;12(5):224–231.
59. First M, Spitzer R, Gibbon M, et al. *Structured Clinical Interview for DSM-IV TR Axis I Disorders, Research Version, Non-Patient Edition*. New York: Biometrics Research, New York State Psychiatric Institute; 2002.
60. Spitzer RL, Williams JBW, Gibbon M, et al. *Structured Clinical Interview for DSM-III-R*. Washington, DC: American Psychiatric Press; 1990.
61. World Health Organization. *The Composite International Diagnostic Interview (CIDI) Version 1.0*. Geneva: World Health Organization; 1990.
62. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (MINI): the development and validation of a structured diagnostic psychiatric interview for *DSM-IV* and *ICD*-10. *J Clin Psychiatry*. 1998;59(suppl 20):22–33, quiz 34–57.
63. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983;67(6):361–370.
64. Herrmann C. International experiences with the Hospital Anxiety and Depression Scale—a review of validation data and clinical results. *J Psychosom Res*. 1997;42(1):17–41.
65. Bjelland I, Dahl AA, Haug TT, et al. The validity of the Hospital Anxiety and Depression Scale: an updated literature review. *J Psychosom Res*. 2002;52(2):69–77.
66. Doyle F, McGee HM, De La Harpe D, et al. The Hospital Anxiety and Depression Scale depression subscale, but not the Beck Depression Inventory-Fast Scale, identifies patients with acute coronary syndrome at elevated risk of 1-year mortality. *J Psychosom Res*. 2006;60(5):461–467.

67. Lewin B, Robertson IH, Cay EL, et al. Effects of self-help post-myocardial-infarction rehabilitation on psychological adjustment and use of health services. *Lancet*. 1992;339(8800):1036–1040.
68. Mayou RA, Gill D, Thompson DR, et al. Depression and anxiety as predictors of outcome after myocardial infarction. *Psychosom Med*. 2000; 62(2):212–219.
69. Roberts SB, Bonnici DM, Mackinnon AJ, et al. Psychometric evaluation of the Hospital Anxiety and Depression Scale (HADS) among female cardiac patients. *Br J Health Psychol*. 2001;6(Part 4):373–383.
70. Cheok F, Schrader G, Banham D, et al. Identification, course, and treatment of depression after admission for a cardiac condition: rationale and patient characteristics for the Identifying Depression As a Comorbid Condition (IDACC) project. *Am Heart J*. 2003;146(6):978–984.
71. Strik JJMH, Honig A, Lousberg R, et al. Sensitivity and specificity of observer and self-report questionnaires in major and minor depression following myocardial infarction. *Psychosomatics*. 2001;42(5):423–428.
72. Costa PTJ, McCrae RR. *Revised NEO Personality Inventory (NEO-PI-R) and NEO Five-Factor Inventory (NEO-FFI): Professional Manual*. Odessa, FL: Psychological Assessment Resources; 1992.
73. Goldberg L. A broad-bandwidth, public-domain personality inventory measuring the lower-level facets of several five-factor models. In: Mervielde I, Deary I, De Fruyt F, et al, eds. *Personality Psychology in Europe*. Tilburg, United Kingdom: Tilburg University Press; 1999.
74. Goldberg L. International Personality Item Pool. 2001; http://ipip.ori.org. Accessed September 21, 2010.
75. Eysenck S, Eysenck H, Barrett P. A revised version of the psychoticism scale. *Pers Individ Dif*. 1985;6(1):21–29.
76. Gow AJ, Whiteman MC, Pattie A, et al. Goldberg's 'IPIP' Big-Five factor markers: Internal consistency and concurrent validation in Scotland. *Pers Individ Dif*. 2005;39(2):317–329.
77. Buchanan T, Johnson J, Goldberg L. Implementing a five-factor personality inventory for use on the internet. *Eur J Psychol Assess*. 2005;21(2): 115–127.
78. Ware JE, Snow KK, Kosinski M, et al. *SF-36 Health Survey: Manual and Interpretation Guide*. Boston, MA: The Health Institute, New England Medical Centre; 1993.
79. Campeau L. The Canadian Cardiovascular Society grading of angina pectoris revisited 30 years later. *Can J Cardiol*. 2002;18(4):371–379.
80. Dolgin M. *Nomenclature and Criteria for the Diagnosis of Diseases of the Heart and Great Vessels*. 9th ed. Boston, MA: Little, Brown & Co; 1994.
81. Stafford L, Berk M, Jackson HJ. Validity of the Hospital Anxiety and Depression Scale and Patient Health Questionnaire-9 to screen for depression in patients with coronary artery disease. *Gen Hosp Psychiatry*. 2007; 29(5):417–424.
82. Sakamoto T, Kojima S, Ogawa H, et al; MUSASHI-AMI Investigators. Usefulness of hydrophilic vs lipophilic statins after acute myocardial infarction: subanalysis of MUSASHI-AMI. *Circ J*. 2007;71(9):1348–1353.
83. Rudisch B, Nemeroff CB. Epidemiology of comorbid coronary artery disease and depression. *Biol Psychiatry*. 2003;54(3):227–240.
84. Horsten M, Wamala SP, Vingerhoets A, et al. Depressive symptoms, social support, and lipid profile in healthy middle-aged women. *Psychosom Med*. 1997;59(5):521–528.
85. Morgan RE, Palinkas LA, Barrett-Connor EL, et al. Plasma cholesterol and depressive symptoms in older men. *Lancet*. 1993;341(8837):75–79.
86. Partonen T, Haukka J, Virtamo J, et al. Association of low serum total cholesterol with major depression and suicide. *Br J Psychiatry*. 1999; 175(3):259–262.
87. Bots S, Tijhuis M, Giampaoli S, et al. Lifestyle- and diet-related factors in late-life depression—a 5-year follow-up of elderly European men: the FINE study. *Int J Geriatr Psychiatry*. 2008;23(5):478–484.
88. Modai I, Valevski A, Dror S, et al. Serum cholesterol levels and suicidal tendencies in psychiatric inpatients. *J Clin Psychiatry*. 1994; 55(6):252–254.
89. Maes M, Smith R, Christophe A, et al. Lower serum high-density lipoprotein cholesterol (HDL-C) in major depression and in depressed men with serious suicidal attempts: relationship with immune-inflammatory markers. *Acta Psychiatr Scand*. 1997;95(3):212–221.
90. Jow GM, Yang TT, Chen CL. Leptin and cholesterol levels are low in major depressive disorder, but high in schizophrenia. *J Affect Disord*. 2006;90(1):21–27.
91. Wells KB, Stewart A, Hays RD, et al. The functioning and well-being of depressed patients: results from the Medical Outcomes Study. *JAMA*. 1989;262(7):914–919.
92. Bovbjerg VE, McCann BS, Retzlaff BM, et al. Effect of cholesterol-lowering diets on indices of depression and hostility. *Ann Behav Med*. 1999;21(1):98–101.