



Original Contribution

Adherence to Lipid-lowering Therapy and the Use of Preventive Health Services: An Investigation of the Healthy User Effect

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Received for publication November 7, 2006; accepted for publication January 31, 2007.

Patients who adhere to preventive therapies may be more likely to engage in a broad spectrum of behaviors consistent with a healthy lifestyle. Because many of these behaviors cannot be measured easily, observational studies of outcomes associated with the long-term use of preventive therapies are subject to the so-called "healthy user bias." To better understand this effect, the authors examined the association between adherence to statin therapy and the use of preventive health services in a Pennsylvania cohort of 20,783 new users of statins between 1996 and 2004. After adjustment for age, gender, and various comorbid conditions, patients who filled two or more prescriptions for a statin during a 1-year ascertainment period were more likely than patients who filled only one prescription to receive prostate-specific antigen tests (hazard ratio (HR) = 1.57, 95% confidence interval (CI): 1.17, 2.19), fecal occult blood tests (HR = 1.31, 95% CI: 1.12, 1.53), screening mammograms (HR = 1.22, 95% CI: 1.09, 1.38), influenza vaccinations (HR = 1.21, 95% CI: 1.12, 1.31), and pneumococcal vaccinations (HR = 1.46, 95% CI: 1.17, 1.83) during follow-up. These results suggest that patients who adhere to chronic therapies are more likely to seek out preventive health services, such as screening tests and vaccinations. Further work is needed to identify study design and analysis methods that can be used to minimize the healthy user bias in studies of preventive therapies.

bias (epidemiology); confounding factors (epidemiology); epidemiologic methods; health behavior; pharmacoepidemiology

Abbreviations: CI, confidence interval; HR, hazard ratio; PACE, Pharmaceutical Assistance Contract for the Elderly.

A recent meta-analysis of 21 randomized clinical trials found that patients who were adherent to placebo had lower rates of mortality than did other patients in the placebo arm who were less adherent (1). One explanation for this intriguing finding is that adherence to treatment is a surrogate marker for a healthy lifestyle. Thus, patients who take their medication as prescribed are more likely to engage in a broad spectrum of health-promoting behaviors that lower the risk of mortality (1, 2). Because many of these behaviors may not be measured easily and others may not even be known to

the investigator, observational studies of the benefits of preventive therapies may be confounded by unmeasured healthy behaviors that are related to both the treatment and study outcome.

The tendency of healthier patients to be more likely to initiate a preventive therapy leads to a bias that has been termed the "healthy user effect" or "healthy user bias" (3–5). This could occur through either selective prescribing of preventive medications to patients in better health and/or through more health conscious patients seeking out

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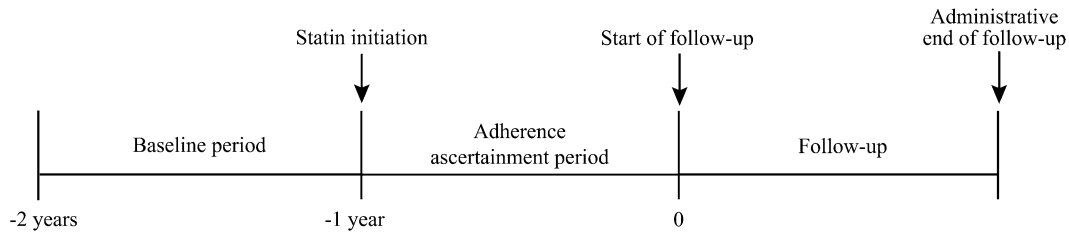


FIGURE 1. Schematic of study design used in a Pennsylvania cohort, 1996–2004.

prescriptions for such medications (6–8). When healthier patients are more likely to adhere to a therapy, the bias has been termed the “healthy-adherer effect” (1, 9, 10), “adherence bias” (4), or “compliance bias” (11, 12). In this paper, we refer to these effects collectively as the healthy user effect or healthy user bias. The biases generated by these effects may lead to spurious or exaggerated protective associations between preventive drug use and adverse clinical outcomes.

The healthy user bias has been suggested as an explanation for the discrepancy between several experimental and observational studies, including studies of the effects of long-term use of estrogen therapy (11–14) and vitamin E (15). It has also been discussed as a potential source of bias in observational studies of the effectiveness of influenza vaccines in the elderly (16) and the association between use of 5-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) and reduced risk of hip fracture (4), Alzheimer’s disease (6), sepsis (5), and cancer (17).

Despite an increasing awareness of the potential importance of the healthy user effect, there has been little effort to study it directly. In the present research, we sought to uncover evidence of a healthy user effect among new users of statins, widely used cholesterol-lowering medications. We hypothesized that patients starting statin therapy vary in their “health-seeking” tendencies, with the more health-conscious patients being both more likely to adhere to their statin regimen and also more likely to seek out other preventive health services. To explore the plausibility of our hypothesis, we examined the association between adherence to statins and the use of various prevention-oriented health services. We conducted our analysis in a large population-based new user cohort in Pennsylvania.

MATERIALS AND METHODS

Data sources and study population

Our study cohort was drawn from a patient population aged 65 years or older enrolled in both Medicare and the Pennsylvania Pharmaceutical Assistance Contract for the Elderly (PACE) program between 1996 and 2004. PACE is a state-run pharmaceutical benefit program for households with incomes less than \$17,200. The PACE drug benefit covers all outpatient drug treatment with a small copayment

from \$6 to \$9. Our cohort consisted of PACE/Medicare enrollees who initiated a statin between 1997 and 2002. We excluded patients who started cerivastatin, which was withdrawn from the market in 2001. We limited our study to a primary prevention population by excluding patients who had evidence of existing coronary artery disease, defined by a history of unstable angina, ischemic heart disease, myocardial infarction, coronary artery bypass graft surgery, or angioplasty. We also excluded patients with a history of diabetes. Statin initiation was defined as filling one statin prescription without having filled one in the past 12 months. To ensure correct ascertainment of drug and health-care system use during this 12-month period, we required that subjects have at least one prescription claim and one physician services claim from Medicare Part B during each half of the year, indicating use of both Medicare and PACE.

The study investigators have data use agreements in place with the Centers for Medicare and Medicaid Services and PACE. Personal identifiers are removed from all analytical data files. The Partners Healthcare Institutional Review Board has approved this research.

Covariates

We obtained baseline demographics, health services use, and health status information from Medicare and PACE enrollment files and claims during the year prior to the initiation of the statin prescription. Recorded covariates were defined during the baseline period and included age, sex, race, number of days spent in the hospital, number of physician visits, and presence of various medical conditions as ascertained from inpatient and outpatient diagnosis codes.

Exposure assessment

To assess statin adherence, we defined an adherence ascertainment period beginning on the baseline date and ending 1 year later. Adherence was assessed by counting the number of statin prescriptions filled during this period. Almost all prescriptions filled through the PACE program are for a 30-day supply, so fully adherent subjects would be expected to receive 12 prescriptions. Subjects without a full 1-year adherence ascertainment period due to death, loss of PACE eligibility, or nursing home admission were omitted from the analysis. A schematic of the study design is given in figure 1.

TABLE 1. Characteristics of Pennsylvania cohort, 1996–2004

Characteristic assessed during 1-year baseline period	Mean (SD)*
Age (years)	76.4 (5.9)
Physician visits (no.)	8.5 (5.8)
Medications used (no.)	7.0 (4.3)
Charlson comorbidity score	1.4 (1.6)
	No. (%)
Female	17,794 (85.6)
Acute care hospitalization	4,096 (19.7)
Nursing home stay	374 (1.8)
History of chronic obstructive pulmonary disease	4,398 (21.2)
History of obesity	634 (3.1)
History of cancer	269 (1.3)
History of liver disease	21 (0.10)
History of osteoarthritis	11 (0.1)
History of rheumatoid arthritis	269 (1.3)
History of atrial fibrillation	7,308 (35.2)
History of peripheral vascular disease	3,002 (14.4)

* SD, standard deviation.

Study outcomes

The outcomes studied were time until receipt of recommended preventive medical tests and services covered by Medicare and were assessed in the year following the adherence ascertainment period. We selected test and service outcomes a priori and excluded those that would be clearly associated with a clinical need for statin therapy, such as cholesterol testing and diabetes screening. Our list of outcomes studied consisted of bone mineral density testing and screening mammography for women, prostate-specific antigen testing for men, and fecal occult blood tests, influenza vaccinations, and pneumococcal vaccinations for both sexes. The time to each outcome was determined, with subjects censored by death, nursing home admission, loss of PACE eligibility, or the administrative end of follow-up (365 days after the start of follow-up).

Statistical analysis

The relation between statin adherence and each outcome was examined by use of both an unadjusted and multivariable-adjusted Cox proportional hazards model. The first Cox model made no statistical adjustments for any covariates. The second model was stratified on age and sex and included the following covariates: Charlson comorbidity score (18), number of drugs, physician visits, days in the hospital, and days in a nursing home during the baseline period, as well as history during the baseline period of chronic obstructive pulmonary disease, obesity, peripheral vascular disease, liver disease, rheumatoid arthritis, osteoarthritis, atrial fibrillation, and cancer. All data analysis was

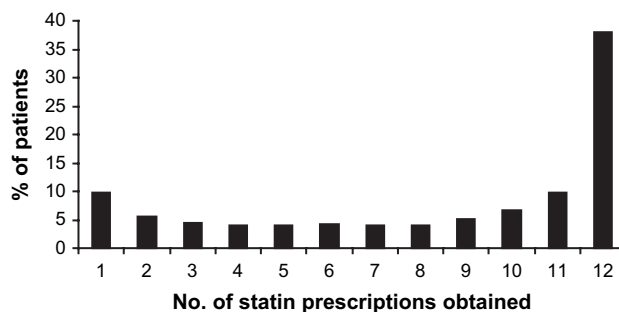


FIGURE 2. Histogram of number of prescriptions obtained during the adherence ascertainment period among a cohort of new users of statins from Pennsylvania's Pharmaceutical Assistance Contract for the Elderly, 1996–2004.

performed in SAS, version 9.0, statistical software (SAS Institute, Inc., Cary, North Carolina).

RESULTS

We identified 46,480 patients who initiated a statin other than cerivastatin during the study period. We omitted 15,271 patients with evidence of existing coronary artery disease and 6,618 with diabetes and then dropped 602 patients who died, 1,269 who were admitted to a nursing home, and 1,937 who lost PACE eligibility during the adherence ascertainment period. We were left with a final cohort of 20,783 patients whose characteristics are given in table 1. The cohort was predominately female (86 percent), had an average age of 76 years, and used seven medications during the 12-month baseline period. During this period, many had an acute care hospitalization (20 percent) and a history of atrial fibrillation (35 percent) and peripheral vascular disease (14 percent). Very few had a history of cancer, osteoarthritis, or liver disease. Of 20,783 total patients, 2,197 (11 percent) had a fecal occult blood test, 7,966 (38 percent) received an influenza vaccination, and 1,184 (6 percent) received a pneumococcal vaccination prior to being censored or reaching the end of the 1-year follow-up period. Of 17,794 women in the cohort, 1,070 (6 percent) had a bone mineral density test, and 3,707 (21 percent) underwent a screening mammography. Finally, of the 2,949 men, 615 (21 percent) received a prostate-specific antigen test.

Figure 2 depicts the distribution of the number of prescriptions filled during the ascertainment period. Approximately 10 percent of patients filled only one prescription (never returned for a refill). Slightly over 50 percent of the patients filled 10 or more prescriptions.

The results of our Cox proportional hazards regression are summarized in table 2. In the full model, stratifying on age and gender and adjusting for various comorbid conditions, we found that patients who filled more than one prescription for a statin during a 1-year ascertainment period were more likely than patients who filled only one prescription to receive prostate-specific antigen testing (hazard ratio

TABLE 2. Hazard ratios of receiving various screening tests and vaccinations, along with two or more fills during the assessment period vs. a single statin fill, in a Pennsylvania cohort, 1996–2004*

Outcome	Unadjusted hazard ratio	95% confidence interval	Multivariable-adjusted hazard ratio†	95% confidence interval
Women only				
Bone mineral density test	1.04	0.84, 1.27	1.08	0.88, 1.33
Screening mammogram	1.22	1.09, 1.38	1.22	1.09, 1.38
Men only				
Prostate-specific antigen test	1.60	1.15, 2.24	1.57	1.17, 2.19
Both sexes				
Fecal occult blood test	1.29	1.10, 1.50	1.31	1.12, 1.53
Influenza vaccination	1.18	1.09, 1.28	1.21	1.12, 1.31
Pneumonia vaccination	1.44	1.15, 1.80	1.46	1.17, 1.83

* Subjects were censored at the end of follow-up, loss of Pharmaceutical Assistance Contract for the Elderly (PACE) eligibility, death, and nursing home admission.

† The analysis is stratified on age and sex. Multivariable adjustments were made for all the other covariates given in table 1.

(HR) = 1.57, 95 percent confidence interval (CI): 1.17, 2.19), fecal occult blood tests (HR = 1.31, 95 percent CI: 1.12, 1.53), mammograms (HR = 1.22, 95 percent CI: 1.09, 1.38), influenza vaccinations (HR = 1.21, 95 percent CI: 1.12, 1.31), and pneumococcal vaccinations (HR = 1.46, 95 percent CI: 1.17, 1.83) during the subsequent follow-up period. However, there was no association between statin adherence and undergoing bone mineral density testing (HR = 1.08, 95 percent CI: 0.88, 1.33). In the model that did not make multivariable adjustments for comorbidities and other covariates, the results were substantively similar. In a sensitivity analysis, we varied the exposure definition by redefining nonadherence as filling three or fewer scripts during the ascertainment period. This resulted in estimates that were unchanged or very slightly attenuated to the null.

DISCUSSION

In a primary prevention cohort of new users of statins in Pennsylvania, we found that patients who adhered to statin therapy during an ascertainment period were more likely than patients who were less adherent to undergo a variety of cancer screening tests during the follow-up period, including prostate-specific antigen testing for prostate cancer, screening mammograms for breast cancer, and fecal occult blood tests for colon cancer. Adherent patients were also more likely to receive influenza and pneumococcal vaccinations. Because adherence to statins does not directly cause use of clinical tests or vaccinations, alternative explanations for these observed associations must be found. We put forward the explanation that patients who are adherent to statin use are more health seeking and are therefore more likely to see their physician and request, or agree to undergo, various screening tests (figure 3).

One test outcome that was not consistent with our hypothesis was bone mineral density screening for osteoporosis. We found no evidence of an association between statin ad-

herence and bone mineral density testing. The choice of this test is problematic, however, because of the potential confounding effects of body mass index, a variable that was not available in our database. Overweight patients are at greater risk of coronary artery disease (11, 19), have a greater clinical need for statin therapy, and therefore may be more likely to adhere to therapy. These same patients are at lower risk of osteoporosis and therefore have less clinical need for bone mineral density testing (20). The confounding due to body mass index would tend to make adherence associated with decreased frequency of bone mineral density testing, possibly canceling out any healthy user effect. Furthermore, the US Preventive Services Task Force has only recently started recommending bone mineral density tests for all women aged 65 years or more (4).

We have suggested that the association between adherence and the use of preventive health services may be due to differences in health-seeking behavior. However, it is also possible that these associations are due to differences in actual health status. Two such aspects of health status would be functional status, that is, an individual's ability to perform normal daily activities of living, and cognitive status. In a related setting, functional status was raised as a possible cause of the association between receipt of influenza vaccinations and mortality during the non-flu season (21). In our study, confounding by functional status could happen if there is significant variation in functional status in our

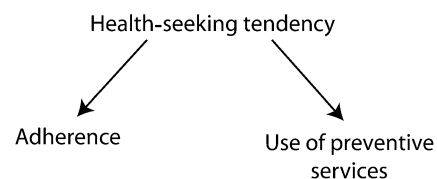


FIGURE 3. Association between adherence and testing due to confounding by health-seeking behaviors.

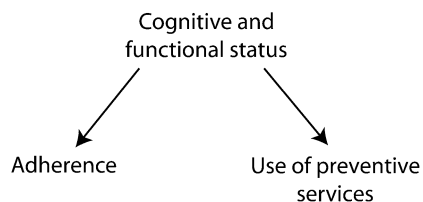


FIGURE 4. Association between adherence and testing due to confounding by health status.

cohort and if individuals with low functional status are less likely to get their statin prescription refilled and also less likely to make it to a physician's office for routine screening tests (figure 4). A similar argument can be made for cognitive status. However, we noted that adjustments for various comorbid conditions, many of which would be associated with functional status (e.g., chronic obstructive pulmonary disease), had little effect on point estimates. This suggests that the observed association between adherence and use of preventive health services is not likely to be attributable to differences in functional status. Nevertheless, the healthy user effect can be usefully thought of as a multidimensional construct that incorporates both aspects of health status as well as health-seeking tendencies.

It is also possible that some of the observed association between adherence and use of preventive health services is due to a provider effect. This would happen if some doctors were more likely to order immunizations and screening tests and were also more successful at encouraging their patients to remain adherent to preventive therapies. We explored this hypothesis by conducting an analysis in which separate physician-specific strata were included in the Cox proportional hazards model. Because many physicians saw just a few patients in our data set, our analysis was limited in power. However, most point estimates were similar to those from our original analysis, and the associations among screening mammography, prostate-specific antigen testing, and fecal occult blood testing remained statistically significant.

We have described various ways that confounding effects could have led to the observed association between adherence and use of preventive health services; however, it is also possible that our sample selection process could have contributed to this observed association. In order for people to be selected into our sample, they must have survived, remained PACE eligible, and not been admitted into a nursing home during the 1-year ascertainment period. If there are variables, such as health status, that lead to selection (e.g., surviving the ascertainment period) and are independent determinants of testing (e.g., people in good health are more likely to get preventive tests) and if adherence to statins also causes selection (e.g., by preventing mortality during the ascertainment period), then adherence may be associated with testing even if health status has no effect on adherence (figure 5). In this hypothetical scenario, selec-

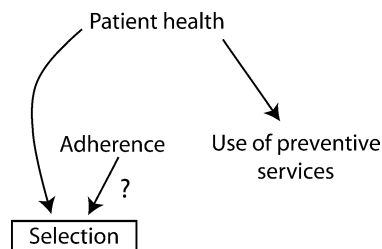


FIGURE 5. Association between adherence and testing due to selection bias.

tion is a “collider” variable (22), and conditioning on it can create an association between adherence and testing (23). However, there is little evidence that statins reduce the risk of all-cause mortality in primary prevention (24), so adherence to statins is unlikely to be influencing sample selection and creating selection bias.

Our study is limited primarily by generalizability. We studied a specific population that is elderly, frail, predominately female, and of low socioeconomic status. Further work will be required to see if the observed associations also apply to younger, healthier, or more affluent populations where variations in health-seeking behavior or actual health status could be substantially different.

Although our study provides evidence of a healthy user effect among new users of statins, it does not make clear the degree of bias this effect might cause in a study of health outcomes and statin exposure. The observed associations between adherence and use of preventive health services could lead directly to some bias in a typical outcomes study. For example, influenza vaccinations and early detection of cancer can each reduce the risk of mortality. However, the association between adherence and testing may be more problematic to the extent that it reveals a possible association between adherence and other unmeasured health-seeking behaviors. Our results raise the possibility that patients who are adherent to statins may be more likely to eat a healthful diet, exercise regularly, drink moderately, and generally take better care of themselves than patients who are less adherent.

To the extent that overall health or health-seeking behaviors can be adequately measured, these biases can be reduced or eliminated through statistical modeling. For example, bias in a study of the mortality risk associated with the use of flu vaccines was attenuated when measures of functional status were included in the model (21). The inclusion of variables that are strongly correlated with the unmeasured confounders should also achieve some reduction in the healthy user bias. For example, observational studies of estrogen that included measures of socioeconomic status yielded effect estimates that were more compatible with randomized, controlled trial results, presumably because overall health and health-seeking tendencies correlate strongly with socioeconomic status (3). However, in our population, which is defined by low socioeconomic status, there still appeared to be strong differences in health-seeking tendencies between patients.

If the initiation or choice of treatment depends strongly on unmeasured aspects of health, quasi-experimental approaches, such as the method of instrumental variables (25), may prove to be useful. These methods require the presence of variables that are related to treatment choice but are independently unrelated to the outcome. Potential instrumental variables may arise from differences in prescribing patterns between geographic regions (26, 27), clinics (28), or physicians (29). However, such methods depend on other strong assumptions and may result in estimates that are more biased than conventional approaches.

More promising approaches to controlling the healthy user effect may come from study design and analytical strategies. For example, a new user design with an active comparator group may help to reduce the confounding that results when healthier patients are more likely to initiate a new therapy. Such an approach was used recently in a study of nonsteroidal antiinflammatory medications in which new users of antiglaucoma drugs were used as a reference group (30). If one assumes that the initiated treatment is continued through the follow-up, that is, by using an analog of the intention-to-treat approach, it may be possible to reduce the “adherence bias” resulting from informative discontinuation of treatment due to unmeasured differences in health or health-seeking tendencies. If nonadherence is high, however, intention-to-treat approaches can result in effect estimates that are strongly attenuated to the null when comparing a treated group with an untreated group. Unfortunately, high nonadherence is typical among users of preventive therapies (31–33). As seen in the present study, a substantial fraction of patients never fill a second prescription for a statin.

Our study contributes to a growing collection of evidence that suggests that patients who initiate and adhere to preventive treatments may be systematically healthier and more health seeking than otherwise comparable patients who do not remain adherent. Additionally, our findings suggest that the healthy user effect might be detectable by examining the association between adherence to treatment and downstream use of preventive health services. Further work in the area is needed to gain a better understanding of circumstances under which the healthy user effect is likely to be a problem, as well as study design, statistical modeling, and analysis methods that can be used to best control this bias.

ACKNOWLEDGMENTS

M. A. B. is supported by a career development grant from the National Institute on Aging (AG-027400). D. H. S. is supported by grants from the National Institutes of Health (AR-48616, DK-02759, and AR-47782), Arthritis Foundation, and the Engalitcheff Arthritis Outcomes Initiative. S. M. C. is supported by a fellowship from the Canadian Institute of Health Research.

The authors thank Jessica Agnew-Blais for her help with document preparation. They thank Helen Mogun for programming assistance.

M. A. B. receives salary support from research grants from Amgen, Inc. (Thousand Oaks, California) for un-

related work. D. H. S. has received research grants from Merck & Co., Inc. (Whitehouse Station, New Jersey), Pfizer, Inc. (La Jolla, California), the Procter & Gamble Company (Cincinnati, Ohio), and Sangart, Inc. (San Diego, California) for unrelated work. There was no pharmaceutical industry support for this study.

REFERENCES

1. Simpson SH, Eurich DT, Majumdar SR, et al. A meta-analysis of the association between adherence to drug therapy and mortality. *BMJ* 2006;333:15–20.
2. White HD. Adherence and outcomes: it's more than taking the pills. *Lancet* 2005;366:1989–91.
3. Humphrey LL, Chan BK, Sox HC. Postmenopausal hormone replacement therapy and the primary prevention of cardiovascular disease. *Ann Intern Med* 2002;137:273–84.
4. Ray WA, Daugherty JR, Griffin MR. Lipid-lowering agents and the risk of hip fracture in a Medicaid population. *Inj Prev* 2002;8:276–9.
5. Majumdar SR, McAlister FA, Eurich DT, et al. Statins and outcomes in patients admitted to hospital with community acquired pneumonia: population based prospective cohort study. *BMJ* 2006;333:999–1003.
6. Haley RW, Dietsch JM. Is there a connection between the concentration of cholesterol circulating in plasma and the rate of neuritic plaque formation in Alzheimer disease? *Arch Neurol* 2000;57:1410–12.
7. Glynn RJ, Knight EL, Levin R, et al. Paradoxical relations of drug treatment with mortality in older persons. *Epidemiology* 2001;12:682–9.
8. Glynn RJ, Schneeweiss S, Wang PS, et al. Selective prescribing led to overestimation of the benefits of lipid-lowering drugs. *J Clin Epidemiol* 2006;59:819–28.
9. Chewning B. The healthy adherer and the placebo effect. *BMJ* 2006;333:18–19.
10. Avorn J. Review: good adherence (compared with poor adherence) to drug therapy is associated with a reduction in mortality. *ACP J Club* 2006;145:80.
11. Petitti DB. Coronary heart disease and estrogen replacement therapy. Can compliance bias explain the results of observational studies? *Ann Epidemiol* 1994;4:115–18.
12. Rossouw JE. Debate: the potential role of estrogen in the prevention of heart disease in women after menopause. *Curr Control Trials Cardiovasc Med* 2000;1:135–8.
13. Barrett-Connor E, Grady D. Hormone replacement therapy, heart disease, and other considerations. *Annu Rev Public Health* 1998;19:55–72.
14. Garbe E, Suissa S. Hormone replacement therapy and acute coronary outcomes: methodological issues between randomized and observational studies. *Hum Reprod* 2004;19:8–13.
15. Redberg RF. Vitamin E and cardiovascular health: does sex matter? *JAMA* 2005;294:107–9.
16. Jackson LA, Jackson ML, Nelson JC, et al. Evidence of bias in estimates of influenza vaccine effectiveness in seniors. *Int J Epidemiol* 2006;35:337–44.
17. Setoguchi S, Glynn RJ, Avorn J, et al. Statins and the risk of lung, breast, and colorectal cancer in the elderly. *Circulation* 2007;115:27–33.
18. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373–83.

19. DiMatteo MR, Sherbourne CD, Hays RD, et al. Physicians' characteristics influence patients' adherence to medical treatment: results from the Medical Outcomes Study. *Health Psychol* 1993;12:93–102.
20. Cadarette SM, Jaglal SB, Kreiger N, et al. Development and validation of the Osteoporosis Risk Assessment Instrument to facilitate selection of women for bone densitometry. *CMAJ* 2000;162:1289–94.
21. Jackson LA, Nelson JC, Benson P, et al. Functional status is a confounder of the association of influenza vaccine and risk of all cause mortality in seniors. *Int J Epidemiol* 2006;35:345–52.
22. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. *Epidemiology* 1999;10:37–48.
23. Hernan MA, Hernandez-Diaz S, Robins JM. A structural approach to selection bias. *Epidemiology* 2004;15:615–25.
24. Thavendiranathan P, Bagai A, Brookhart MA, et al. Primary prevention of cardiovascular diseases with statin therapy: a meta-analysis of randomized controlled trials. *Arch Intern Med* 2006;166:2307–13.
25. Angrist JD, Imbens GW, Rubin DB. Identification of causal effects using instrumental variables. *J Am Stat Assoc* 1996; 81:444–55.
26. Wen SW, Kramer MS. Uses of ecologic studies in the assessment of intended treatment effects. *J Clin Epidemiol* 1999; 52:7–12.
27. Brooks JM, Chrischilles EA, Scott SD, et al. Was breast conserving surgery underutilized for early stage breast cancer? Instrumental variables evidence for stage II patients from Iowa. *Health Serv Res* 2003;38:1385–402. Erratum in: *Health Serv Res* 2004;39:693.
28. Johnston SC. Combining ecological and individual variables to reduce confounding by indication: case study—subarachnoid hemorrhage treatment. *J Clin Epidemiol* 2000;53: 1236–41.
29. Brookhart MA, Wang PS, Solomon DH, et al. Evaluating short-term drug effects using a physician-specific prescribing preference as an instrumental variable. *Epidemiology* 2006; 17:268–75.
30. Solomon DH, Avorn J, Sturmer T, et al. Cardiovascular outcomes in new users of coxibs and nonsteroidal antiinflammatory drugs: high-risk subgroups and time course of risk. *Arthritis Rheum* 2006;54:1378–89.
31. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med* 2005;353:487–97.
32. Benner JS, Glynn RJ, Mogun H, et al. Long-term persistence in use of statin therapy in elderly patients. *JAMA* 2002;288: 455–61.
33. Solomon DH, Avorn J, Katz JN, et al. Compliance with osteoporosis medications. *Arch Intern Med* 2005;165: 2414–19.