

Safety and Effectiveness of Mail Order Pharmacy Use in Diabetes

Julie A. Schmittiel, PhD; Andrew J. Karter, PhD; Wendy T. Dyer, MS;
James Chan, PharmD, PhD; and O. Kenrik Duru, MD, MSHS

Background: Although research suggests that mail order pharmacy use is associated with greater medication adherence and cardiovascular disease risk factor control, no research has examined the potential impact of mail order pharmacy use on patient safety and utilization.

Objectives: To compare safety and utilization outcomes in patients using mail order versus local pharmacies.

Study Design: Cross-sectional, observational study of 17,217 Kaiser Permanente Northern California adult diabetes patients prescribed new cardiometabolic medications in 2006.

Methods: Multivariate logistic regressions assessed the association between mail order pharmacy use and all-cause and preventable hospitalizations and emergency department (ED) visits; laboratory tests for monitoring persistent medications; and overlapping days of supply of contraindicated medications. Results were stratified by patient age and converted to adjusted predicted percentages.

Results: Patients aged less than 65 years using mail order had fewer ED visits (33.8% vs 40.2%; $P < .001$); preventable ED visits (7.7% vs 9.6%; $P < .01$); and serum creatinine laboratory monitoring tests after angiotensin-converting enzyme inhibitor/angiotensin receptor blocker or diuretic initiation (41.2% vs 47.2%; $P < .01$). Among patients aged 65 or more years, mail order users had fewer preventable ED visits (13.4% vs 16.3%; $P < .01$); but slightly more occurrences of overlapping days of supply of contraindicated medications (1.1% vs 0.7%; $P < .01$).

Conclusions: Mail order pharmacy use is not associated with adverse outcomes in most diabetes patients, and is associated with lower ED use. Interventions to increase mail order pharmacy use should use a patient-centered approach that is sensitive to primary and preventive care access.

Am J Manag Care. 2013;19(11):882-887

For author information and disclosures,
see end of text.

Mail order pharmacies are widely used to deliver medications in the United States, with up to one-third of chronic illness medications delivered by mail.^{1,2} Research suggests a positive association between mail order pharmacy use and greater adherence to diabetes and antihypertensive medications,³⁻⁶ and with better low-density lipoprotein cholesterol control.⁷ These favorable outcomes may reflect improved access to medications with mail order pharmacy use,⁸ which may be of particular value to patients with disabilities, time constraints, or limited transportation (Figure).^{3,8} However, there may be unintended consequences to using mail order pharmacies. When medical offices and pharmacies are in the same location, patients who use mail order pharmacies may be less likely to access preventive care services. This may increase the risk of hospitalizations and emergency department (ED) visits that are sensitive to preventive care quality.^{9,10} Diabetes patients, who often take multiple medications, may be particularly at risk for exposure to contraindicated medications.^{11,12} Mail order pharmacy users may miss face-to-face consultations with pharmacists and physicians designed to prevent contraindicated medication use. Finally, many medications require laboratory monitoring to reduce the risk of potential adverse drug events,¹³ and mail order pharmacy use may inadvertently reduce the likelihood that such tests are ordered by physicians and completed by patients. The purpose of this study was to examine the relationship between mail order pharmacy use and safety and healthcare outcomes in diabetes patients, and whether effects vary by key patient characteristics.

METHODS

Study Population and Setting

This study was conducted within Kaiser Permanente Northern California (KPNC), an integrated health system providing comprehensive medical care to more than 3 million members. We selected subjects from the KPNC Diabetes Registry. The registry, established in 1993, is updated annually by adding patients with diabetes identified from automated databases of pharmacy data, laboratory data, hospitalization records, and outpatient diagnoses.^{3,14} Study subjects were required to be at least 18 years of age by January

In this article
Take-Away Points / p883
www.ajmc.com
Full text and PDF

1, 2006, and to have been prescribed a new antiglycemic, antihypertensive, or lipid-lowering medication from January 1 through May 31, 2006. We defined having a new medication as having no history of any medication prescription fill within the same therapeutic drug class within the past 24 months. If patients were prescribed multiple new cardiometabolic medications during this period, the earliest prescription was defined as the index medication. We excluded the small proportion (<5%) of members who lacked KPNC drug benefits during the study period.

KPNC maintains a mail order pharmacy distribution system in coordination with more than 120 local walk-in KPNC pharmacies located within outpatient clinics and hospitals.^{3,7} The first fill of a medication is typically at a local KPNC pharmacy and includes a pharmacist consultation. Patients may then refill existing prescriptions either by mail or at any KPNC local pharmacy. Mail delivery of medications with free shipping can be requested by phone or online. While KPNC members also have the option of filling prescriptions at non-KPNC pharmacies, the cost of these fills is not covered by the patient's pharmacy benefit. Pharmacists are available via telephone to answer medication-related questions regardless of the mode of delivery. There is no proscribed days of supply of pills required for mail delivery; KPNC typically dispenses 100-day supplies through both mail order and local pharmacies. Some patients have a financial incentive to use mail order in the form of a lower copayment for the same number of days of supply. For this analysis, patients were defined as local KPNC pharmacy users if they never used the mail order pharmacy to fill the new index medication in the 12 months after initiation, and as mail order pharmacy users if they filled the index medication at least once via mail during that time frame.

Outcome Variables

All-cause hospitalizations, preventable hospitalizations, all-cause ED use, and preventable ED use were defined as no episodes versus 1 or more episodes in the 3 years after the index medication initiation date. Preventable hospitalizations and preventable ED visits were defined using published and validated lists of encounters that are considered sensitive to primary care access and quality (eg, hospitalizations and ED visits for asthma).^{9,10,15}

Among patients whose index medication was an angiotensin-converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), or diuretic, we examined whether there was

Take-Away Points

Mail order pharmacy use is associated with better medication adherence and cardiovascular disease risk factor control, but its impact on patient safety and utilization is unknown. Among mail order users, we found:

- Diabetes patients aged less than 65 years had fewer emergency department (ED) visits, but fewer monitoring tests after angiotensin-converting enzyme inhibitor/angiotensin receptor blocker or diuretic initiation.
- Diabetes patients aged 65 or more years had fewer preventable ED visits, but slightly more overlapping days of supply of contraindicated medications.
- Interventions to increase mail order pharmacy use may improve outcomes, but should employ patient-centered approaches sensitive to care access.

an appropriate potassium or serum creatinine lab test within 30 days after the index date.^{13,16} These tests monitor for the possibility of electrolyte abnormalities or decreased renal function in patients new to these medications.

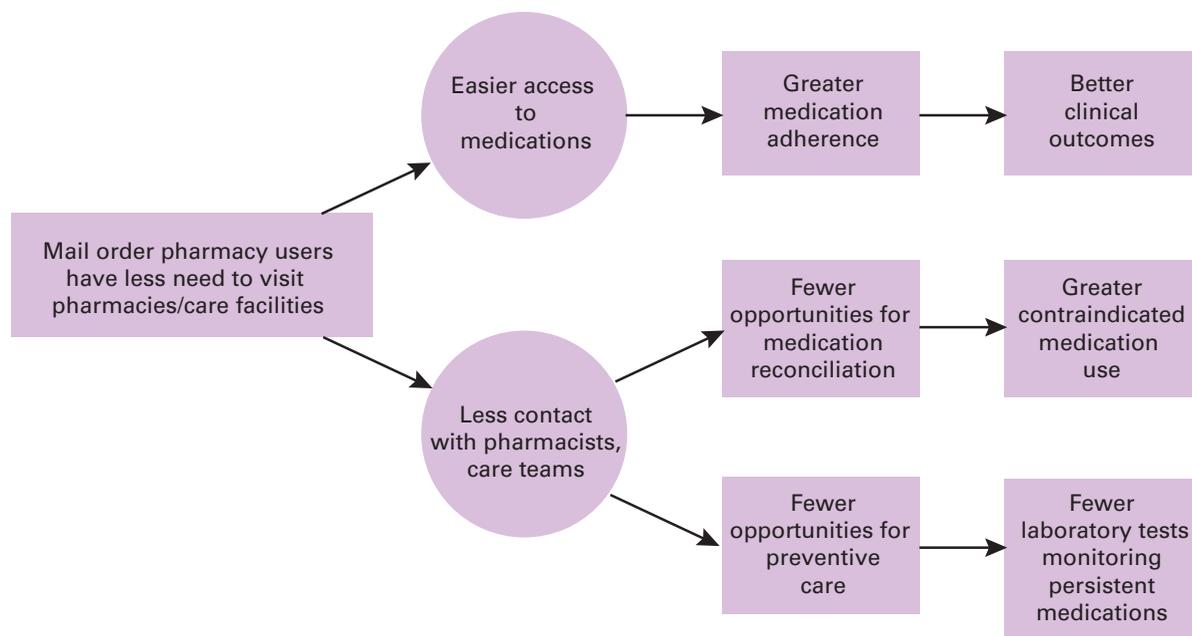
Potential for serious medication interaction was defined using a published list of contraindicated medications¹⁷ and was operationalized as 2 or more occurrences of overlapping days of supply of contraindicated drugs (eg, anticoagulants and thyroid hormones) for 1 or more days in the 15 months after the index date.

Statistical Analysis

We estimated separate logistic regression models to examine the relationship between mail order pharmacy use and each outcome variable. In each analysis we adjusted for age; sex; race/ethnicity; neighborhood deprivation score calculated with geocoded census socioeconomic data^{18,19}; number of comorbidities; smoking status; use of nonformulary medications, antidepressants, or insulin; whether the index medication was generic or brand name; length of therapy with the index medication; days of supply of the first refill; distance from the patient's home to their nearest local KPNC pharmacy; and the patient's KPNC primary outpatient medical facility (operationalized as a series of dichotomous variables). Detailed definitions of these variables have been published previously.³ Patients with missing covariates ($n = 85$) were excluded from the analysis. Models included interaction terms for mail order use with age, race/ethnicity, and deprivation score to assess whether different groups of patients might be more vulnerable to potential safety concerns when using the mail order pharmacy. Since the age interaction was the only interaction term that was significant, we present the results as adjusted percentages from models stratified by age less than 65 years versus age 65 years or older.

Omitted (unmeasured) variable bias may be of particular concern when studying the impact of mail order pharmacy use on patient safety outcomes. It is possible that patients who used the mail order pharmacy were different from those

■ **Figure.** Potential Impact of Mail Order Pharmacy Use on Outcomes



who did not in ways we were unable to measure (eg, patient motivation). As a sensitivity analysis, we examined the potential impact of unmeasured variables on the relationship between mail order pharmacy use and our outcomes using methods that test the robustness of effect sizes in the presence of confounding.²⁰⁻²²

All analyses were performed using Stata release 10.1 (StataCorp, College Station, Texas). The study protocol was approved by the KPNC Institutional Review Board.

RESULTS

A total of 17,217 diabetes patients met study eligibility criteria. Of these, 5890 (34.2%) used the mail order pharmacy at least once to refill their new cardiometabolic medication during the study period (Table 1). Mail order pharmacy users were more likely to be white (56.7% vs 37.1%; $P < .001$) and to live in census tracts with higher socioeconomic status ($P < .001$).

Table 2 shows the adjusted predicted percentages of patients experiencing each outcome, stratified by age. After adjustment for demographic, clinical, and census-block characteristics, patients aged less than 65 years using the mail order pharmacy were less likely to have an all-cause ED visit (33.8% vs 40.2%; $P < .001$); less likely to have a preventable ED visit (7.7% vs 9.6%; $P < .01$); and less likely to receive a recommended serum creatinine lab test within 30 days if their index medication was an ACE, ARB, or diuretic (41.2% vs 47.2%; $P < .01$). Among patients aged 65 or more years, those

using mail order were less likely to experience a preventable ED visit (13.4% vs 16.3%; $P < .05$) and slightly more likely to experience 2 or more occurrences of overlap in days of supply of contraindicated medications (1.1% vs 0.7%; $P < .01$).

Our sensitivity analysis found that our observed effects of mail order use on ED visits, hospitalizations, and overlapping days of supply of contraindicated medications were very robust to the presence of a hypothetical unmeasured confounder; for example, even an unmeasured confounder strongly related to an outcome such as ED use (assuming a relative risk of 2.0) and prevalent in more than 50% of the mail order pharmacy–using population would not change the relationship seen in our findings.²⁰⁻²²

DISCUSSION

This is the first study to examine the relationship between mail order pharmacy use and patient safety and utilization outcomes. We found that mail order use was not negatively associated with patient safety outcomes overall, suggesting that mail order use does not serve as a barrier to receiving primary and preventive care services for most patients. Patients aged less than 65 years who used the mail order pharmacy did have slightly lower rates of serum creatinine testing with ACE, ARB, or diuretic use (41.4% vs 47.2%; $P < .01$). While there was no statistically significant difference in potassium laboratory testing in this group, or for any lab testing in patients aged 65 or more years, our findings suggest that in-person pharmacy refills may increase opportunities for moni-

■ **Table 1.** Patient Characteristics

Characteristics	Entire Sample (n = 17,217)	Mail Order Pharmacy Users (n = 5890)	Local Pharmacy Users (n = 11,327)
Female, %	46.4	46.0	46.7
Age, y, mean (SD)	62 (11.9)	63 (11.7)	62 (12.0) ^a
Race/ethnicity, %			
White, non-Latino	43.8	56.7	37.1 ^a
African American, non-Latino	9.1	4.7	11.4 ^a
Latino	8.8	6.0	10.2 ^a
Asian	10.9	9.5	11.6 ^a
Native American	1.7	1.9	1.6
Mixed race	11.0	9.2	12.0 ^a
Missing race	14.7	11.9	16.1 ^a
Socioeconomic deprivation, %			
First quartile (least deprived)	20.5	25.8	17.8 ^a
Second quartile	28.9	30.0	28.3 ^b
Third quartile	26.3	23.3	27.8 ^a
Fourth quartile (most deprived)	17.9	12.0	21.0 ^a
Socioeconomic status missing	6.5	9.0	5.2 ^a
Number of comorbidities, mean (SD)	0.81 (1.1)	0.83 (1.0)	0.80 (1.1) ^b
Smoker, %	7.7	7.0	8.0 ^b
History of medication for depression, %	22.1	24.0	21.1 ^a
History of insulin use, %	19.1	17.8	19.8 ^a
History of nonformulary medication use, %	6.0	6.4	5.8
New medication is brand name, %	22.3	24.0	21.4 ^a
Medication days of supply, %			
1-30	5.2	5.0	5.3
31-60	5.4	5.5	5.4
61-90	5.7	6.1	5.4
>90	83.7	83.3	83.9
Number of days from first fill to last fill, mean (SD)	349 (100)	362 (87)	342 (106) ^a

SD indicates standard deviation.
^aP < .001 for the difference between groups.
^bP < .05 for the difference between groups.

toring of persistent medications in settings where laboratories and pharmacies are co-located.

Our study also found that patients aged 65 or more years had slightly higher rates of 2 or more occurrences of overlapping days of supply of contraindicated medications. While these rates were extremely low for both mail order and local pharmacy users (1.1% and 0.7%, respectively), our analysis adds to the evidence suggesting that older patients using multiple medications may require additional monitoring for adverse events.^{12,13} It is important that pharmacies provide increased access to chronic illness medications while also main-

taining appropriate systems for preventing contraindicated medication use.

We found mail order pharmacy use was associated with lower overall ED use in patients aged less than 65 years, as well as lower preventable ED use in patients in all age groups. Previous studies have shown mail order use is associated with greater medication adherence³⁻⁶ and low-density lipoprotein cholesterol control.⁷ Since good medication adherence and cardiovascular disease risk factor control are associated with reduced hospitalizations and better outcomes,²³⁻²⁵ mail order use may lead to lower preventable utilization over time.

■ **Table 2.** Adjusted Predicted Percentages^a

Outcome	Age <65 y (n = 9822)		Age ≥65 y (n = 7269)	
	Local Pharmacy Users, %	Mail Order Pharmacy Users, %	Local Pharmacy Users, %	Mail Order Pharmacy Users, %
At least 1 hospitalization, all cause	12.2	11.2	23.0	22.5
At least 1 hospitalization, preventable	1.9	1.4	4.2	3.6
At least 1 ED visit, all cause	40.2 ^b	33.8 ^b	52.3	49.8
At least 1 ED visit, preventable	9.6 ^c	7.7 ^c	16.3 ^c	13.4 ^c
Had potential serious medication interaction	0.4	0.4	0.7 ^c	1.1 ^c
	n = 2549		n = 2019	
Had potassium lab test within 30 days	43.5	39.5	50.6	55.1
Had serum creatinine lab test within 30 days	47.2 ^c	41.2 ^c	52.7	56.2

ED indicates emergency department.

^aAdjusted for distance (in miles) to patient's home medical center; sex; race/ethnicity; neighborhood deprivation score; number of comorbidities; smoking status; use of nonformulary medications, antidepressants, or insulin; whether the index medication was generic or brand name; days of supply of the first refill; length of therapy with the index medication; and Kaiser Permanente Northern California service area.

^b*P* < .001.

^c*P* < .01.

Mail order pharmacy services, which are provided at the healthcare delivery system level rather than the physician or practice level, can be considered a structural or system-level intervention for improving access to chronic illness medications.^{3,7} While this study and others³⁻⁷ suggest that using mail order pharmacy services may improve outcomes, our study also suggests that certain patients may be more sensitive to any potential negative impact of mail order pharmacy use on healthcare access. System-level efforts to promote mail order use should preserve patient choice in pharmacy services and maintain a patient-centered approach to meeting an individual's overall healthcare needs. Future research should continue to address the important issue of how to appropriately target and promote mail order pharmacy services while preserving the benefits of in-person interaction with pharmacists and other care providers.

This study has several limitations. Observational studies cannot entirely control for differences between patients who use mail order pharmacy services and those who do not. While our sensitivity analysis demonstrated that the relationship between mail order pharmacy use and our outcomes would still be observed even in the presence of a powerful, prevalent confounder, future research should leverage randomized controlled trial designs to examine the impact of mail order pharmacy use on intermediate outcomes, healthcare utilization, and patient safety.

We were unable to ascertain pharmacy utilization at non-KPNC pharmacies. However, we limited our analyses to members with a drug benefit, which is only recognized at KPNC pharmacies. This under-ascertainment should be minimal, as previous research suggests that diabetes patients

with drug benefits report extremely low use of non-KPNC pharmacies.²⁶

This study was conducted in an integrated delivery system where patients access prescription medications differently than in many other settings. Use of "brick and mortar" pharmacies to fill prescriptions is primarily limited to KPNC local pharmacies; KPNC's mail order and local pharmacies do not differ in the standard days of supply of pills issued; and mail order pharmacy does not require physician enrollment of the prescription. In addition, KPNC local pharmacies are primarily co-located with medical offices and laboratories, which is often not the case in other settings. This co-location may make any relationship between in-person pharmacy use and preventive care services stronger than in cases where patients obtain in-person refills from brick-and-mortar pharmacies that are not integrated with outpatient care. It is therefore possible that the use of mail order pharmacy services in KPNC has a different impact on outcomes than it would have in other settings.

CONCLUSION

Mail order pharmacy use is not associated with adverse events in most diabetes patients and may be associated with improved health outcomes. System-level interventions to increase mail order pharmacy use may be an important strategy for improving processes and outcomes of care for patients with chronic illness; however, these interventions should use a patient-centered approach that does not increase risk in older patients and others who may be sensitive to primary and preventive care access.

Author Affiliations: From Division of Research (JAS, AJK, WTD), Pharmacy Outcomes Research Group (JC), Kaiser Permanente Northern California, Oakland, CA; David Geffen School of Medicine (KD), University of California, Los Angeles; Los Angeles, CA.

Funding: This study was funded by the Division of Diabetes Translation, Centers for Disease Control and Prevention, contract CDC U58 DP002641. This activity was also supported by the Health Delivery Systems Center for Diabetes Translational Research (National Institute of Diabetes and Digestive and Kidney Diseases [NIDDK] grant 1P30-DK092924), the Diabetes Study of Northern California (NIDDK grant R01 DK080726), and the Diabetes and Aging Study (NIDDK grant R01 DK0817960); the Harold Amos Medical Faculty Development Program from the Robert Wood Johnson Foundation; and the National Institute on Aging (grant K08 AG033630). The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the funding organizations.

Author Disclosures: The authors (JAS, AJK, WTD, JC, OKD) report no relationship or financial interest with any entity that would pose a conflict of interest with the subject matter of this article.

Authorship Information: Concept and design (JAS, AJK, OKD); acquisition of data (JAS, AJK, WTD); analysis and interpretation of data (JAS, WTD, JC, OKD); drafting of the manuscript (JAS); critical revision of the manuscript for important intellectual content (AJK, JC, OKD); statistical analysis (WTD); obtaining funding (JAS, AJK); administrative, technical, or logistic support (JC); and supervision (JAS).

Address correspondence to: Julie A. Schmittiel, PhD, Division of Research, Kaiser Permanente, 2000 Broadway, Oakland, CA 94612. E-mail: Julie.A.Schmittiel@kp.org.

REFERENCES

1. Medel M; for the Pharmaceutical Strategies Group. *PBM 101*. http://www.psgconsults.com/resources/pbm_101.pdf. Published 2011. Accessed June 24, 2011.
2. Federal Trade Commission. *Pharmacy Benefit Managers: Ownership of Mail-Order Pharmacies*. Washington, DC: Federal Trade Commission; 2005.
3. Duru OK, Schmittiel J, Dyer W, et al. Mail-order pharmacy use and adherence to diabetes-related medications. *Am J Manag Care*. 2010;16(1):33-40.
4. Pittman DG, Tao Z, Chen W, Stettin GD. Antihypertensive medication adherence and subsequent health care utilization and cost. *Am J Manag Care*. 2010;16(8):568-576.
5. Devine S, Vlahiotis A, Sundar H. A comparison of diabetes medication adherence and healthcare costs in patients using mail order pharmacy and retail pharmacy. *J Med Econ*. 2010;13(2):203-211.
6. Zhang L, Zakharyan A, Stockl KM, Harada AS, Curtis BS, Solow BK. Mail-order pharmacy use and medication adherence among Medicare Part D beneficiaries with diabetes. *J Med Econ*. 2011;14(5):562-567.
7. Schmittiel J, Karter A, Dyer W, et al. The comparative effectiveness of mail order pharmacy vs. local pharmacy use on LDL-C control in new statin users. *J Gen Intern Med*. 2011;26(12):1396-1402.
8. Duru OK, Gerzoff RB, Selby JV, et al. Identifying risk factors for racial disparities in diabetes outcomes: the Translating Research Into Action for Diabetes Study. *Med Care*. 2009;47(6):700-706.
9. Parchman ML, Culler SD. Preventable hospitalizations in primary care shortage areas: an analysis of vulnerable Medicare beneficiaries. *Arch Fam Med*. 1999;8(6):487-491.
10. Ballard DW, Price M, Fung V, et al. Validation of an algorithm for categorizing the severity of hospital emergency department visits. *Med Care*. 2010;48(1):58-63.
11. Steinman MA, Hanlon JT. Managing medications in clinically complex elders: "There's got to be a happy medium." *JAMA*. 2010;304(14):1592-1601.
12. Good CB. Polypharmacy in elderly patients with diabetes. *Diabetes Spectrum*. 2002;15(4):240-248.
13. Raebel MA, Lyons EE, Andrade SE, et al. Laboratory monitoring of drugs at initiation of therapy in ambulatory care. *J Gen Intern Med*. 2005;20(2):1120-1126.
14. Karter AJ, Ferrara A, Liu JY, Moffet HH, Ackerson LM, Selby JV. Ethnic disparities in diabetic complications in an insured population [published correction appears in *JAMA*. 2002;288(1):46]. *JAMA*. 2002;287(19):2519-2527.
15. Kruzikas DT, Jiang HJ, Remus D, et al. *Preventable Hospitalizations: A Window Into Primary and Preventive Care, 2000*. HCUP Fact Book No. 5. AHRQ Publication No. 04-0056. Agency for Healthcare Research and Quality. <http://archive.ahrq.gov/data/hcup/factbk5/>. Published September 2004. Accessed December 5, 2011.
16. Moffet HH, Parker MM, SkarKare U, et al. Adherence to laboratory test requests by patients with diabetes: the Diabetes Study of Northern California (DISTANCE). *Am J Manag Care*. 2011;17(5):339-344.
17. Malone DC, Abarca J, Hansten PD, et al. Identification of serious drug-drug interactions: results of the partnership to prevent drug-drug interactions. *J Am Pharm Assoc (2003)*. 2004;44(2):142-151.
18. Messer LC, Laraia BA, Kaufman JS, et al. The development of a standardized neighborhood deprivation index. *J Urban Health*; 83(6):1041-1062.
19. Laraia B, Karter AJ, Warton RM, Schillinger D, Moffet HH, Adler N. Place matters: neighborhood deprivation and cardiometabolic risk factors in the Diabetes Study of Northern California (DISTANCE). *Soc Sci Med*. 2012;74(7):1082-1090.
20. Schneeweiss S. Sensitivity analysis and external adjustment for unmeasured confounders in epidemiologic database studies of therapeutics. *Pharmacoepidemiol Drug Saf*. 2006;15(5):291-303.
21. Rosenbaum PR. Discussion hidden bias in observational studies. *Ann Intern Med*. 1991;115(11):901-905.
22. Chang VW, Hillier AE, Mehta NK. Neighborhood racial isolation, disorder and obesity. *Soc Forces*. 2009;87(4):2063-2092.
23. Ho PM, Rumsfeld JS, Masoudi FA, et al. Effect of medication nonadherence on hospitalizations and mortality among patients with diabetes mellitus. *Arch Intern Med*. 2006;166(17):1836-1841.
24. Lau DT, Nau DP. Oral antihyperglycemic medication nonadherence and subsequent hospitalization among individuals with type 2 diabetes. *Diabetes Care*. 2004;27(9):2149-2153.
25. Sokol MC, McGuigan KA, Verbrugge RR, Epstein RS. Impact of medication adherence on hospitalization risk and healthcare cost. *Med Care*. 2005;43(6):521-530.
26. Karter AJ, Parker MM, Moffet HH, Ahmed AT, Schmittiel JA, Selby JV. New prescription medication gaps: a comprehensive measure of adherence to new prescriptions. *Health Serv Res*. 2009;44(5, pt 1):1640-1661. ■