You have been assigned to literature critique session #5, Wednesday, 12/2/09, at 3:00 p.m. Individual paper assignments are given below. Electronic versions of the papers can be found on the course website under the heading of “TA Handouts.” Remember, in addition to organizing and writing a critique of your assigned paper, you must come prepared to discuss all of the papers that will be presented during your session - at the very least, you must read all four papers included in this packet. If you have any questions, please let me know.

Best regards,
John

Michael Okura -
“Factors Associated With Racial Differences in Myocardial Infarction Outcomes”

Adrienne Victor -
“Anaplastic Large-Cell Lymphoma in Women with Breast Implants”

Pavni Mehrotra -
“Omega-3 Fatty Acid Supplementation Effects on Weight and Appetite in Patients with Alzheimer’s Disease: The Omega-3 Alzheimer’s Disease Study”

Yunhee Im -
“Selective Serotonin Reuptake Inhibitors and Risk of Suicide: A Systematic Review of Observational Studies”
Factors Associated With Racial Differences in Myocardial Infarction Outcomes

John A. Spertus, MD, MPH; Philip G. Jones, MD; Frederick A. Masoudi, MD, MSPH; John S. Rumsfeld, MD, PhD; and Harlan M. Krumholz, MD, SM*

Background: Little information is available about factors associated with racial differences across a broad spectrum of post-myocardial infarction outcomes, including patients’ symptoms and quality of life.

Objective: To determine racial differences in mortality, rehospitalization, angina, and quality of life after myocardial infarction and identify the factors associated with these differences.

Design: Prospective cohort study.

Setting: 10 hospitals in the United States.

Patients: 1849 patients who had myocardial infarction, 28% of whom were black.

Measurements: Demographic, economic, clinical, psychosocial, and treatment characteristics and outcomes were prospectively collected. Outcomes included time to 2-year all-cause mortality, 1-year rehospitalization, and Seattle Angina Questionnaire—assessed angina and quality of life.

Results: Black patients had higher unadjusted mortality (19.9% vs. 9.3%; P < 0.001) and rehospitalization rates (45.4% vs. 40.4%; P = 0.130), more angina (28.0% vs. 17.8%; P < 0.001), and worse mean quality of life (80.6 [SD, 22.5] vs. 85.9 [SD, 17.2]; P < 0.001). Adjustment for patient characteristics, black patients trended toward greater mortality (hazard ratio, 1.29 [95% CI, 0.92 to 1.81]; P = 0.142), fewer rehospitalizations (hazard ratio, 0.82 [CI, 0.66 to 1.02]; P = 0.071), and higher likelihood of angina at 1 year (odds ratio, 1.41 [CI, 1.03 to 1.94]; P = 0.032) but similar quality of life (mean difference, −0.6 [CI, −3.4 to 2.2]). Adjustment for site of care further attenuated mortality differences (hazard ratio, 1.04 [CI, 0.71 to 1.52]; P = 0.84). Adjustment for treatments had minimal effect on any association.

Limitation: Residual confounding and missing data may have introduced bias.

Conclusion: Although black patients with myocardial infarction have worse outcomes than white patients, these differences did not persist after adjustment for patient factors and site of care. Further adjustment for treatments received minimally influenced observed differences. Strategies that focus on improving baseline cardiac risk and hospital factors may do more than treatment-focused strategies to attenuate racial differences in myocardial infarction outcomes.

Funding: The National Heart, Lung, and Blood Institute Specialized Center of Clinically Oriented Research in Cardiac Dysfunction and Disease, CV Therapeutics, and Cardiovascular Outcomes.

See also:

Print
Editors’ Notes .................................................. 315
Summary for Patients ................................. I-42

Web-Only
Appendix
Conversion of graphics into slides

Consistent with the national priority of eradicating racial disparities in U.S. health care (1–3), many studies have examined differences in treatment and outcomes between black and white patients with acute coronary syndromes (4–7). Such studies are important for documenting differences in care and disparities in outcomes; however, they have not provided much insight into what patient or treatment characteristics are most associated with the observed differences in outcomes. Although causation is difficult to establish from observational studies, such studies can illuminate patient characteristics or processes of care that attenuate observed disparities in outcomes and form an important basis for the design and testing of subsequent interventions that can minimize such disparities.

Moreover, death and readmission after myocardial infarction are not the only relevant outcomes. From the patient’s perspective, health status (symptoms, function, and quality of life) is equally, or more, important (8–12). Although most previous studies that examined mortality outcomes did not find differences in survival after adjustment for demographic, socioeconomic, clinical, and treatment factors (13–20), the only study to examine health status outcomes found worse fully adjusted 1-year health status outcomes among black patients (21). Underscoring the importance of evaluating the magnitude and mediators of racial differences in outcomes, a recent study of U.S. residents found that health status differences in black patients with and without coronary heart disease were greater than those of white patients, which emphasizes the need for more research to “address predictors and determinants of optimum [health-related quality of life] as a guide to developing interventions aimed at minimizing impairments in . . . health status” (22).

Achieving racial equity in outcomes requires research to illuminate the root cause of observed disparities in outcomes, including factors that explain the differences. We
conducted a multicenter observational study to investigate racial differences in outcomes, including health status, in the year after acute myocardial infarction. We further analyzed patient, hospital, and treatment characteristics that may mediate the association between race and outcome to determine potential factors that might account for observed disparities and to serve as a foundation for future studies that seek to eradicate such disparities.

**METHODS**

**Patient Population**

A detailed discussion of the purpose, conceptual framework of data collection, patient selection, generalizability, and site characteristics of PREMIER (Prospective Registry Evaluating Myocardial Infarction: Events and Recovery) has been published (23). Patients were eligible for participation if they were age 18 years or older, had myocardial infarction, and were admitted to 1 of 19 hospitals with biochemical evidence of myocardial necrosis and prolonged (>20 minutes) symptoms of myocardial ischemia or diagnostic electrocardiography changes. An institutional review board at each participating center approved the study, and patients gave signed informed consent for baseline and follow-up interviews. We restricted our analyses to white and black patients and included only the 10 centers that enrolled at least 10 patients in each racial group. In addition, we excluded patients who died during the initial hospitalization in order to focus on long-term outcomes as a target for future quality improvement efforts.

**Data Collection**

During the index myocardial infarction admission, trained data collectors performed chart abstractions and a detailed baseline patient interview that included the patient’s self-identified racial category, our primary independent variable. Racial categories mirrored the classifications used by the Congressional Office of Management and Budget. The PREMIER was designed to quantify a broad range of potential mediators of outcomes, including demographic characteristics, patients’ health, economic and psychosocial status, comorbid medical conditions, disease severity, site, treatments (both quality of care [24] and invasive procedures), discharge medications, and discharge instructions (Table). For such domains as depression (25), optimism (26, 27), social support (28, 29), and economic status (30), validated instruments were used (23).

**Outcome Assessment**

Telephone interviews were conducted at 1, 6, and 12 months. Interviews included the Seattle Angina Questionnaire (SAQ), a 19-item health status measure that quantifies a patient’s coronary artery disease–specific health status, including frequency of angina and quality of life (31, 32). Scores on these domains range from 0 to 100, with higher scores representing fewer symptoms and better quality of life. The SAQ is valid, reliable, responsive, and prognostic of subsequent mortality and acute coronary syndromes (33). In addition, the interviewers asked about interval hospitalizations since the patient’s last contact. Mortality was assessed through the Social Security Administration Death Master File as of 30 June 2006.

**Statistical Analysis**

We compared 59 patient, hospital, and treatment factors between black and white patients, classified into 11 domains (Table) according to 3 phases of myocardial infarction care: patient characteristics present before seeking care (demographic characteristics, socioeconomic status, social support, medical history, psychological factors, and disease severity), the presenting hospital, and processes of care received in hospital (invasive treatments, quality of care performance measures, discharge medications, and discharge instructions). We assessed 4 outcomes: time to mortality from any cause through 2 years, time to rehospitalization for any cause through 1 year, presence of angina at 1 year (defined by an SAQ Angina Frequency score <100), and 1-year SAQ Quality of Life score. We compared continuous variables by using t tests and categorical variables by using chi-square tests. We summarized time to mortality and rehospitalization by using Kaplan–Meier methods and compared them by using log-rank tests.

We evaluated the contribution of each of the 11 domains to observed racial differences in outcomes by sequential, cumulative adjustment. In the first step, we adjusted only for demographic characteristics; in the second, for demographic characteristics and socioeconomic status; and so on up to the final step, in which we simultaneously adjusted for all domains. Comparing the adjusted race estimates between adjacent steps thus indicates the incre-

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**Context**

Substantial evidence documents that black patients fare worse than white patients after myocardial infarction. However, evidence is lacking about factors associated with these differences.

**Contribution**

This study examined mortality, rehospitalization, angina, and quality of life in 1849 patients with myocardial infarction at 10 U.S. hospitals. Adjustment for hospital and patient characteristics, such as cardiac risk factors, eradicated significant black–white disparities in outcomes that were present in unadjusted analyses. Treatments received did not explain disparities.

**Implication**

Strategies to improve patient and hospital factors could help to reduce ethnic disparities in myocardial infarction outcomes. Disparities do not seem to be caused by black patients receiving different treatments than white patients.

—The Editors
mental contribution of a given domain after adjustment for all previous variables (for example, the contribution of the presenting hospital after adjustment for all patient factors). We designed the order of the domains to reflect the temporal relationship of the factors, adjusting first for patient characteristics, then location of care, and finally processes of care.

We used propensity score methods to perform the adjustments. At each step, we estimated propensity scores for being black by using nonparsimonious logistic regression on all variables up to and including the current domain. We entered continuous variables into the propensity model nonlinearly by using restricted cubic splines. We evaluated overlap of propensity scores between groups by using histograms and scatterplots. We examined 3 methods of adjusting for propensity score: regression (inclusion of the propensity scores as a covariate in the outcome models), stratification by first digit of the propensity score, and matching. For regression adjustment, we used the logit of the propensity score and allowed for nonlinearity by using restricted cubic splines. For matching, we used the method of optimal full matching implemented in the R package optmatch (R, Foundation for Statistical Computing, Vienna, Austria), which allows for a variable number of black and white patients in matched strata (34, 35). We matched on the logit of the propensity score by using a caliper width of 0.2 times the pooled standard deviation of the logits (36). Of these 3 methods, regression adjustment had the best balancing properties, as assessed by adjusted chi-square values and $P$ values for each of the 59 covariates on race (mean $P = 0.92$ [range, 0.37 to 0.99] vs. 0.90 [range, 0.41 to 0.99] for stratification and 0.79 [range, 0.23 to 0.99] for matching in the final model). Furthermore, even though stratification and matching yielded similar results to those obtained by using regression adjustment, they also produced more erratic race effect estimates from step to step because of the variability in the matched or stratified groups obtained at each step. We therefore chose regression adjustment as our primary method of analysis.

We estimated race effects (black vs. white) by using proportional hazards models for time to mortality and time to rehospitalization, logistic regression for angina, and linear models for SAQ Quality of Life score. We included the propensity score as a covariate at each step of adjustment. For the angina and quality of life models, we also included the associated baseline SAQ score.

The first 6 adjustment steps included patient-related factors only, not location or processes of care, and thus represent population-average estimates of racial differences across all sites in the study. We used robust standard errors to account for within-site correlations. Beginning with the seventh step, all models adjusted for hospital by using stratified proportional hazards regression for mortality and rehospitalization, conditional logistic regression for angina, and a hierarchical linear model for quality of life, including within-center effects for race. Thus, the race effect estimates in the last 5 steps (presenting hospital, invasive treatments, quality of care, discharge medications, and discharge instructions) are hospital-specific (37).

Because previous research (38, 39) has documented the association of lower socioeconomic status (which is known to be more prevalent in black patients with myocardial infarction) with worse clinical outcomes, we repeated our analyses using only patients with a self-reported annual household income less than $30 000 and formally tested race-by-income interaction terms in the entire cohort. We also replicated the analyses while stratifying by type of myocardial infarction (ST-segment elevation vs. non–ST-segment elevation) and found no differences compared with the primary analysis.

Approximately 39% of patients had missing covariate data (26% were missing 1 value, 10% were missing 2 values, and 3% were missing 3 or more values; the highest missing rate for any single variable was 14%). Twenty-two percent of the 1-year assessments were incomplete because the patient died (8%), declined to participate (3%), or was lost to follow-up (11%). To correct for biases due to observed factors, we used multiple imputation methods in all analyses, incorporating all variables listed in the Table; site of enrollment; 1-, 6-, and 12-month health status scores; rehospitalization; and death during follow-up. We generated 10 imputed data sets, replicated our analyses on each, and pooled the results. The primary analyses presented here include imputation of baseline covariates but are restricted to patients with complete follow-up data. We also conducted sensitivity analyses that included full imputation of all baseline and outcome data; these yielded results that were similar to those presented.

We used SAS, version 9.1.3 (SAS Institute, Cary, North Carolina), and R, version 2.7.0, to conduct our analyses. All analyses were prespecified, and a 2-sided $P$ value less than 0.05 was considered statistically significant.

Role of the Funding Source

This study was supported by the National Heart, Lung, and Blood Institute Specialized Center of Clinically Oriented Research in Cardiac Dysfunction and Disease (grant no. P50 HL077113); CV Therapeutics, Palo Alto, California; and Cardiovascular Outcomes, Kansas City, Missouri. The study was designed, executed, analyzed, interpreted, and reported by the investigators without input from the sponsors.

Results

Between 1 January 2003 and 28 June 2004, we prospectively screened 2498 patients with myocardial infarction and enrolled them into PREMIER. We excluded 129 patients of other or unknown race, as well as sites that enrolled fewer than 10 black or 10 white patients (9 sites, comprising 491 white patients and 15 black patients). In addition, we excluded 14 patients (0.8%; 1 black and 13
### Table. Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>White Patients</th>
<th>Black Patients</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD), y</td>
<td>61.7 (12.9)</td>
<td>57.3 (13.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>White Patients (n = 1335)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black Patients (n = 514)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>942 (70.6)</td>
<td>283 (55.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Socioeconomic status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school education, n (%)</td>
<td>1078 (82.3)</td>
<td>309 (61.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Health insurance, n (%)</td>
<td>1158 (90.5)</td>
<td>369 (77.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Insurance coverage for medications, n (%)</td>
<td>1026 (78.0)</td>
<td>325 (64.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Monthly financial situation</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Some money left over</td>
<td>768 (60.4)</td>
<td>137 (27.8)</td>
<td></td>
</tr>
<tr>
<td>Just enough to make ends meet</td>
<td>363 (28.6)</td>
<td>197 (40.0)</td>
<td></td>
</tr>
<tr>
<td>Not enough to make ends meet</td>
<td>140 (11.0)</td>
<td>159 (32.3)</td>
<td></td>
</tr>
<tr>
<td>Medical costs have been an economic burden, n (%)</td>
<td>367 (27.9)</td>
<td>203 (40.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Have avoided getting health care because of cost, n (%)</td>
<td>230 (17.7)</td>
<td>124 (24.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Have not taken medication because of cost, n (%)</td>
<td>156 (11.9)</td>
<td>103 (20.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Social support</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married, n (%)</td>
<td>897 (68.0)</td>
<td>178 (35.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean ENRICHD social support score (SD)</td>
<td>29.7 (5.5)</td>
<td>28.4 (6.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Psychological status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Patient Health Questionnaire depression score (SD)</td>
<td>5.2 (5.2)</td>
<td>6.7 (6.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean Life Orientation Test-Revised optimism score (SD)</td>
<td>15.9 (3.7)</td>
<td>15.3 (3.4)</td>
<td>0.004</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean body mass index (SD), kg/m²</td>
<td>29.2 (6.4)</td>
<td>29.1 (7.1)</td>
<td>0.87</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>335 (25.1)</td>
<td>207 (40.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic heart failure, n (%)</td>
<td>109 (8.2)</td>
<td>135 (26.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic lung disease, n (%)</td>
<td>188 (14.1)</td>
<td>79 (15.4)</td>
<td>0.48</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>431 (32.6)</td>
<td>208 (41.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic renal failure, n (%)</td>
<td>79 (5.9)</td>
<td>138 (26.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Arthritis, n (%)</td>
<td>166 (12.4)</td>
<td>61 (11.9)</td>
<td>0.74</td>
</tr>
<tr>
<td>Cancer (other than skin), n (%)</td>
<td>114 (8.5)</td>
<td>29 (5.6)</td>
<td>0.037</td>
</tr>
<tr>
<td>Family history of coronary artery disease, n (%)</td>
<td>490 (36.7)</td>
<td>135 (26.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>801 (60.0)</td>
<td>406 (79.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>681 (51.0)</td>
<td>212 (41.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of vascular disease, n (%)</td>
<td>428 (32.1)</td>
<td>181 (35.2)</td>
<td>0.196</td>
</tr>
<tr>
<td>Previous cerebrovascular accident, n (%)</td>
<td>15 (0.9)</td>
<td>57 (11.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Disease severity</td>
<td></td>
<td></td>
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<tr>
<td>Mean estimated glomerular filtration rate on admission (SD), mL/min per 1.73 m²</td>
<td>40.4 (5.8)</td>
<td>38.4 (6.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean glucose level on admission (SD)</td>
<td>8.3 (4.1)</td>
<td>8.8 (5.8)</td>
<td>0.047</td>
</tr>
<tr>
<td>Mean heart rate on admission (SD), beats/min</td>
<td>79.1 (20.3)</td>
<td>85.9 (22.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean hemoglobin on admission (SD), g/dL</td>
<td>149.4 (74.3)</td>
<td>158.1 (104.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Mean international normalized protein (SD), %</td>
<td>40.4 (5.8)</td>
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<td>Mean systolic blood pressure on admission (SD), mm Hg</td>
<td>136.7 (29.5)</td>
<td>143.8 (33.5)</td>
<td>&lt;0.001</td>
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<tr>
<td>Mean estimated glomerular filtration rate on admission (SD), mL/min per 1.73 m²</td>
<td>74.5 (26.5)</td>
<td>68.3 (38.0)</td>
<td>&lt;0.001</td>
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<td>Mean hematocrit on admission (SD), %</td>
<td>40.4 (5.8)</td>
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</tbody>
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Factors Associated With Racial Differences in Myocardial Infarction Outcomes

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Table—Continued

<table>
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<th>White Patients (n = 1335)</th>
<th>Black Patients (n = 514)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Quality of care†</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin within 24 hours, n (%)</td>
<td>1270 (97.3)</td>
<td>479 (96.2)</td>
<td>0.21</td>
</tr>
<tr>
<td>β-Blocker within 24 hours, n (%)</td>
<td>1139 (93.7)</td>
<td>406 (89.8)</td>
<td>0.006</td>
</tr>
<tr>
<td>Acute reperfusion§, n (%)</td>
<td>527 (74.9)</td>
<td>79 (46.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aspirin at discharge, n (%)</td>
<td>1237 (95.3)</td>
<td>434 (89.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>β-Blocker at discharge, n (%)</td>
<td>1188 (93.3)</td>
<td>403 (88.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ACE inhibitor or angiotensin-receptor blocker for left ventricular systolic dysfunction at discharge, n (%)</td>
<td>303 (90.4)</td>
<td>121 (81.8)</td>
<td>0.007</td>
</tr>
<tr>
<td>Smoking cessation counseling, n (%)</td>
<td>352 (76.5)</td>
<td>122 (58.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean eligible quality-of-care indicators (SD), n</td>
<td>89.4 (15.0)</td>
<td>83.6 (20.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean eligible quality-of-care indicators received (SD), %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Other discharge medications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statin, n (%)</td>
<td>1110 (83.1)</td>
<td>371 (72.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Thienopyridine, n (%)</td>
<td>1002 (75.1)</td>
<td>249 (48.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diuretic, n (%)</td>
<td>237 (17.8)</td>
<td>150 (29.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nitrate, n (%)</td>
<td>352 (26.4)</td>
<td>192 (37.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Discharge instructions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discharge medication instructions, n (%)</td>
<td>1197 (89.7)</td>
<td>458 (89.1)</td>
<td>0.73</td>
</tr>
<tr>
<td>Whom to call if symptoms worsen, n (%)</td>
<td>912 (68.3)</td>
<td>341 (66.3)</td>
<td>0.42</td>
</tr>
<tr>
<td>Exercise counseling, n (%)</td>
<td>817 (61.2)</td>
<td>168 (32.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diet counseling, n (%)</td>
<td>1071 (80.2)</td>
<td>395 (76.8)</td>
<td>0.108</td>
</tr>
<tr>
<td>Follow-up appointment scheduled, n (%)</td>
<td>1275 (95.5)</td>
<td>487 (94.7)</td>
<td>0.49</td>
</tr>
</tbody>
</table>

ACE = angiotensin-converting enzyme; ENRICHED = ENHanced Recovery In Coronary Heart Disease; TIMI = Thrombolyis in Myocardial Infarction.

* <0.05.
† Myocardial infarction, percutaneous coronary intervention, or coronary artery bypass grafting.
‡ Among patients eligible for each measure.
§ Among patients with ST-segment elevation myocardial infarction.

white) who died in the hospital. Thus, the present analyses include 1849 patients with myocardial infarction from 10 centers, of whom 514 (27.8%) were black (range, 5% to 93% per site).

The Table shows the differences in patient and treatment characteristics between white and black patients. On average, black patients were younger, were more likely to be female, had more comorbid conditions, were more likely to present with non–ST-segment elevation myocardial infarction, and had worse socioeconomic and psychosocial status than white patients. Black patients were also less likely to be treated with current quality of care indicators and invasive therapy.

Two-year survival status was available for 99% of patients, and mean follow-up time was 26 months (SD, 8 months). Unadjusted Kaplan–Meier estimates of 2-year mortality were 19.9% for black patients versus 9.3% for white patients, and the crude hazard ratio (HR) was 2.31 (CI, 1.77 to 3.00) (Figure, A). The HR decreased to 1.29 (CI, 0.92 to 1.81) after we adjusted for patient factors and was nearly completely attenuated after we adjusted for presenting hospital (HR, 1.04 [CI, 0.71 to 1.52]). In-hospital treatments had no further influence on racial differences in mortality (fully adjusted HR, 0.98 [CI, 0.67 to 1.43]). Although adjustment for demographic characteristics slightly increased the estimated mortality risk in black patients because of their younger age, the 2 most significant shifts in the risk estimates (attenuations of racial differences in mortality) occurred when we adjusted for comorbid medical conditions and presenting hospital.

Unadjusted Kaplan–Meier estimates of 1-year rehospitalization rates were 45.4% for black patients versus 40.4% for white patients (HR, 1.14 [CI, 0.96 to 1.36]) (Figure, B). After adjustment for patient factors, however, black patients were less likely than white patients to be hospitalized within 1 year (HR, 0.82 [CI, 0.66 to 1.02]). Socioeconomic status and comorbid medical conditions were associated with the largest attenuations. Neither the presenting hospital nor treatment had much effect on racial differences in rehospitalization rates (fully adjusted HR, 0.78 [CI, 0.61 to 0.99]).

In unadjusted analyses, black patients were significantly more likely than white patients to have angina 1 year after myocardial infarction (28.0% vs. 17.8%; odds ratio [OR], 1.80 [CI, 1.35 to 2.39]) (Figure, C). The risk was similar after we adjusted for angina at baseline (SAQ Angina Frequency score) (OR, 1.74 [CI, 1.41 to 2.16]). Adjusting for patient factors attenuated the difference by about 40% (OR, 1.41 [CI, 1.02 to 1.95]), which mostly persisted even after adjustment for hospital and treatments, although the fully adjusted effect was not statistically significant (OR, 1.32 [CI, 0.88 to 1.99]). We observed the largest attenuation after we adjusted for racial differences in socioeconomic status.

The mean unadjusted 1-year quality of life of black patients was significantly worse than that of white patients
(SAQ Quality of Life score, 80.6 [SD, 22.5] vs. 85.9 [SD, 17.2]; mean difference, −5.3 [CI, −7.6 to −2.9]) (Figure, D). The difference was similar after we adjusted for baseline quality of life (mean, −3.8 [CI, −6.0 to −1.5]). Patient factors accounted for most of the difference (adjusted mean difference, −0.6 [CI, −3.4 to 2.2]), and further adjustment for hospital and treatments did not influence this (fully adjusted mean difference, −1.2 [CI, −4.2 to 1.8]). Demographic characteristics and socioeconomic status attenuated racial differences in quality of life the most.

Given the importance of socioeconomic status in attenuating the unadjusted racial differences in outcomes, we conducted a secondary analysis restricted to the 625 patients (260 black and 365 white) with a self-reported an-
annual household income less than $30,000. The unadjusted differences in outcomes in this cohort were nearly identical to those observed in the overall population. Specifically, the 2-year mortality rate was 21.5% for black patients versus 10.4% for white patients (HR, 2.19 [CI, 1.45 to 3.31]), the rehospitalization rate was 51.5% versus 45.1% (HR, 1.10 [CI, 0.85 to 1.43]), the rate of angina at 1 year was 32.5% versus 21.8% (OR, 1.73 [CI, 1.12 to 2.67]), and the mean 1-year SAQ Quality of Life score was 78.5 (SD, 22.6) versus 83.5 (SD, 19.8) (mean difference, −5.0 [CI, −9.1 to 0.8]). Fully adjusted models showed a trend toward greater residual mortality among black patients (HR, 1.49 [CI, 0.80 to 2.75]), as well as significant residual angina (OR, 1.96 [CI, 1.03 to 3.75]), although no outcome showed a significant race-by-income interaction in the overall cohort (P > 0.26 for all).
Black patients were significantly more likely than white patients to have incomplete 1-year assessments (37.2% vs. 16.4%; \( P < 0.001 \)), primarily because of greater 1-year mortality (14.2% vs. 5.5%) and losses to follow-up (19.1% vs. 7.9%). To examine the effect of incomplete follow-up on racial differences in rehospitalization and health status outcomes (we established death on the basis of Social Security Number queries, which were 99% complete), we expanded our multiple imputation analyses to include imputation of outcomes as well. In these fully imputed analyses, the odds ratios for angina at 1 year among black versus white patients were similar to those in the complete data cohort: 2.26 (CI, 1.68 to 3.04) unadjusted, 1.41 (CI, 1.03 to 1.94) after adjustment for patient factors, and 1.20 (CI, 0.87 to 1.66) after full adjustment. Quality of life and rehospitalization results were nearly identical to those among patients with complete 1-year assessments.

**DISCUSSION**

We found that black patients had higher crude rates of death and rehospitalization, greater frequency of angina, and worse quality of life after myocardial infarction than did white patients. The unadjusted outcome differences were clinically significant and demonstrate that, on average, black patients bear a disproportionate burden of adverse outcomes after myocardial infarction. We also determined that the characteristics and treatment of black and white patients differ significantly. After full adjustment for these differences, black patients had similar mortality, quality of life, and frequency of angina and a trend toward lower rates of rehospitalization. In general, the outcome differences between black and white patients were most attenuated by adjusting for patient characteristics present before admission (such as socioeconomic status and comorbid conditions) and were only marginally affected by adjusting for differences in treatment. Our findings suggest that racial disparities in outcome are associated with a myriad of racial differences in risk factors for adverse outcomes and that focusing on the processes of care for myocardial infarction may not be the most effective strategy for achieving equity in outcomes.

In contrast to the racial disparities in other outcomes, we also found that the admitting hospital explained nearly all of the residual racial differences in 2-year mortality after we adjusted for patient characteristics—an effect described by Skinner and colleagues (40). Although this may be attributable to unmeasured patient characteristics that vary by region, it may also indicate unmeasured variations in hospital quality and performance or disparities in outpatient management. Larger multicenter studies should further explore between-center differences in care that may be modified to improve racial disparities in mortality.

Our study expands the traditional outcomes used to evaluate racial disparities by including assessments of patients’ symptoms and quality of life. Whereas previous studies of racial disparities have focused on survival (13–20), patients are often equally, if not more, interested in their symptoms, function, and quality of life (9, 10, 41–43). We demonstrate that not only do black patients with myocardial infarction have poorer survival rates, but those who do survive are more likely to have angina and worse quality of life after myocardial infarction. The persistent disparities in quality of life that we observed in a previous study (21) were attenuated in this multicenter study, which included more centers and a broader spectrum of characteristics that differ by race. Fortunately, several interventions exist to improve the health status of patients with coronary artery disease (44–46). In particular, the recent results of the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial (44) suggest that optimal medical therapy, with or without revascularization, can have a dramatic effect on improving symptoms and quality of life in patients with chronic angina. Although this study did not explicitly examine differences in access to care after myocardial infarction discharge, for which black and white patients are known to differ (47–49), it seems logical that following patients after myocardial infarction for persistent symptoms or diminished quality of life could identify candidates for more intensive treatment and potentially reduce the unadjusted differences in health status that we observed.

An observational study cannot conclusively demonstrate causation when associating a patient’s characteristics with outcomes. This is particularly true for race, which could be a marker for a myriad of potential risk factors that contribute to outcomes after a myocardial infarction. After sequentially adjusting for a broad range of clinical, socioeconomic, and psychosocial differences between black and white patients who had myocardial infarction, we found few residual disparities in outcome, which suggests that the worse outcomes of black patients can probably be attributed to a greater prevalence of other risk factors for poorer outcomes rather than to an inherent characteristic of race itself. Because some of these patient characteristics (such as socioeconomic disparities or comorbid conditions) may be partially attributable to race, these analyses illuminate potential explanations for the observed differences in outcomes rather than to provide unconfounded estimates of the effect of race on outcome. For example, it has been noted that poor socioeconomic status is both more prevalent among black persons and associated with worse outcome (38, 39). Because lower socioeconomic status may be associated with poorer access to care or adherence to secondary prevention, it is possible that improving access and adherence may reduce racial disparities in outcomes. However, even among patients in the lowest economic class, black patients had worse unadjusted survival, angina control, and quality of life than similarly disadvantaged white patients, which suggests that racial differences, even among the poorest patients, will require additional interventions to achieve equity.

Our study suggests that no single omission in the care offered black patients would, if overcome, eradicate the
Factors Associated With Racial Differences in Myocardial Infarction Outcomes

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We conducted a multi-center study to examine differences in patient characteristics and outcomes between black and white patients who underwent myocardial infarction. We used propensity-based methods to balance the differences in characteristics between black and white patients. We found that the distributions of the estimated propensity scores exhibited increasing degrees of nonoverlap between black and white patients. We added additional variables, from 0.5% of black or white patients who could not be matched with a member of the opposite race in the first step (demographic characteristics only) to 17% in the final step that included all variables. This reflects the marked differences in patient characteristics between racial groups. We retained all patients throughout each of our analyses by performing regression adjustment on propensity scores to maximize the generalizability of our findings. A consequence of this approach is the extrapolation of effects—the assumption that our observed results apply equally to patients with nonoverlapping propensity scores. Although we cannot conclusively test this assumption, we detected no significant interaction between propensity score and race for any outcome, which suggests that the effects of race on outcome may be similar throughout the range of patients.

In conclusion, we found significant racial differences in observed outcomes. Previous investigators (4–7) have extensively documented racial differences in the use of invasive treatments; however, adjustment for these procedures had little effect on the relative risk for adverse outcomes among black patients. Although a recent study (50) suggested that differences in the transfer of black Medicare patients and the use of revascularization may account for the adverse mortality observed among black patients, that investigation, which was based on administrative claims data, could not include the depth of clinical and socioeconomic data of our prospectively conducted study. Given the importance of socioeconomic status and comorbid medical conditions in attenuating the racial differences in outcomes that we observed, further research is needed to identify the mechanisms of these associations and achieve greater equity in clinical outcomes. For example, interventions directed at primary prevention and prevention of comorbid conditions, such as diabetes and renal disease, may be effective in minimizing observed racial disparities in outcomes. Therefore, although we do not address the complexity of integrating socioeconomic and clinical considerations when selecting care for individual patients, we suggest that public policies that merely address in-hospital treatments may not achieve their desired intent of eliminating disparities in outcomes.

Several aspects of our study warrant consideration when interpreting the results. A fair comparison of the outcomes of black and white patients requires adjustment for characteristics that differ between these populations. We used propensity-based methods to balance the differences in characteristics between black and white patients (36, 51–54). We found, however, that the distributions of the 11 estimated propensity scores exhibited increasing degrees of nonoverlap between black and white patients as we added additional variables, from 0.5% of black or white patients who could not be matched with a member of the opposite race in the first step (demographic characteristics only) to 17% in the final step that included all variables. This reflects the marked differences in patient characteristics between racial groups. We retained all patients throughout each of our analyses by performing regression adjustment on propensity scores to maximize the generalizability of our findings. A consequence of this approach is the extrapolation of effects—the assumption that our observed results apply equally to patients with nonoverlapping propensity scores. Although we cannot conclusively test this assumption, we detected no significant interaction between propensity score and race for any outcome, which suggests that the effects of race on outcome may be similar throughout the range of patients.

Another important potential limitation is that follow-up was not complete for all patients, and black patients were less likely than white patients to participate in the 1-year interviews. When we used multiple imputation to examine biases in outcomes, however, we found similar crude and adjusted differences between black and white patients for frequency of angina and quality of life. This suggests minimal bias due to observed patient characteristics and outcomes, although it does not rule out biases due to unmeasured variables associated with both incomplete follow-up and patient health status outcomes. An additional potential concern is that we included patients from only 10 centers; although they were well distributed geographically, few were rural centers or small-volume hospitals. Although we found no differences in the unadjusted differences between black and white patients across our hospitals, site is known to be associated with both race and outcomes (40), and our findings may not be applicable to the entire United States. In addition, our analyses do not include racial differences in postdischarge care. Although we found little residual difference in outcomes after we adjusted for presenting clinical profile, future efforts to quantify the processes of post–myocardial infarction care could be important. Finally, even though we used each patient’s self-designation of race, heterogeneity and misclassification certainly occurred when assigning patients to the white or black racial groups (55).

In conclusion, we found significant racial differences in a broad spectrum of outcomes that were attenuated after adjustment for patient factors that differed by race. Given that we observed few differences between black and white patients after adjusting for patient factors before presentation and site of care, it is unlikely that altering the processes of care alone would overcome the unadjusted differences in outcomes. Further research is needed to determine how best to address these patient-centered factors and achieve the goal of equity in U.S. health care (1, 3).

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Reproducible Research Statement: Study protocol, statistical code, and data set: Available from Dr. Spertus (SpertusJ@umkc.edu).

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APPENDIX: PARTICIPATING CARDIOVASCULAR OUTCOMES RESEARCH CONSORTIUM SITES AND INVESTIGATORS

Mid America Heart Institute, Kansas City, Missouri: John Spertus, MD, MPH; Carole Decker, RN, PhD; Philip Jones, MS; and Kimberly Reid, MS.

Baptist Health System, Little Rock, Arkansas: Gary Collins, MD.

Barnes Jewish Hospital and Washington University, St. Louis, Missouri: Richard Bach, MD.

Beth Israel-Deaconess Medical Center and Harvard University, Boston, Massachusetts: David Cohen, MD, MSc.

Denver General Health System, Denver, Colorado: Edward Havranek, MD, and Frederick Masoudi, MD, MSPH.

Denver Veterans Affairs Medical Center, Denver, Colorado: John Rumsfeld, MD, PhD.

Duke University, Durham, North Carolina: Eric Peterson, MD, MPH.

Emory University, Atlanta, Georgia: Susmita Parashar, MD; Viola Vaccarino, MD, PhD; and William S. Weintraub, MD.

Henry Ford Medical Center, Detroit, Michigan: Sanjaya Khanal, MD, Jane Jie Cao, MD, MPH.

Kaiser Permanente, Denver, Colorado: David Magid, MD, MPH.

MeritCare, Fargo, North Dakota: Wallace Radke, MD, and Mohamed Rahman, MD.

Sentara Health System (both Sentara and Sentara Lee Hospitals), Norfolk, Virginia: John E. Brush, Jr., MD.

Stanford University and Palo Alto Veterans Affairs Medical Center, Palo Alto, California: Paul Heidenreich, MD.

Swedish Medical Center, Seattle, Washington: Timothy Dewhurst, MD.

Truman Medical Center and the University of Missouri–Kansas City, Kansas City, Missouri: Annette Quick, MD.

University of Alabama, Birmingham, Alabama: John Canto, MD.

University of Colorado Health System, Denver, Colorado: John Messenger, MD.

Yale University, New Haven, Connecticut: Harlan Krumholz, MD, SM.
Anaplastic Large-Cell Lymphoma in Women With Breast Implants

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Wies L. E. Vasmel, MD, PhD  
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Ellis Barbé, MD  
Mariel K. Casparie, MD, PhD  
Flora E. van Leeuwen, PhD

Since the late 1970s, silicone breast implants have been under constant challenge for suspected association with systemic disease and malignancy.¹⁻⁴ Although no health risk had been proven, the use of silicone-filled breast implants was banned by the US Food and Drug Administration in 1992. Saline-filled, silicone-covered implants stayed on the market. Also with these implants, contracture and rupture are frequent events, and interference with breast cancer detection may be a problem. Large observational epidemiological studies in populations in Canada and Sweden have not shown consistent associations with breast cancer or other specific cancer sites or with autoimmune disease.⁵⁻⁶

Several cases of non-Hodgkin lymphoma in women with breast implants have been described. Of these, the majority were anaplastic large-cell lymphoma (ALCL), negative for anaplastic lymphoma kinase (ALK-negative). Only a single case of follicular lymphoma, 1 of lymphoplasmacytic lymphoma, and 1 of primary effusion lymphoma, human herpesvirus 8-associated, have been reported.⁷⁻¹⁶ In population-based studies, ALCL at all sites represents only 0.5% to 3% of non-Hodgkin lymphoma in adults (eg, 0.6% in the population-based database of the Comprehensive Cancer Center West, 3% in the World Health Organization blue book).¹⁷ Moreover, primary lymphomas of the breast are reported to be predominantly of B-cell type and T-cell lymphomas in general are exceedingly rare. Therefore, an increased risk

**Context**  Recently, we identified 2 patients with anaplastic large T-cell lymphoma (ALCL) negative for tyrosine kinase anaplastic lymphoma kinase (ALK-negative) in the fibrous capsule of silicone breast prostheses, placed for cosmetic reasons. Similar cases have been reported in the literature. Although an increased risk of ALCL in patients with breast prostheses has been speculated, no studies have been conducted so far.

**Objective**  To determine whether ALCL risk is associated with breast prostheses.

**Design**  A search for all patients with lymphoma in the breast diagnosed in the Netherlands between 1990 and 2006 was performed through the population-based nationwide pathology database. Subsequently, we performed an individually matched case-control study. Conditional logistic regression analysis was performed to estimate the relative risk of ALCL associated with breast prostheses.

**Setting and Patients**  Eleven patients with breast ALCL were identified in the registry. For each case patient with ALCL in the breast, we selected 1 to 5 controls with other lymphomas in the breast, matched on age and year of diagnosis. For all cases and controls (n=39), pathological and clinical information was obtained with special emphasis on the presence of a breast prosthesis.

**Main Outcome Measure**  Association between breast implants and ALCL of the breast.

**Results**  The 11 patients with ALCL of the breast were diagnosed between 1994 and 2006 at a median age of 40 years (range, 24-68 years). In 5 of these patients, bilateral silicone breast prostheses had been placed 1 to 23 years before diagnosis. All received prostheses for cosmetic reasons. Lymphoma classes of 35 eligible control patients were 12 diffuse large B-cell lymphomas, including 1 T-cell rich B-cell lymphoma; 5 Burkitt lymphomas; 10 mucosa-associated lymphoid tissue-type lymphoma; 3 follicular lymphomas; 3 peripheral T-cell lymphomas; and 2 indolent B-cell lymphomas, unclassified. One of 35 control patients had a breast implant placed before diagnosis of lymphoma. The odds ratio for ALCL associated with breast prostheses was 18.2 (95% confidence interval, 2.1-156.8).

**Conclusions**  These preliminary findings suggest an association between silicone breast prostheses and ALCL, although the absolute risk is exceedingly low due to the rare occurrence of ALCL of the breast (11 cases in the Netherlands in 17 years). These findings require confirmation in other studies.

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of ALCL in patients with breast prostheses has been speculated. However, to our knowledge, no epidemiological studies examining this association have been conducted so far.

METHODS

We recently observed 2 patients diagnosed with ALCL located in the fibrous capsule of a saline-filled silicone breast implant at primary diagnosis. Reports on similar cases in the literature initiated a comprehensive search to identify all patients with biopsy-proven primary non-Hodgkin lymphoma of the breast diagnosed between 1990 and 2006 in the Netherlands.7,10-16 Since 1971, all reports on cytological and histological diagnoses generated by all pathology departments (academic and nonacademic) in the Netherlands are centrally archived with complete national coverage since 1989.18 Standardized coding allows for anonymized comprehensive searches for specific diagnoses and patient cohorts.

From this population-based database (PALGA, Pathologisch Anatomisch Landelijk Geautomatiseerd Archief), 429 cases were retrieved with a histologically proven diagnosis of lymphoma in the breast between 1990 and 2006 without a previously listed diagnosis of lymphoma at another site (389 women, 40 men). Of the 389 female patients, 11 patients had a diagnosis of ALCL, including the 2 initially observed patients. All histological material was retrieved for confirmation of the diagnosis, additional immunohistochemical analysis, and molecular studies. Information on the complete medical history, including staging results and mammography results, was collected. Immunohistochemistry and immunoglobulin and T-cell receptor rearrangement analyses were performed according to standard methods.19,20

Subsequently, we performed an individually matched case-control study, nested in the same cohort of 389 female patients. For each case patient with ALCL in the breast, we attempted to select 3 to 7 controls with other lymphomas in the breast, matched on age at diagnosis (±5 years) and year of diagnosis (±2 years). For all 47 potential controls, we obtained pathology reports. Furthermore, for all cases and controls, we sent a standardized questionnaire to the treating physician to obtain information on medical history, including previous malignancies, staging results, and presence of a breast prosthesis, including mammography results.

Conditional logistic regression analysis was performed to estimate the odds ratio (OR) of ALCL associated with breast prosthesis, using EGRET for Windows, 1999 (CYTEL Inc, Cambridge, Massachusetts).21 The OR was used as a valid risk estimate of relative risk and is therefore referred to as such. An estimate for absolute risk was made based on breast prosthesis sales figures for 1999 to extrapolate the number of women with breast prostheses.

This study was performed according to the current Dutch laws and regulations for medical record–based research with coded data and approved by the scientific advisory council of PALGA.

RESULTS

Our search in the national database for all patients with a histologically proven diagnosis of lymphoma in a breast specimen retrieved 389 female patients with probable primary disease diagnosed between 1990 and 2006. All 11 patients with ALCL in the breast included in our study were histologically confirmed based on review of the slides and with further immunohistochemistry and T-cell receptor analy-

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at Diagnosis, y</th>
<th>Year of Diagnosis Stage</th>
<th>Breast Involvement</th>
<th>Other Involved Sites</th>
<th>Breast Implant Placement, y</th>
<th>Removal or Replacement, y</th>
<th>Prosthesis Type</th>
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<td>61</td>
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<td>8</td>
<td>43</td>
<td>2005</td>
<td>IV</td>
<td>Right</td>
<td>1992</td>
<td>2007 Removal of left side implant</td>
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<td>Right</td>
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<td></td>
<td>Textured silicone Nagor R</td>
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<td>1996</td>
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</tbody>
</table>

Table 1. Clinical Information on 11 Patients With Anaplastic Large T-cell Lymphoma With Dominant Breast Involvement (5 Patients With a Breast Implant)
sis. In 1 additional patient, a suggested diagnosis of ALCL could not be confirmed and that case was excluded from this study.

Clinical and histological features are listed in Table 1. Patients were diagnosed between 1994 and 2006 and were a median age of 40 years (range, 24-68 years). Eight patients had unilateral breast involvement and 3 had bilateral involvement. Eight patients had limited-stage disease with breast involvement with or without axillary lymph node localizations (stage I and II); 3 patients had more disseminated disease with the dominant lymphoma localizations in the breast. In all cases, ALCL was diagnosed on the basis of an infiltrate of large, polymorphic lymphoid tumor cells with a varying background of small lymphocytes, macrophages, and eosinophils (Figure). There was uniform expression of CD30 on tumor cells, and T-cell immunophenotype could be confirmed in all cases on the basis of expression of CD3, CD2, and/or granzyme B expression. There was no expression of ALK-1. In 5 patients, bilateral silicone-covered, saline-filled breast prostheses were placed 1, 3, 4, 13, and 23 years before diagnosis, all for cosmetic reasons. Lymphoma was seen in the fibrous capsules of these prostheses that were all in situ at the time of diagnosis.

Forty-seven potential control women with breast lymphomas other than ALCL were retrieved from the cohort of 389 patients as described above. After receiving all requested clinical and pathological information, 12 of these were excluded: for 6, the lymphoma localization in the breast was found to be recurrent disease after a previous episode of nodal or extranodal lymphoma; for 4, the diagnosis of lymphoma could not be confirmed; and for 2, the lymphoma localization was not in situ at the time of diagnosis.

Figure. Anaplastic Large-Cell Lymphoma in the Fibrous Capsule of a Breast Implant

A, Overview of tumor in patient 9 (original magnification \( \times 20 \)) and B, cellular detail at a higher magnification (original magnification \( \times 400 \)). C, The tumor cells show uniform expression of CD30 (original magnification \( \times 400 \)) and D, CD5 expression in some tumor cells (original magnification \( \times 400 \)). The presence of CD30 on the tumor cells and CD5 protein on tumor cells and reactive T-cells is visualized by the brown chromogen. Immunohistochemistry was performed with BerH2 monoclonal antibody for CD30 (DAKO, Glostrup, Denmark) and CD5-4C7 antibody for CD5 (Novocastra, Newcastle Upon Tyne, England), biotin peroxidase detection system (Powervision, Immunologic, Duiven, the Netherlands), diaminobenzidine as chromogen, and hematoxylin counterstain.
Table 2. Clinical Information on 35 Patients With Non-Hodgkin Lymphoma Other Than Anaplastic Large T-cell Lymphoma With Dominant Breast Involvement

<table>
<thead>
<tr>
<th>Matched Control</th>
<th>Age at Diagnosis, y</th>
<th>Year of Diagnosis</th>
<th>Diagnosis</th>
<th>Stage</th>
<th>Breast Localization</th>
<th>Other Involved Sites</th>
<th>Previous Malignancies</th>
<th>Placement of Breast Implant and Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>44</td>
<td>1996</td>
<td>MALT</td>
<td>IE</td>
<td>Left</td>
<td></td>
<td></td>
<td>1984, textured silicone McGhan</td>
</tr>
<tr>
<td>1</td>
<td>39</td>
<td>1999</td>
<td>DLBCL</td>
<td>IE</td>
<td>Left</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>43</td>
<td>1998</td>
<td>Follicular lymphoma</td>
<td>IV</td>
<td>Right</td>
<td>Mediastinal and abdominal lymph nodes, bone marrow</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>36</td>
<td>1992</td>
<td>DLBCL</td>
<td>IE</td>
<td>Left</td>
<td></td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>61</td>
<td>2004</td>
<td>Follicular lymphoma</td>
<td>IE</td>
<td>Left</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>31</td>
<td>2003</td>
<td>Burkitt lymphoma</td>
<td>IE</td>
<td>Right</td>
<td></td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>32</td>
<td>2002</td>
<td>Burkitt lymphoma</td>
<td>IIE</td>
<td>Bilateral</td>
<td>Cervical lymph nodes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>28</td>
<td>2003</td>
<td>DLBCL</td>
<td>IE</td>
<td>Right</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>68</td>
<td>1998</td>
<td>DLBCL</td>
<td>IE</td>
<td>Left</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>66</td>
<td>1997</td>
<td>TCRBCL</td>
<td>IIIA</td>
<td>Right</td>
<td>Unknown</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>69</td>
<td>1997</td>
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<td>IE</td>
<td>Left</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>70</td>
<td>1997</td>
<td>MALT</td>
<td>IE</td>
<td>Left</td>
<td>Pancreatic carcinoma in 1990</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>70</td>
<td>1997</td>
<td>Indolent B-NHL</td>
<td>IIE</td>
<td>Right</td>
<td>Right axillary and para-aortal lymph nodes</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>55</td>
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<td>DLBCL</td>
<td>IIE</td>
<td>Right</td>
<td></td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>54</td>
<td>2002</td>
<td>MALT</td>
<td>IE</td>
<td>Left</td>
<td>Skin</td>
<td>Unknown</td>
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<tr>
<td>6</td>
<td>55</td>
<td>2000</td>
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<td>IE</td>
<td>Right</td>
<td>Unknown</td>
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<td></td>
</tr>
<tr>
<td>6</td>
<td>55</td>
<td>2000</td>
<td>DLBCL</td>
<td>IE</td>
<td>Left</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>55</td>
<td>2000</td>
<td>MALT</td>
<td>IIE</td>
<td>Right</td>
<td>Abdominal lymph nodes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>51</td>
<td>1999</td>
<td>MALT</td>
<td>IE</td>
<td>Left</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>7</td>
<td>50</td>
<td>1998</td>
<td>DLBCL</td>
<td>IE</td>
<td>Right</td>
<td>Unknown</td>
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<td></td>
</tr>
<tr>
<td>7</td>
<td>48</td>
<td>1998</td>
<td>DLBCL</td>
<td>IE</td>
<td>Right</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>7</td>
<td>50</td>
<td>1998</td>
<td>Burkitt lymphoma</td>
<td>IE</td>
<td>Right</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>42</td>
<td>2001</td>
<td>Indolent B-NHL</td>
<td>IIE</td>
<td>Left</td>
<td>Iliac lymph nodes, soft tissue abdominal wall</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>41</td>
<td>2003</td>
<td>MALT</td>
<td>IE</td>
<td>Left</td>
<td></td>
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</tr>
<tr>
<td>8</td>
<td>38</td>
<td>2003</td>
<td>Follicular lymphoma</td>
<td>IV</td>
<td>Bilateral</td>
<td>Bilateral axillary and inguinal lymph nodes, bone marrow</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>33</td>
<td>1999</td>
<td>MALT</td>
<td>IE</td>
<td>Right</td>
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<tr>
<td>9</td>
<td>26</td>
<td>1999</td>
<td>PTCL</td>
<td>IVB</td>
<td>Bilateral</td>
<td>Generalized lymph adenopathy</td>
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<td>9</td>
<td>32</td>
<td>1997</td>
<td>Burkitt lymphoma</td>
<td>IV</td>
<td>Right</td>
<td>Ovaria, cecum Unknown</td>
<td></td>
<td></td>
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<tr>
<td>10</td>
<td>34</td>
<td>1995</td>
<td>DLBCL</td>
<td>IE</td>
<td>Left</td>
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<td>10</td>
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<td>10</td>
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<td>1995</td>
<td>Burkitt lymphoma</td>
<td>IV</td>
<td>Left</td>
<td>Stomach, cerebrospinal fluid</td>
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<td>10</td>
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<td>1995</td>
<td>MALT</td>
<td>IE</td>
<td>Left</td>
<td>Mediastinal and abdominal lymph nodes</td>
<td>Pituitary adenoma in 1986</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>24</td>
<td>1997</td>
<td>PTCL</td>
<td>IIE</td>
<td>Left</td>
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</tr>
<tr>
<td>11</td>
<td>25</td>
<td>1994</td>
<td>PTCL</td>
<td>IIE</td>
<td>Right</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: B-NHL, B-cell non-Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma; MALT, mucosa-associated lymphoid tissue; NSCLC, non–small-cell lung cancer; PTCL, peripheral T-cell lymphoma; TCRBCL, T-cell rich B-cell lymphoma.
confirmed; and for 2, double entry in the database occurred.

Patient characteristics of the remaining 35 patients are listed in Table 2 and represent 1 to 5 controls for each ALCL patient. Ten patients were diagnosed with marginal-zone lymphoma, mucosa-associated lymphoid tissue-type, 12 with diffuse large B-cell lymphoma, including 1 T-cell rich B-cell lymphoma; 5 with Burkitt lymphoma; 3 with indolent follicular lymphoma; 3 with peripheral T-cell lymphoma; unclassified (CD30 negative); and 2 with indolent B-cell lymphoma, not further classified. Three patients had developed primary breast lymphoma during pregnancy (2 Burkitt lymphoma and 1 diffuse large B-cell lymphoma). Among control patients, 1 patient was identified with bilateral silicone breast implants, placed 14 years before the diagnosis of indolent follicular lymphoma with a dominant localization in the right breast and further nodal localization above and below the diaphragm as well as microscopic bone marrow involvement (Table 2). The odds ratio for ALCL in the breast associated with silicone breast prosthesis placed for cosmetic reasons was 18.2 (95% confidence interval, 2.1-156.8).

**COMMENT**

Several small series of patients and case reports have been published on lymphoma in the fibrous capsules of breast implants. Of the 16 reported cases that we are aware of, the majority are of ALK-1–negative ALCL nodal-type (n = 10) with the exception of 1 case of indolent follicular lymphoma, 1 case of human herpesvirus 8–associated primary effusion lymphoma, 1 case of lymphoplasmacytic lymphoma, and 3 cases of primary cutaneous ALCL. Because nodal-type ALCL is a very rare disease with a frequency in population-based studies of approximately 3%, the unusual distribution of this lymphoma type in case reports supports an association between ALCL and breast implants. A recent epidemiological study by McLaughlin et al did not support an increased risk for lymphoma. However, this study did not have sufficient power to address subtypes of non-Hodgkin lymphoma, with only 3 unspecified cases of non-Hodgkin lymphoma included.

Strengths of our study include the complete identification of women with ALCL in the breast in the period 1990-2006, the selection of control subjects from the same cohort, and the complete retrieval of information on breast prosthesis in all women, rendering selection bias implausible. We selected as controls women who had another type of lymphoma in the breast because we assumed that the treating physicians of cases and controls with breast lymphoma would be equally likely to be aware of a patient's breast prosthesis; in addition, mammographic information could be collected on all patients. A limitation of our design is that, if silicone breast prostheses are also associated with breast lymphomas other than ALCL, we have underestimated the strength of association between breast prostheses and ALCL in the breast. Moreover, our study concerns a small number of ALCL cases included, despite nationwide coverage, due to the rarity of the disease.

To explain the biological mechanism of the association of ALCL and breast implants, 3 hypotheses may be proposed: direct immunological drive, indirect cytokine-mediated drive, and toxic damage by silicone products. Although a specific immunological drive by silicone components would be suggestive as an explanation, this is not very likely. Importantly, it has been shown that ALCL lacks a functional T-cell receptor signaling system either by a defect of the T-cell receptor molecules or of downstream signaling components, precluding direct antigenic stimulation. The typical organ-related autoimmunity-driven lymphoma of marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue-type has been described in the breast but not in relation to silicone breast implants, further excluding this model for ALCL. An indirect association driven by a specific cytokine response may be assumed and indeed, extensive inflammatory and histiocytic reactions to silicone are seen both in fibrous capsules as well as in draining lymph nodes. Alternatively, toxic substances from the prostheses could be directly oncogenic to a precursor population of ALCL but apparently not to other organ-specific lymphoid cell populations, including B-cells. Indeed, outside the context of breast implants, primary lymphoma of the breast is mostly of B-cell type with 49% diffuse large B-cell lymphoma and 17% marginal zone lymphoma, mucosa-associated lymphoid tissue-type in our series of 389 women diagnosed between 1990 and 2006. Similar frequencies are reported by others, suggesting for B-cell lymphomas, other risk factors—including autoimmune-related factors—apply more than may be presumed for ALCL.

Although an 18-fold increased odds for the development of a specific lymphoma in the breast may cause significant concern among women with breast prostheses, it should be realized that the absolute risk remains very low due to the exceedingly rare occurrence of ALCL in the population (estimated incidence at all sites 0.1/100 000 per year). Indeed, only 11 cases of breast ALCL occurred in the Netherlands (population of 8 million women) in 17 years. Based on rather uncertain data (sales figures for 1999), we estimate that there may be 100 000 to 300 000 women with cosmetic breast prostheses in the Netherlands. This implies that the incidence of ALCL in the breast would vary between 0.1 to 0.3 per 100 000 women with prostheses per year (5 cases in 1.7-5.1 million person-years). Therefore, the absolute risk of developing breast cancer in a prosthesis-containing breast is much higher than the risk of ALCL, despite the absence of a prosthesis-related increased risk of breast cancer (http://www.ikcnet.nl).

In conclusion, these preliminary findings suggest an association between silicone breast prosthesis and ALCL, although the absolute risk is exceedingly low due to the rare occur-
REFERENCES

Omega-3 Fatty Acid Supplementation Effects on Weight and Appetite in Patients with Alzheimer’s Disease: The Omega-3 Alzheimer’s Disease Study

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OBJECTIVES: To study the effects of omega (Ω)-3 fatty acid (FA) supplements on weight and appetite in patients with mild to moderate Alzheimer’s disease (AD) in relation to inflammatory biomarkers and apolipoprotein E e4 (APOEe4).

DESIGN: Randomized, double-blind, placebo-controlled trial.

SETTING: Specialist memory clinics in the Stockholm catchment area.

PARTICIPANTS: Two hundred four patients (aged 73 ± 9, 52% women) with mild to moderate AD.

INTERVENTION: Patients with AD received 1.7 g of docosahexaenoic acid (DHA) and 0.6 g of eicosapentaenoic acid (EPA) (Ω-3/Ω-3 group; n = 89, aged 73 ± 9, 57% women) or placebo 0.6 g of linoleic acid per day (placebo/Ω-3 group; n = 85, aged 73 ± 9, 46% women) for 6 months. After 6 months, all patients received DHA and EPA for another 6 months.

MEASUREMENTS: Anthropometry, biochemical nutritional and inflammatory markers, and appetite assessed by caregiver.

RESULTS: Mean weight and body mass index (kg/m²) at baseline were 70.0 ± 11.8 kg and 24.3 ± 3.0 kg/m², respectively. At 6- and 12-month follow-up, weight had increased 0.7 ± 2.5 kg (P = .02) and 1.4 ± 2.9 kg (P < .001) in the Ω-3/Ω-3 group. In the placebo group, weight was unchanged at 6 months but had increased (P = .01) at 12 months follow-up after Ω-3 supplementation was initiated. Appetite improved in the Ω-3/Ω-3 group over the treatment period (P < .01). In logistic regression analyses, not carrying the APOEe4 allele and high plasma DHA concentrations were independently related to weight gain in the combined group of patients at 6 months follow-up.

CONCLUSION: A DHA-enriched Ω-3 FA supplement may positively affect weight and appetite in patients with mild to moderate AD. Not carrying the APOEe4 allele and high DHA were independently associated with weight gain. J Am Geriatr Soc 57:11–17, 2009.

Key words: Ω-3 fatty acids; weight gain; Alzheimer’s disease; dementia; appetite; nutrition; APOE

Cross-sectional studies show that patients with dementia weigh less and have lower body mass index than cognitively intact elderly.1 Weight loss might precede the diagnosis of Alzheimer’s disease (AD).2,3 Even though weight loss is present in the early stages of the disease, it increases with the severity and progression of AD.4 The etiology of the weight loss is probably multifactorial. Potential contributing factors are inflammatory components of the disease; impaired olfaction and taste;5 and behavior problems like agitation, restlessness,6 and wandering, which lead to increased energy expenditure.7

Although it has been suggested that inflammatory processes in the brain are of etiologic importance in AD,8 only a few studies have reported high levels of proinflammatory cytokines in the plasma or cerebrospinal fluid of patients with AD.9,10 Tumor necrosis factor alpha (TNF-α) derived from the local central nervous system (CNS) inflammatory reaction in AD may account for the AD-related anorexia and weight loss.11 It has been reported that antiinflammatory...
treatment that reduces TNF-\(\alpha\) in geriatric patients might prevent cachexia.\(^{12}\) Omega (\(\Omega\))-3 fatty acids (FAs) have been shown to have antiinflammatory effects through several mechanisms (e.g., they decrease levels of proinflammatory eicosanoids and cytokines and produce anti-inflammatory resolvins). Such administration may have the potential to reduce anorexia and weight loss in patients with AD. Fish fat and fish oils are the most important sources of \(\Omega\)-3 FAs in humans. Several prospective studies have reported protective associations between fish and the risk of incident AD.\(^{13–15}\) The content of \(\Omega\)-3 FAs in the brain, as well as in plasma, is low in patients with AD, and progression of the disease appears to aggravate this.\(^{16}\)

One of the major risk factors for developing late-onset AD (LOAD) is the occurrence of the apolipoprotein E \(e4\) (\(APOEe4\)) genotype. \(APOE\) is the major lipoprotein in the brain and an important cholesterol-transporting protein.\(^{17}\) Dietary interventions in midlife in individuals carrying the \(APOEe4\) allele might modify the risk of dementia and AD.\(^{18,19}\)

The primary aim of this study was to evaluate the effects of \(\Omega\)-3 FA supplementation on weight, appetite, and other nutritional parameters. In addition, the importance of inflammation and \(APOEe4\) on weight was evaluated.

**METHODS**

**Patients**

Two hundred four patients (aged 73 ± 9, 52% women) with mild to moderate AD were included in the Omega-3 Alzheimer’s Disease (OmegAD) Study, previously described in detail.\(^{20}\) The study was conducted between December 2001 and March 2004. All subjects were recruited from specialist memory clinics in the Stockholm catchment area.

The inclusion criteria required that patients have a diagnosis of AD according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, criteria,\(^{21}\) and a Mini-Mental State Examination (MMSE)\(^{22}\) score between 15 and 30, be living in their own homes, be treated with a stable dose of acetylcholine esterase inhibitors (AChEIs) for at least 3 months before study start, and plan to remain on AChEI for the study period. Patients were excluded if they were being treated with nonsteroidal antiinflammatory drugs (low-dose acetylsalicylic acid was excluded if they were being treated with nonsteroidal anticoagulation agents; abused alcohol; suffered from a concomitant serious disease; or did not have a caregiver.

**Procedures and Study Design**

Before inclusion in the study, all 204 patients had undergone a medical examination at one of the memory clinics, including information about history from a close informant and assessment of somatic, neurological, and psychiatric status. Computerized brain tomography or magnetic resonance imaging and psychometric testing of cognition were performed, blood samples for \(APOE\) genotype analyses were extracted from peripheral blood cells using standard methods,\(^{23}\) and \(APOE\) genotype was determined using a microsequencing method on microtiter plates (AffiGene \(APOE\) Sangtec Medical Bromma, Stockholm, Sweden). A member of the study team (YFL) reassessed the AD diagnosis.

Two hundred four patients (110 women and 94 men) completed the baseline assessments, and 174 patients completed the study. The study was designed as a double-blind randomized placebo-controlled study. Patients were randomized in blocks of four, using sealed envelopes and according to a computerized table of random numbers, to receive four 1-g capsules daily, each containing 430 mg DHA and 150 mg EPA (EPAX1050TG from Pronova Biocare A/S, Lysaker, Norway) or an isocaloric placebo oil (containing 1 g of corn oil, including 0.6 g of linoleic acid) for 6 months, followed by 6 months of open treatment with \(\Omega\)-3 for all patients. The two groups were denoted the \(\Omega\)-3/\(\Omega\)-3 and placebo/\(\Omega\)-3 group, respectively. The dropout rate was 15% (14 in the \(\Omega\)-3/\(\Omega\)-3 group and 16 in the placebo/\(\Omega\)-3 group). The reasons for leaving the study were mainly gastrointestinal symptoms, such as diarrhea (\(n = 9\)) and dysphagia (due to the size of the capsules; \(n = 9\)), intervening serious somatic disease (\(n = 10\)), nonadherence (\(n = 1\)), and withdrawn informed consent (\(n = 1\)). The \(\Omega\)-3 preparation was well tolerated and safe.

EPAX1050TG is a 60% \(\Omega\)-3 concentrate in triglyceride form produced according to Good Manufacturing Practices. Four mg of vitamin E (tocopherol) was added to each EPAX1050TG and placebo capsule.

**Methods**

Included patients underwent the following evaluations at baseline and 6 and 12 months described in detail previously:\(^{20}\) routine blood and urine samples, blood pressure assessments, global function using the Clinical Dementia Rating Scale (CDR), and cognitive function using the MMSE and the modified cognitive subscale of the Alzheimer’s Disease Cognitive Assessment (ADAS-Cog) Scale. Neuropsychiatric symptoms were analyzed using the Neuropsychiatric Inventory (NPI)\(^{24}\) and are presented elsewhere.\(^{25}\) The NPI covers 12 domains (e.g., apathy, depression, and appetite), and the caregiver rates the answers. The appetite domain was analyzed in this study. The caregiver rated the appetite of the study participant at three levels (decreased, unchanged, or increased) at baseline, assessed in comparison with habitual status and at 6- and 12-month follow-up from the previous assessments). Changes were categorized into four frequencies ranging from 1 (<1/week) to 4 (daily or constantly). Thus, a score of 1 to 9 was constructed, with 1 corresponding to constantly or always decreased appetite, 5 indicated unchanged appetite, and 9 equaled constantly or always increased appetite compared with habitual status at baseline or previous assessments.

Nutritional assessment was performed using anthropometric and biochemical assessments at baseline and 6 and 12 months and included body mass index (BMI, kg/m\(^2\)), triceps skinfold (TSF, mm) measured using a Harpenden Skinfold caliper, and arm muscle circumference (AMC, cm) calculated according to Jelliffe.\(^{26}\) The measurements were made between the acromion and the olecranon on the nondominant arm.

Blood samples for analysis of plasma FA levels were assessed using gas chromatography (TR-Fame-column 30 m × 32 mm ID × 0.25 \(\mu\)m film gas chromatography columns; Thermo Electron Corp., Walheim, Beverly, MA). Results are given as the relative abundance of individual FAs.\(^{27}\)
Plasma albumin was analyzed using the routine methods and reference range of the Laboratory of Clinical Chemistry at Karolinska University Hospital. To measure inflammation, high-sensitivity plasma C-reactive protein (hs-CRP) and plasma interleukin (IL)-6 were analyzed. Routine hs-CRP measurements were made using nephelometry at the Department of Clinical Chemistry at the hospital. Subclinical inflammation was defined as a hs-CRP level higher than 3 mg/L. IL-6 levels were analyzed in plasma samples according to enzyme-linked immunosorbent assay using commercially available kits (R&D Systems, Abingdon, Oxon, UK). The detection range was 0.156 to 10 pg/mL for IL-6.

Insulin-like growth factor (IGF)-I was determined in plasma according to radioimmune assay after separation of IGFs from IGF binding proteins using acid ethanol extraction and cryoprecipitation. The intra- and interassay coefficients of variation were 4% and 11%, respectively. Plasma levels of IGF-I decrease with age, so IGF-I values were also expressed as standard deviation scores calculated from the regression of the values of 247 healthy adult subjects.

Statistical Analyses

Before the start of the study, power analyses were performed as described previously. Because cognition was the primary overall outcome of the study, no specific power analysis with weight as outcome measure was performed.

Data are presented as means ± standard deviations, 95% confidence intervals (CIs), and medians (25th–75th percentiles). To analyze the variations between two groups the Student t-test, the Mann Whitney U-test and the chi-square test were used in accordance with the type and distribution of the variables. Possible changes at 6- and 12-month follow-up were evaluated using the Student paired t-test or Wilcoxon matched pair test. To analyze longitudinal changes within and between the two groups, analysis of variance repeated measures was used. The Fisher least significant difference (LSD) test was used for post hoc analyses. For correlation analyses, Pearson and Spearman correlation coefficients were calculated depending on the type and distribution of the variables. Logistic regression was performed to evaluate the independent relationship between different relevant variables and weight gain. For the statistical analyses, APOEε4 was dichotomized into carriers and noncarriers of the APOEε4 allele, and appetite was dichotomized into increased or stable and decreased appetite, as assessed by caregivers and compared with earlier habitual status or previous assessments. The Statistica 7.0 software package (Statsoft, Tulsa, OK) was used for the statistical calculations.

Table 1. Apolipoprotein E ε4 (APOEε4) Allele, Mini-Mental State Examination (MMSE) Score, and Anthropometric Variables in Patients with Alzheimer’s Disease at Baseline and at 6 and 12 Months

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ω-3/ε3-3 (n = 89)</th>
<th>Placebo/ε3-3 (n = 85)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>6 Months</td>
</tr>
<tr>
<td>Age, mean ± SD</td>
<td>72.6 ± 9</td>
<td>72.9 ± 8.6</td>
</tr>
<tr>
<td>Female, %</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>APOEε4, n (%)</td>
<td></td>
<td>21 (24)</td>
</tr>
<tr>
<td>0</td>
<td>46 (52)</td>
<td>39 (46)</td>
</tr>
<tr>
<td>1</td>
<td>22 (25)</td>
<td>18 (21)</td>
</tr>
<tr>
<td>MMSE, score, mean ± SD (range 0–30)</td>
<td>23.6 ± 3.8</td>
<td>22.8 ± 4.4</td>
</tr>
<tr>
<td>Weight, kg, mean ± SD</td>
<td>69.6 ± 12.2</td>
<td>70.2 ± 12.2</td>
</tr>
<tr>
<td>Men</td>
<td>78.2 ± 10.9</td>
<td>79.1 ± 10.9</td>
</tr>
<tr>
<td>Women</td>
<td>63.1 ± 8.5</td>
<td>63.7 ± 8.5</td>
</tr>
<tr>
<td>Body mass index (kg/m²), mean ± SD</td>
<td>24.5 ± 3.1</td>
<td>24.8 ± 3.1*</td>
</tr>
<tr>
<td>Triceps skinfold thickness, mm, median (25th–75th percentile)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men (normal range &gt; 6)</td>
<td>10.2 (7.6–12)</td>
<td>8.9 (7.6–11.4)</td>
</tr>
<tr>
<td>Women (normal range &gt; 10)</td>
<td>16.7 (13.8–19.4)</td>
<td>16.6 (13.8–19)</td>
</tr>
<tr>
<td>Arm muscle circumference, cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men (normal range &gt; 21)</td>
<td>26.7 (24.5–28.7)</td>
<td>26.8 (24.5–27.9)</td>
</tr>
<tr>
<td>Women (normal range &gt; 19)</td>
<td>22.6 (21.3–23.9)</td>
<td>22.8 (21.6–24.1)</td>
</tr>
<tr>
<td>Appetite score (1–9)</td>
<td>4.8 ± 2</td>
<td>5.1 ± 2.3</td>
</tr>
</tbody>
</table>

* P < .05, † P < .01 indicate significance levels in changes over time within the groups at 0–6 and 0–12 months, respectively. No significant variations were noticed in changes between the groups at either 6 or 12 months.

Ω-3/ε3-3 = intervention group (subjects who received Ω-3 fatty acids from baseline to 12 months; 38 men and 51 women); Placebo/ε3-3 = control group (subjects who received placebo oil from baseline to 6 months and Ω-3 fatty acids from 6 to 12 months; 46 men and 39 women).

SD = standard deviation.

Ethical Considerations

The study was conducted according to Good Clinical Practice guidelines and the ethical principles of the Declaration

...
of Helsinki. Patients and caregivers gave written informed consent before study entry. The local ethics committee at Karolinska University Hospital Huddinge approved the study.

RESULTS

Baseline Characteristics

Baseline data were similar for the two groups and are shown in Tables 1 and 2. Almost one-third of the \( \Omega-3/\Omega-3 \) group and one-quarter of the placebo/\( \Omega-3 \) group scored higher than 27 on the MMSE, indicating mild AD. Approximately two-thirds of the patients were carriers of the APOE\( \varepsilon4 \) allele (Table 1). Approximately one-third of each group had a BMI less than 23 (not significant between the groups). Median TSF and AMC were in the normal range in both groups. Mean plasma albumin (Table 2) was within the reference range, but approximately one-fifth of each group had values below this range. Six and eight subjects in the \( \Omega-3/\Omega-3 \) group and placebo/\( \Omega-3 \) group, respectively, had plasma IGF-1 levels below reference values for elderly healthy controls. A hs-CRP level greater than 3 mg/L was found in seven individuals in the healthy controls. A hs-CRP level greater than 3 mg/L was found in seven individuals in the healthy controls.

Twenty-three individuals (26%) in the \( \Omega-3/\Omega-3 \) group and 23 (27%) in the placebo/\( \Omega-3 \) group lost weight during the 12-month study period (mean 2.1 \( \pm \) 1.9 kg (1.5%) and 3.3 \( \pm \) 4.1 kg (2.5%), respectively).

Appetite as assessed by the caregiver seemed to improve with the intervention, and a significant increase was noticed after 12 months of treatment in the \( \Omega-3/\Omega-3 \) group (\( P < 0.05 \); Table 1). During placebo treatment the appetite score was unchanged but improved when \( \Omega-3 \) FA treatment was initiated (Table 1). The variation was nonsignificant between the groups.

Table 2 lists biochemical changes over the observation period. The plasma levels of EPA and DHA increased after the \( \Omega-3 \) FA treatment. Unexpectedly, plasma albumin

<table>
<thead>
<tr>
<th>Variable</th>
<th>( \Omega-3/\Omega-3 ) (n = 89)</th>
<th>Placebo/( \Omega-3 ) (n = 85)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage eicosapentaenoic acid 20:5, mean ( \pm ) SD</td>
<td>1.8 ( \pm ) 0.9</td>
<td>1.8 ( \pm ) 0.8</td>
</tr>
<tr>
<td>Percentage docosahexaenoic acid 22:6, mean ( \pm ) SD</td>
<td>3.1 ( \pm ) 1.3</td>
<td>3.2 ( \pm ) 1.2</td>
</tr>
<tr>
<td>Plasma albumin, g/L (normal range 36–45)</td>
<td>38 ( \pm ) 2.6</td>
<td>37.7 ( \pm ) 2.7</td>
</tr>
<tr>
<td>Plasma IGF-I, ( \mu g/L ) (normal range 84–115)</td>
<td>141 ( \pm ) 41</td>
<td>138 ( \pm ) 42</td>
</tr>
<tr>
<td>Plasma high-sensitivity C-reactive protein, mg/L</td>
<td>0.4 ( \pm ) 1.1</td>
<td>0.3 ( \pm ) 1.0</td>
</tr>
<tr>
<td>Plasma interleukin-6, pg/mL</td>
<td>0.75 (0.5–1.2)</td>
<td>0.7 (0.5–1.2)</td>
</tr>
</tbody>
</table>

\* Fatty acids are given as the relative amount in percentage of all fatty acids analyzed in total plasma.

\* Mean values in 171 healthy controls 70–96 years of age.

\* Number of standard deviations (SDs) from the mean in a reference population.

\*\* Standard deviation.

6- and 12-Month Follow-Up

Weight had increased significantly in the \( \Omega-3/\Omega-3 \) group at 6 months and even more at 12 months (Figure 1, Table 1). The weight of the placebo-treated patients remained the same at 6 months, whereas significant weight gain was seen after 6 months of active treatment with \( \Omega-3 \) FAs. The difference between the groups was not significant at any time point. The weight gain associated with \( \Omega-3 \) FA treatment was observed mainly in patients with BMI less than 23 at study start. Their weight increment was significant at 6 and 12 months, which contrasted with a nonsignificant weight increase in \( \Omega-3 \) FA–treated patients with BMI of 23 or greater (data not shown). The variations were nonsignificant between the leaner and less-lean subjects.

![Figure 1](https://example.com/figure1.png)
Correlations and Logistic Regressions
There was a univariate correlation between increase in weight and increase in appetite in the combined group of individuals at 6 (correlation coefficient \( r = 0.33, P < .001 \)) and 12 \( (r = 0.28, P < .001) \) months. Weight gain and changes in CRP correlated inversely between 6 and 12 months in the combined group \( (r = -0.18, P = .02) \).

Logistic regression analyses were performed to evaluate the independent relationship between different relevant variables and weight gain. Not carrying the \( APOEe4 \) allele \( (OR = 2.19, 95\% CI = 1.0–4.6) \) and increased DHA levels \( (OR = 3.3, 95\% CI = 1.0–11.0) \) were positively associated with weight gain at 6 months (Table 3).

**DISCUSSION**
This is the first study to report nutritional effects of \( \Omega-3 \) FA supplementation given to patients with mild to moderate AD. Weight gain was noted after supplementation with \( \Omega-3 \) FA, although not significantly different from the placebo group. Likewise, \( \Omega-3 \) FA treatment significantly improved appetite after 12 months of treatment in the \( \Omega-3/\Omega-3 \) group. An inverse correlation was found between weight gain and change in plasma hs-CRP. Higher plasma DHA levels during the treatment period and not carrying the \( APOEe4 \) allele were related to weight gain in logistic regression models in the combined group of patients.

The gain in weight was modest but increased steadily during active treatment in both groups. Appetite seemed to follow the same pattern.

EPA and DHA levels in plasma were measured and indicated good patient adherence to the supplementation throughout the study. EPA has been the predominant FA over DHA in supplementation trials of patients with somatic disorders (e.g., rheumatoid arthritis and cardiovascular disease). In this study, DHA and EPA were given at a ratio of 3:1. More DHA than EPA was given, because previous data indicate a specific deficiency of DHA in the brains of people with AD. Moreover, experimental data support the notion that DHA is of particular importance for cognitive function.

The participants were diagnosed with AD of mild to moderate severity. Although mean BMI and median TSF and AMC were within the reference ranges in the combined group of patients, a mean BMI of 24, as found in this group, might be regarded as suboptimal, because a BMI less than 23 has been found to be related to poorer 7-year survival in AD patients. Weight loss is one of the principal features of AD and indicates deterioration. Thus, it is important to monitor weight in order to monitor the condition of a patient with AD. The number of patients who lost weight during the study period was modest in comparison with some other 1-year follow-up studies in patients with mild to moderate dementia.

Inflammation (i.e., high plasma hs-CRP concentrations) has been associated with poor memory, vascular dementia, and AD in some population-based studies, whereas others have found no associations. One study reported that higher baseline hs-CRP in women was associated with poor memory at 12-year follow-up. The present study found no such association. Hs-CRP was low \((\sim 1 \text{mg/L in both groups of participants})\) and did not change significantly during the treatment period. The mild to moderate degree of disease probably explains why systemic inflammation was not detected in these patients, although there was a correlation between low hs-CRP and weight gain during the second part of the trial in the combined group. This finding may nevertheless indicate a role for inflammation in appetite regulation in people with AD, which would be in line with several reports on appetite in people with other chronic illnesses. Further studies in this field are needed.

Unexpectedly, plasma albumin decreased after 6 months of \( \Omega-3 \) treatment in the \( \Omega-3/\Omega-3 \) group and after 6 months of treatment in the \( \Omega-3/\text{placebo} \) group at 12 months. The result from the present study is in line with such results, because it was found that not carrying the \( APOEe4 \) allele was independently associated with weight gain. Subjects who did not carry the \( APOEe4 \) allele showed weight gain at 6 months. Some reports have suggested that the relationship between the \( APOEe4 \) allele and weight loss may converge in the medial temporal lobe (the earliest site of AD pathology). For example \( APOEe4 \) carriers seem more prone to suffering from impaired olfactory function before the onset of cognitive impairment. In addition, the response in serum lipid profiles to dietary interventions varies between individuals with and without the \( APOEe4 \). Furthermore, elderly individuals with the \( APOEe4 \) allele with a high intake of calories and fats are at higher risk of AD than

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apolipoprotein E4 noncarrier</td>
<td>2.19</td>
<td>1.04–4.61</td>
<td>.04</td>
</tr>
<tr>
<td>( \Omega-3 ) fatty acid treatment</td>
<td>0.48</td>
<td>0.16–1.42</td>
<td>.18</td>
</tr>
<tr>
<td>Appetite increment</td>
<td>0.54</td>
<td>0.23–1.28</td>
<td>.16</td>
</tr>
<tr>
<td>Docosahexaenoic acid increment</td>
<td>3.34</td>
<td>1.01–11.00</td>
<td>.045</td>
</tr>
<tr>
<td>Eicosapentaenoic acid increment</td>
<td>0.89</td>
<td>0.26–2.98</td>
<td>.84</td>
</tr>
<tr>
<td>C-reactive protein decrease</td>
<td>1.17</td>
<td>0.59–2.31</td>
<td>.64</td>
</tr>
</tbody>
</table>


individuals without the APOEε4 allele. There were no clear relationships between the occurrence of the APOEε4 allele and plasma levels of Ω-3 FAs and no clear Ω-3 FA treatment effects in the current study (data not shown).

One limitation of the study is the lack of food intake data. The patients and their caregivers were advised not to change their dietary habits during the study. Data from food frequency questionnaires were collected in a subsample of the patients and will be presented separately. Another limitation of the study is that power calculations were not performed with weight as the outcome variable, because the main purpose of the OmegAD Study was to evaluate cognitive effects of Ω-3 FA treatment.

In summary, patients with mild to moderate AD who received Ω-3 FA supplementation, especially enriched with DHA, gained weight over treatment periods of 6 to 12 months. However, no firm conclusions can be drawn because there was no significant difference between the treatment groups. It has been suggested that Ω-3 FAs reduce anorexia and cachexia in patients with malignant diseases, although this hypothesis is still not proven. Supportive of the assumption that Ω-3 FAs may improve appetite and result in weight gain in patients with AD was the positive association between elevations in plasma DHA and gain in weight noticed in the logistic regression analyses.

ACKNOWLEDGMENTS
The assistance of Mrs. A-C Tysén-Bäckström, RN, and Mr. Andreas Svensson, RN, for patient data management is acknowledged.

Conflict of Interest: JP and TC have received travel grants from the sponsor. Financial support was provided through the Regional Agreement on Medical Training and Clinical Research (ALF) between Stockholm County Council and the Karolinska Institute, Funds of Capio, Demensförsäkringet, Gamla Tjänarinnor, Swedish Alzheimer Foundation, Odd Fellow, Swedish Nutrition Foundation, Gun och Bertil Stohnes Stiftelse, Swedish Society of Physicians, and Lion’s Sweden. The OmegAD study was initially partly funded by Pronova Biocare A/S, Lysaker, Norway.

Author Contributions: Tommy Cederholm had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Tommy Cederholm and Jan Palmblad: design of the experiment, analysis of data, preparation and writing of the manuscript. Yvonne Freund-Levi: design of the experiment, collection of data, preparation and writing of the manuscript. Gerd Faxén-Irving: design of the experiment, analysis of data, preparation and writing of the manuscript. Hans Basun, Maria Eriksdotter-Jönhagen, Inger Vedin, and Lars-Olof Wahlund: design of the experiment and preparation of the manuscript. Kerstin Brismar analyses of plasma IGF-1. Erik Hjorth analyses of plasma IL-6. Bengt Vessby: design of the experiment and analyses of the FA profiles. All authors have approved the manuscript.

Sponsor’s Role: Pronova Biocare A/S was represented in the trial steering committee with regard to study design and provided the EPAX1050TG and placebo preparations; the company was not involved in the data and patient collection, analyses or interpretation of scientific data.

REFERENCES


Selective serotonin reuptake inhibitors and risk of suicide: a systematic review of observational studies

Corrado Barbui MD, Eleonora Esposito MD, Andrea Cipriani MD

ABSTRACT

Background: It is unclear whether the use of selective serotonin reuptake inhibitors (SSRIs) and other antidepressant drugs reduce the risk of suicide in people with depression. We explored the association between exposure to SSRIs and risk of suicide completion or attempt.

Methods: We conducted a systematic review of observational studies that reported completed or attempted suicide in depressed individuals who were exposed to SSRIs compared with those who were not exposed to antidepressants. We assessed the overall risk of completed or attempted suicide.

Results: Eight studies involving more than 200 000 patients with moderate or severe depression were included in the meta-analysis. Although exposure to SSRIs increased the risk of completed or attempted suicide among adolescents (odds ratio [OR] 1.92, 95% confidence interval [CI] 1.51–2.44), the risk was decreased among adults (OR 0.57, 95% CI 0.47–0.70). Among people aged 65 or more years, exposure to SSRIs had a protective effect (OR 0.46, 95% CI 0.27–0.79). Sensitivity analyses did not change these findings. In particular, for studies that used completed suicide as an outcome, exposure to SSRIs was associated with increased risk among adolescents (OR 5.81, 95% CI 1.57–21.51) and decreased risk among adults (OR 0.66, 95% CI 0.52–0.83) and older people (OR 0.53, 95% CI 0.26–1.06).

Interpretation: Based on data from observational studies, use of SSRIs may be associated with a reduced risk of suicide in adults with depression. Among adolescents, use of SSRIs may increase suicidality.

There is uncertainty about the safety of selective serotonin reuptake inhibitors (SSRIs), which may cause worsening of suicidal thoughts in vulnerable people. In 2005, a systematic review of published randomized controlled trials comparing SSRIs with another active treatment or placebo found an almost 2-fold increase in the odds of fatal and nonfatal suicide attempts among those exposed to SSRIs. No increase in risk was observed, however, when only fatal suicide attempts were included. Another systematic review, which included both published and unpublished randomized controlled trials submitted by pharmaceutical companies to the safety review of the Medicine and Healthcare products Regulatory Agency compared the use of SSRIs and placebo in adults with depression and other clinical conditions. This review showed no evidence of increased risk of completed suicide and only weak evidence of increased risk of self-harm.

More recently, the US Food and Drug Administration (FDA) performed a meta-analysis of individual patient data from 372 randomized placebo-controlled trials of antidepressants with a total of nearly 100 000 patients. This study reported that the incidence of reported suicidal behaviour was strongly related to age. The risk associated with antidepressant use relative to placebo was increased among patients aged 25 or fewer years, and it was reduced among patients aged 65 or more years. The risk among patients aged 25–64 years was neutral; however, risk was reduced when suicidal behaviour and ideation were considered together. Based on these findings, in May 2007 the FDA ordered that all antidepressant drugs carry an expanded black-box warning on their label that included information about increased risk of suicidal behaviour in young adults aged 18–24 years.

A controversial point of the FDA analysis is that the included trials were not primarily designed to measure suicidality (a composite outcome that includes suicide ideas, preparatory acts, suicide attempts and deaths by suicide). Of all suicidality events, less than 30% were serious suicide attempts or deaths. Additionally, considering that suicidality was self-reported rather than observed by others in most clinical trials, it is possible that antidepressant treatment, particularly in younger individuals, enhanced communication about suicidality, which may have allowed them to become more articulate and open about their thoughts and actions. Alternatively, antidepressant treatment might have enhanced communication about suicidality in all age groups, but increased attention to adverse effects might have led to enhanced detection of suicidality in younger individuals.

It is unlikely that individual randomized trials will be designed to primarily investigate the effect of antidepressant use on suicidality, and future systematic reviews of clinical trial data will not be able to overcome the limitations of the FDA analysis. Therefore, we sought to further explore the association be-
between SSRI exposure and risk of completed or attempted suicide by conducting a systematic review and meta-analysis of observational studies. By including a large, broad spectrum of individuals followed under naturalistic circumstances, systematic reviews of observational studies may offer an added dimension in the evaluation of drug safety that is complementary to that provided by clinical trials. Additionally, observational studies may allow researchers to move from the controversial concept of suicidality to hard outcomes such as suicide attempt and completion. Specifically, we set out to quantify the risk of completed or attempted suicide among people in different age groups with depression after exposure to SSRIs.

Methods

Study selection and data collection

Included and excluded studies were collected following the Quality of Reporting of Meta-analysis (QUOROM) guidelines. Because the included studies were observational in design, we also followed the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines published by Stroup and colleagues for the meta-analysis of the design, performance and reporting of observational studies (Appendix 1, available at www.cmaj.ca/cgi/content/full/180/3/291/DC2).

We included observational cohort and case–control studies that reported data on completed or attempted suicide among people exposed to SSRIs and among those who were not exposed to antidepressants. We included studies that reported relative risk (RR) estimates suitable for re-analysis. Only studies that used International Classification of Disease (ICD, ninth or tenth revision) definitions of completed or attempted suicide were retained. This criterion corresponds to coding 1 (completed suicide) and 2 (suicide attempt) of the FDA classification of suicide events. We did not include the following suicide-related events: preparatory acts toward imminent suicidal behaviours, suicidal ideation, and self-injurious behaviour (intent unknown; FDA coding 3–5). Study participants were of either sex and any age with a diagnosis of major depression. Studies adopting proxy measures to identify patients with depression were included. As recommended by the MOOSE guidelines, we used broad inclusion criteria and performed sensitivity analyses to relate design features to the outcomes.

We identified relevant studies by searching MEDLINE and EMBASE using the search terms “antidepressive agents” or “antidepressive agents second generation” AND “suicide” or “suicide attempted” (Appendix 2, available at www.cmaj.ca/cgi/content/full/180/3/291/DC2). We searched the reference lists of relevant articles, including review articles, by hand for other relevant studies. The search covered the period from January 1990 to June 2008. We examined all titles and abstracts, and we obtained full texts of potentially relevant papers. Working independently and in duplicate, we read the papers and determined whether they met inclusion criteria. We resolved disagreement by consensus, and we extracted data independently in duplicate using a standardized form (Appendix 3, available at www.cmaj.ca/cgi/content/full/180/3/291/DC2). We did not exclude articles published in languages other than English.

We assessed study quality using a 10-point scale adapted from a recently published quality scale for observational studies (Appendix 4, available at www.cmaj.ca/cgi/content/full/180/3/291/DC2). A score of 7 or above indicated high quality, and a score of 6 or below indicated low quality. This threshold was derived from Eteman and colleagues. Scoring of quality assessment was performed independently by 2 of the authors (C.B. and E.E.). There was high concordance between the 2 authors (kappa 0.78, standard error 0.26), suggesting no evidence of systematic disagreement bias. As recommended by the MOOSE study group, the quality scores were included in the sensitivity analyses, but they were not used as weights in the analyses.

Data synthesis

The outcome measure included in this analysis was completed or attempted suicide. Suicide attempts had to be sufficiently serious to have led to medical contact. A patient was considered to have made a suicide attempt if there were ICD-9 or ICD-10 diagnostic codes in his or her records for inpatient stay or outpatient visit. These codes included self-inflicted injury from poisoning, hanging, submersion, firearms, cutting or piercing, jumping from high places, or other means. For each study, we used the most adjusted RRs,
odds ratios (ORs) or hazard ratios with the corresponding 95% confidence intervals (CIs).8,15

We visually inspected the graphs to investigate the possibility of statistical heterogeneity. This was primarily supplemented by use of the $I^2$ statistic. This statistic provides an estimate of the percentage of variability due to heterogeneity rather than chance alone. Where the $I^2$ estimate was greater than or equal to 50%, we interpreted this as indicating the presence of high levels of heterogeneity.16

The results of studies were pooled, and an overall OR was obtained from fixed- and random-effects models. To maintain a conservative approach, the random-effects model was presented, because this takes into account any differences among studies even if there is no statistically significant heterogeneity.17 The possibility of publication bias was examined by use of the funnel plot method described by Egger and colleagues.18

Sensitivity analyses and metaregression
We performed sensitivity analyses to examine effect sizes when only the following types of studies were included: studies that used completed suicide as an outcome measure; studies that used a formal diagnosis of depression; studies that used an “external” control group (that is, we excluded studies that compared the risk of suicide during SSRI use with the risk during no antidepressant use in the same cohort); studies with a quality score of 7 or above; studies including data for both adolescents and adults; and studies that had a cohort design. Additionally, given the small number of included studies, we tested for the possible excessive influence of individual studies using a meta-analysis influence test that eliminated each of the included studies one at a time.

Results
Based on the titles and abstracts of 1492 citations, we identified 33 potentially relevant studies (Figure 1). Of these, we excluded 4 studies because SSRI use was not the exposure of interest.19–22 We excluded 18 studies because the comparison group was not individuals who had not been exposed to antidepressant treatment.21,23–39 Two additional studies were excluded because a diagnosis of major depression or a proxy measure to identify patients suffering from depression was not used,40,41 and 1 was excluded because it did not report

$\begin{array}{lll}
\text{Group; study} & \text{Age, yr} & \text{Odds ratio (95% CI)} \\
\hline
\text{Adolescents} & & \\
\text{Olfson et al.} & 6–18 & 11.26 (0.97–130.70) \\
\text{Olfson et al.} & 6–18 & 1.91 (0.90–4.07) \\
\text{Sondergard et al.} & 10–17 & 4.47 (0.95–20.96) \\
\text{Tiitinen et al.} & 10–19 & 1.91 (1.43–2.55) \\
\text{Valuck et al.} & 12–18 & 1.59 (0.89–2.82) \\
\text{Overall} & & 1.92 (1.51–2.44) \\
\hline
\text{Adults} & & \\
\text{Gibbons et al.} & 18–25 & 0.35 (0.14–0.85) \\
\text{Gibbons et al.} & 26–45 & 0.44 (0.29–0.65) \\
\text{Gibbons et al.} & 46–65 & 0.42 (0.30–0.58) \\
\text{Olfson et al.} & 19–64 & 0.87 (0.44–1.73) \\
\text{Gibbons et al.} & 19–64 & 0.80 (0.74–1.38) \\
\text{Sondergard et al.} & 56* & 0.58 (0.50–0.66) \\
\text{Tiitinen et al.} & 38* & 0.76 (0.57–1.10) \\
\text{Overall} & & 0.57 (0.47–0.70) \\
\hline
\text{Elderly} & & \\
\text{Gibbons et al.} & \geq 65 & 0.38 (0.16–0.91) \\
\text{Rahme et al.} & 75* & 0.53 (0.27–1.06) \\
\text{Overall} & & 0.46 (0.27–0.79) \\
\end{array}$

Figure 2: Random-effect meta-analysis of the risk of suicide attempt and completion associated with the use of selective serotonin reuptake inhibitors compared with no exposure to any antidepressants. *Mean age. Note: CI = confidence interval.
Additionally, we observed little or no effect of eliminating each association with SSRI exposure (Appendix 6, available at www.cmaj.ca/cgi/content/full/180/3/291/DC2).

Two studies provided data suitable for analysis of the risk of completed or attempted suicide associated with individual antidepressant agents (Figure 4). Among adults, no individual antidepressant was significantly associated with completed or attempted suicide. Among adolescents, exposure to paroxetine (random-effect OR 1.77, 95% CI 1.05–2.99, $I^2$ 48.1%) and venlafaxine (random-effect OR 2.43, 95% CI 1.47–4.02, $I^2$ 0.0%) was significantly associated with increased risk (Figure 4).

**Interpretation**

We found that the relation between exposure to SSRIs and the risk of suicide is influenced by age. Exposure to SSRIs decreased the risk of suicide by over 40% among adults and decreased the risk by over 50% among elderly people. However, among adolescents, exposure to SSRIs almost doubled the risk of suicide. These results are consistent with the main conclusion of the recent FDA meta-analysis of clinical trial data. However, our risk estimates were very similar to those obtained by the FDA only for the elderly and adolescent groups. Although the FDA reported a neutral effect of SSRIs (or a promoting effect among adults aged 18–25), we found a strong protective effect associated with SSRI treatment.

We tested the robustness of these results in several ways. First, sensitivity analyses showed similar results when more homogeneous subgroups of studies (i.e., outcome measure, diagnostic criteria, control group and quality score) were included. This effect was maintained when only studies with data simultaneously about adolescents and adults were re-included. This effect was maintained when only studies with data simultaneously about adolescents and adults were re-included. Second, we found little or no effect of eliminating each of the studies from the analysis (Appendix 7, available at www.cmaj.ca/cgi/content/full/180/3/291/DC2).

Of the included studies from the analysis (Appendix 7, available at www.cmaj.ca/cgi/content/full/180/3/291/DC2), 43–50 Among adults, no individual antidepressant was significantly associated with completed or attempted suicide. Among adolescents, exposure to paroxetine (random-effect OR 1.77, 95% CI 1.05–2.99, $I^2$ 48.1%) and venlafaxine (random-effect OR 2.43, 95% CI 1.47–4.02, $I^2$ 0.0%) was significantly associated with increased risk (Figure 4).

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Observational studies have limited ability to adjust for baseline differences and are prone to bias and confounding; thus, alternative explanations for the results of this analysis cannot be excluded. All of the included studies enrolled individuals with major depression or used proxy measures of major depression, and, therefore, confounding by indication should not have occurred.

Confounding by severity of illness cannot be excluded. However, this confounder would have to have varied systematically with age to explain the very different findings in adolescents and adults. Among adolescents, SSRI treatment is often reserved for very severe cases, and prescription of antidepressant drugs might have been triggered by suicidal ideas. Thus, the excess risk might be explained by confounding by severity. That is, adolescents who received SSRIs

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**Figure 3:** The funnel plot and visual inspection suggested that there might be a lack of small studies that failed to show an excess risk associated with SSRI exposure (Figure 3). The funnel plot and visual inspection suggested that there might be a lack of small studies that failed to show an excess risk associated with SSRI exposure (Figure 3).
Table 1: Random-effect sensitivity analyses of the risk of suicide attempt and completion associated with exposure to selective serotonin reuptake inhibitors

<table>
<thead>
<tr>
<th>Included studies</th>
<th>Adolescents</th>
<th>Adults</th>
<th>Elderly</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Study</td>
<td>Odds ratio (95% CI)</td>
<td>p, %</td>
</tr>
</tbody>
</table>
| Studies that used completed suicides as an outcome measure | • Olsson et al. \(^{64}\)  
• Sondégard et al. \(^{68}\) | 5.81 (1.57–21.51) | 0  | • Olsson et al. \(^{66}\)  
• Sondégard et al. \(^{67}\)  
• Tilhonen et al. \(^{69}\) | 0.66 (0.52–0.83) | 48  | • Rahme et al. \(^{66}\)  
• Sondégard et al. \(^{67}\)  
• Tilhonen et al. \(^{69}\) | 0.53 (0.26–1.06) | 0  |
| Studies that used a formal diagnosis of depression | • Olsson et al. \(^{64}\)  
• Olsson et al. \(^{65}\)  
• Valuck et al. \(^{50}\) | 1.86 (1.10–3.13) | 15  | • Gibbons et al. \(^{45}\)  
• Olsson et al. \(^{65}\)  
• Olsson et al. \(^{66}\)  
• Sondégard et al. \(^{67}\) | 0.54 (0.43–0.66) | 43  | • Gibbons et al. \(^{45}\)  
• Rahme et al. \(^{66}\) | 0.46 (0.27–0.79) | 0  |
| Studies that used an external control group \(^*\) | • Olsson et al. \(^{64}\)  
• Olsson et al. \(^{65}\)  
• Sondégard et al. \(^{68}\)  
• Valuck et al. \(^{50}\) | 2.04 (1.22–3.40) | 16  | • Gibbons et al. \(^{45}\)  
• Olsson et al. \(^{65}\)  
• Olsson et al. \(^{66}\)  
• Sondégard et al. \(^{67}\) | 0.54 (0.43–0.66) | 43  | • Gibbons et al. \(^{45}\)  
• Rahme et al. \(^{66}\) | 0.38 (0.16–0.91) | 0  |
| Studies that scored \(\geq 7\) \(^\dagger\) | • Olsson et al. \(^{64}\)  
• Olsson et al. \(^{65}\)  
• Tilhonen et al. \(^{69}\)  
• Valuck et al. \(^{50}\) | 1.88 (1.47–2.40) | 0  | • Gibbons et al. \(^{45}\)  
• Olsson et al. \(^{65}\)  
• Olsson et al. \(^{66}\)  
• Sondégard et al. \(^{67}\)  
• Tilhonen et al. \(^{69}\) | 0.57 (0.47–0.70) | 52  | • Gibbons et al. \(^{45}\)  
• Rahme et al. \(^{66}\) | 0.46 (0.27–0.79) | 0  |
| Studies including data for both adolescents and adults | • Olsson et al. \(^{64}\)  
• Olsson et al. \(^{65}\)  
• Tilhonen et al. \(^{69}\)  
• Valuck et al. \(^{50}\) | 1.95 (1.49–2.55) | 0  | • Olsson et al. \(^{65}\)  
• Olsson et al. \(^{66}\)  
• Tilhonen et al. \(^{69}\) | 0.78 (0.61–0.98) | 0  |
| Studies with a cohort design | • Sondégard et al. \(^{68}\)  
• Tilhonen et al. \(^{69}\)  
• Valuck et al. \(^{50}\) | 1.88 (1.46–2.43) | 0  | • Gibbons et al. \(^{45}\)  
• Sondégard et al. \(^{67}\)  
• Tilhonen et al. \(^{69}\) | 0.53 (0.43–0.67) | 59  | • Gibbons et al. \(^{45}\)  
• Rahme et al. \(^{46}\) | 0.46 (0.27–0.79) | 0  |

Note: CI = confidence interval.
*Studies that used 2 cohorts to compare the risk of suicide between those taking SSRIs and those not exposed to antidepressants.
†Scored on a 10-point scale (Appendix 4, available at www.cmaj.ca/cgi/content/full/180/3/291/DC2). Studies that scored \(\geq 7\) were considered to be high quality.
might have been more severely depressed (or more suicidal) than adolescents who did not receive SSRIs. In contrast, among adults SSRIs may be similarly prescribed in severe and less severe cases, and confounding by indication might not have occurred. In some studies, confounding by severity has been taken into account. For example, Olfson and colleagues\(^4\) limited their analysis to individuals who received inpatient treatment for depression, thus ensuring a fairly comparable level of illness severity. In 2 other studies, comparability between groups was increased by the comparison of the risk of suicide during SSRI use with the risk during no antidepressant use in the same cohort\(^4\),\(^6\). Although these designs likely limited the confounding effect of the severity of illness, we cannot exclude the fact that residual confounding might have inflated the excess risk found among adolescents.

The incidence of depression is higher among women than among men; however, the reverse pattern is observed for suicide.\(^5\) Thus, it would have been interesting to investigate the effect of sex on the risk of suicide. Similarly, the timing of the attempted or completed suicide in relation to the onset of exposure is another moderator variable that would have been clinically useful to analyze, because the risk of death by suicide may not be significantly higher in the month after starting medication than in subsequent months.\(^6\) However, information about these variables was not homogeneously reported, and re-analyses of aggregate data cannot answer issues related to patient-level moderators of treatment effect. Re-analyses of data from individual patients may have the potential to address these issues.

Differences between individual drugs need confirmation. Only 2 of the included studies provided data on specific antidepressants, and confounding by indication might have affected our results in unpredictable ways. Additionally, it is not clear why the use of some antidepressants, such as paroxetine and venlafaxine, increases the risk of suicide more than others. Intriguingly, previous re-analyses of randomized studies, including the FDA study, reported similar differences between antidepressants.\(^3\),\(^8\)–\(^6\) Differences in long-term efficacy and safety should be confirmed in trials of head-to-head comparisons.\(^7\) Such an evidence base would assist clinicians in making choices about optimal antidepressant treatment.

**Conclusion**

Data from observational studies should reassure doctors that prescribing SSRIs to patients with major depression is safe. However, children and adolescents should be followed very closely because of the possibility of increased risk suicidal thoughts and suicide. Paroxetine and venlafaxine may be better avoided based on the increasing evidence from randomized and observational studies that the risks might outweigh the benefits for most adolescents.

This article has been peer reviewed.

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