# Association Between Adherence to Pharmacotherapy and Outcomes in Type 2 Diabetes: A Meta-analysis

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## OBJECTIVE

**A previous study suggests an association between poor medication adherence and excess mortality in chronic disease. The purpose of this study was to assess the association between medication adherence and risk of cardiovascular disease (CVD), all-cause mortality, and hospitalization in type 2 diabetes.**

## RESEARCH DESIGN AND METHODS

**We conducted an electronic search on many electronic databases from inception to 27 April 2016. We selected randomized controlled trials and case-control and cohort studies reporting on CVD, all-cause mortality, or hospitalization outcomes by adherence in adults with type 2 diabetes. Two reviewers independently screened for eligible studies and extracted outcome data. Pooled relative risks (RRs) were calculated using a random-effects meta-analysis; risk of bias in each of the included studies was assessed using the GRADE approach.**

## RESULTS

**Eight observational studies were included ($n$ = 318,125). The mean rate of poor adherence was 37.8% (95% CI 37.6–38.0). Adjusted estimates were provided by five studies only. The RRs of good (≥80%) versus poor adherence to medication were 0.72 (95% CI 0.62–0.82, $I^2$ = 0%, three studies) for all-cause mortality and 0.90 (0.87–0.94, $I^2$ = 63%, seven studies) for hospitalization. No evidence of small study bias was observed. Only one study reported CVD outcomes by adherence.**

## CONCLUSIONS

**We identified no trials reporting on outcomes by adherence, suggesting a systematic failure to include this information. Pooled estimates from available observational studies suggest that good medication adherence is associated with reduced risk of all-cause mortality and hospitalization in people with type 2 diabetes, although bias cannot be excluded as an explanation for these findings.**


META-ANALYSIS

Adherence refers to the extent to which patients take their medication regimen as prescribed by their health care provider (1). Pooled data suggest around a quarter of patients are nonadherent, and rates of adherence are higher among patients with acute conditions when compared with chronic conditions (2). Even in the resource-intensive setting of clinical trials, the average adherence rates for trial drugs in chronic disease are between 43 and 78% (3–5). A systematic review of 11 studies in patients with type 2 diabetes remaining on treatment with oral hypoglycemic agents (OHAs) for 6–24 months reported adherence rates of between 36 and 93% (6). Evidence from individual studies suggests that adherence is poorer among patients with depression

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(7) and multimorbidity (8,9) and those on polytherapy or twice-daily regimens compared with monotherapy and once-daily regimens, respectively (7,10,11).

The increasing global prevalence of type 2 diabetes, driven by rising rates of obesity and population aging (12), accounts for considerable cardiovascular morbidity and mortality. Despite evidence from randomized controlled trials demonstrating reductions in microvascular and macrovascular complications with improved control of glycemia (13–15), achievement of $HbA_{1c}$ goals has been elusive on a population level in Europe and the U.S. (16–18). Based on findings in patients with a range of chronic diseases (1), it is hypothesized that poor adherence, in part, contributes to adverse outcomes and higher health care costs (1). In a meta-analysis of 21 studies including participants across a range of conditions, good adherence was associated with an almost halving of all-cause mortality compared with poor adherence (19). Reports linking suboptimal adherence rates with poor control of modifiable risk factors in previous studies (20,21) suggest that failure to meet targets may be due, in part, to poor adherence. Whether these associations hold true in patients with type 2 diabetes remains unclear and will be important to resolve in order to guide strategies to reduce overall risk and attenuate premature mortality in type 2 diabetes. We conducted a systematic review and meta-analysis of relevant studies to quantify the relationship between medication adherence in type 2 diabetes and incident cardiovascular disease (CVD), all-cause mortality, and all-cause hospitalization.

## RESEARCH DESIGN AND METHODS

### Study Selection

We sought randomized controlled trials and case-control and cohort studies that determined adherence at baseline and then recorded CVD (defined as fatal CVD, nonfatal myocardial infarction, or ischemic stroke) during follow-up. Data from studies recording cases of all-cause mortality and hospitalization (secondary outcomes) were also extracted. Prespecified inclusion criteria required studies that reported an objective measure of adherence with separate reporting of the primary or secondary outcome(s) among groups with good and poor adherence to antihyperglycemic or cardiovascular drug therapy. In the absence of a gold-standard method for estimation of adherence (22,23), acceptable methods to quantify adherence included pharmacy refill data, pill count, electronic drug monitoring systems, and self-reported measures in questionnaire or patient diaries. A threshold of 80% was used to define good adherence, the level at which patients have generally been categorized as adherent in the literature and trials outside those treating patients with HIV (1,24).

We searched electronic databases without language restrictions (AMED, CINAHL, Embase, ERIC, HealthSTAR, Medline, PsycINFO, and Web of Science) from inception date to 27 April 2016. Both medical subject heading (MeSH) and keywords were used to search for terms related to type 2 diabetes, adherence, CVD, mortality, and hospitalization (Supplementary Fig. 1). We supplemented the search by examining reference lists of included studies, reviews (1,24), and meta-analyses (6,19).

Information on the following variables was independently obtained by two contributors: study design, study location, study size, measure of adherence, patient characteristics, and absolute event rates. Any conflicts were resolved by the lead author. Where studies reported duplicate data, the most recent report from the same cohort was used to reflect contemporary practice and increase power. This meta-analysis was conducted according to the protocol registered with PROSPERO (registration no. CRD42016041380) and in accordance with PRISMA and MOOSE guidelines (25,26) (Supplementary Tables 1 and 2).

### Statistical Analysis

Where available, summary characteristics of subjects with good and poor adherence are presented as mean values weighted by study size. The relative risks (RRs) and 95% CIs for good versus poor adherence to medication were calculated for CVD, all-cause mortality, and all-cause hospitalization based on observed data for individual studies. Study-specific estimates were pooled using a random-effects meta-analysis with the DerSimonian and Laird method (27). A random-effects approach was taken in response to between-study heterogeneity anticipated in the effect size. Statistical heterogeneity of RR estimates was quantified using the $I^2$ statistic (28). The $I^2$ statistic is a measure of the proportion of total variation in effect size that is due to heterogeneity. Where not directly reported, crude event rates were calculated by dividing the absolute number of events by the total person-years of follow-up. Publication bias was assessed using Begg funnel plots and Egger regression symmetry tests where five or more studies were available for pooled analyses (29,30). Study quality was assessed using the Newcastle-Ottawa Scale for cohort studies, which awards a maximum of 9 points based on categories of selection (4 points), comparability (2 points), and outcome (3 points) (31). The quality of studies with scores of 7–9 was considered "good," and those with scores between 4 and 6 and $<4$ as "moderate" and "poor," respectively. Statistical analyses were two sided with a significance level of 0.05; calculations were performed with Stata release 11 (StataCorp, College Station, TX).

## RESULTS

Of 8,175 citations, we identified 105 studies for full-text review. Eight studies published between 2004 and 2015, reporting on 318,125 patients and 461,747 person-years of follow-up, were included in the final analyses (Fig. 1). All eligible studies reported on retrospective cohorts, sourced from a combination of administrative claims data ($n$ = 6) (32–37), diabetes registry data ($n$ = 1) (38), or primary care data sets ($n$ = 1) (39). Observer agreement on which studies were eligible for inclusion was good (Cohen unweighted $\kappa$ = 0.79). Only one study reported on the primary outcome (CVD) by adherence (32,39), whereas three and seven studies reported on all-cause mortality and all-cause hospitalization, respectively. Table 1 lists the characteristics of the included studies. All studies monitored adherence of antihyperglycemic medications as the exposure variable, with the exception of one study that measured combined adherence of OHAs, antihypertensives, and statins (38). Despite similarities in calculations used to define medication possession ratio and proportion of days covered, disparities exist between how included studies combined measures across different antihyperglycemic medication classes and other cardiovascular medications. A more detailed assessment of methodology used to determine adherence is available in Supplementary Table 3. Sample sizes ranged from 900 to 96,734, and

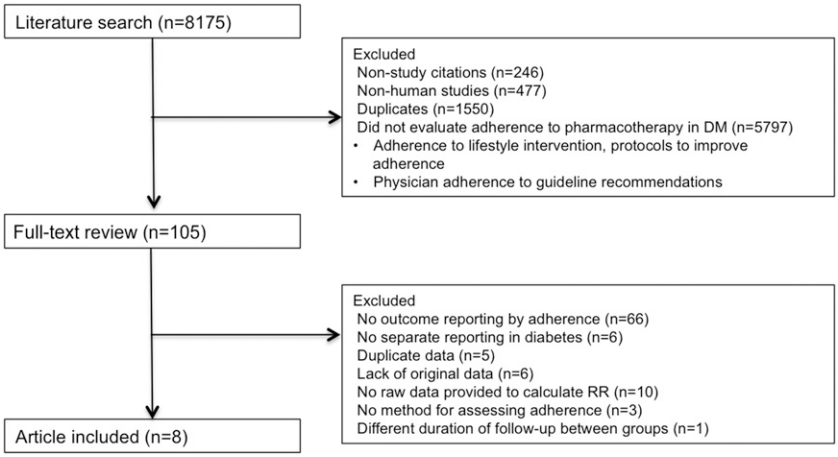


**Figure 1**—Study selection. DM, diabetes.

the mean length of follow-up ranged from 12 to 24 months. The proportion of study participants with poor adherence varied from 25 to 91%, with a weighted mean of 37.8% (120,209 of 318,125). Mean quality scores (Newcastle-Ottawa Scale) were 8.0 and 7.1 for studies reporting on all-cause mortality and hospitalization, respectively (Supplementary Table 4).

Table 2 shows the crude event rates by adherence group in each of the included studies, in addition to adjusted estimates provided. The only study to report cardiovascular outcomes by adherence (32) showed a significant reduction in CVD events with good adherence (RR 0.68 [95% CI 0.66–0.71], $P < 0.001$). During a total of 193,468 person-years of follow-up, there were 10,396 incident cardiovascular events (crude event rate 53.7 per 1,000 person-years). Male sex, increasing age, greater comorbidity burden (Charlson comorbidity index), and high income were all associated with improved levels of adherence.

The association between medication adherence and all-cause mortality was reported in three studies involving 75,681 participants, 119,568 person-years of follow-up, and 1,189 deaths (1.6%). The pooled RR from these studies was 0.72 (95% CI 0.62–0.82, $P < 0.001$) for all-cause mortality when comparing good with poor adherence (Fig. 2). No heterogeneity was observed in the effect size between studies analyzed ($I^2 = 0.0\%$, Q statistic $P = 0.65$). Of three studies included in the pooled estimates for all-cause mortality, the prevalence of poor adherence varied widely. Zhu et al. (39) reported a prevalence of 90.6%, whereas the studies by Ho et al. (38) and Jha et al. (35) reported the prevalence of poor adherence as 21.3 and 24.8%, respectively. The RR after exclusion of the data from the Zhu et al. (39) study was not qualitatively different from the overall estimate presented above (RR 0.71 [95% CI 0.61–0.82]).

Data on all-cause hospitalization were recorded across seven studies involving 221,391 individuals, 265,279 person-years of follow-up, and 46,535 hospitalization events. Good adherence was associated with benefits in reduced hospitalization rates (RR 0.90 [95% CI 0.87–0.94], $P < 0.001$). Each individual study considered in this analysis reported lower hospitalization rates among a group with good adherence (Fig. 3). Moderate heterogeneity was observed between studies; the $I^2$ was 63.4% and Q statistic $P = 0.012$. There was no evidence of small study bias, such as publication bias with Egger test for hospitalization ($P = 0.61$) (Supplementary Fig. 2). Consistent with the analyses for all-cause mortality, two studies included in the pooled estimate for hospitalization reported a prevalence of poor adherence that was high as compared with the other studies. Whereas Zhu et al. (39) and Hong and Kang (33) noted poor adherence in 90.6 and 70.6%, respectively, the remaining studies' prevalence of poor adherence ranged from 21.3 to 47.5%. Exclusion of these studies from the analysis produced an RR of 0.89 (95% CI 0.88–0.91, $P < 0.001$). In further subgroup analysis of studies using the medication possession ratio versus percentage of days covered methodology for measuring adherence, no qualitative differences were observed in effect size for all-cause hospitalization (Supplementary Fig. 3).

## CONCLUSIONS

This meta-analysis found that individuals with good adherence had a significant 10% lower rate of hospitalization events and a significant 28% lower rate of all-cause mortality when compared with a group with poor adherence. This study advances the existing literature on the impact of adherence on outcomes in diabetes in several ways. First, our analyses update and extend those of a report examining the association between adherence to drug therapy and mortality across a range of conditions, including HIV, myocardial infarction, heart failure, and hyperlipidemia (19). In that study conducted in 2006, good adherence corresponded with an ~50% reduction in the risk of mortality when compared with individuals with poor drug compliance. The present meta-analysis provides additional estimates for the association between medication adherence and mortality specific to individuals with type 2 diabetes and adds new information on the risk of hospitalization. Second, another previous systematic review that described the extent of poor adherence among individuals with diabetes receiving OHAs reported adherence rates on a continuous scale that varied between 36 and 93% (6). This study did not evaluate any clinical outcomes, and because we found no information on our prespecified end points stratified by adherence on a continuous scale, our estimates are based on a binary measure of adherence (good vs. poor adherence). Our study goes beyond identifying the prevalence of poor adherence in diabetes by quantifying the association between adherence and clinically meaningful outcomes.

A previous systematic review previously reported on an association between better adherence and improved glycemic control (40). In that study, although better adherence was found to confer reduced health care utilization, this did not translate into reduced health care costs. These findings suggest that a possible explanation for a mortality benefit seen in this study among individuals with good adherence may, in part, relate to improved glycemic control given the established relationship between hyperglycemia and mortality (41). It is important

to note that no causal association between adherence and poor outcome has been demonstrated in the current study, and previous work suggests the presence of a healthy adherer effect, whereby adherence to medication may be a proxy marker for good health behavior that reduces overall mortality (19). It was not possible to confirm the healthy adherer effect in our analyses as it relies on the reporting of outcomes among patients with good adherence to placebo therapy, which was not assessed in the observational studies included.

Despite consistent improvements in the quality of care for diabetes in recent decades (18,42), it remains a harbinger of substantial premature mortality. The presence of diabetes is associated with a 1.8-fold increase in the risk of death, and more than half of deaths are attributable to CVD (43). Recent data from the Swedish National Diabetes Register suggest that mortality in type 2 diabetes may be falling (44) as a result of more aggressive treatment with statins and blood pressure medications, in addition to improvements in glycemic control over time. The earlier use of diabetes drug classes with the ability to modify cardiovascular risk beyond glycemia may have a role in further reducing overall mortality; however, their full benefit will only be realized if patients can adhere to the prescribed regimens. Given that patients with type 2 diabetes can expect to take as many as five or more medications daily (45,46), the association between polypharmacy and poor adherence represents an additional challenge in this high-risk population (47,48).

Greater attainment of treatment targets for $HbA_{1c}$ (20,21), blood pressure (49), and LDL cholesterol (38) have all been linked to medication adherence. It is therefore vital that health care professionals can recognize and treat poor adherence. This is particularly relevant in type 2 diabetes where patients require increasingly complex treatment regimens that result from deterioration in glycemia with disease progression and the development of multiple comorbidities. Unfortunately, interventions to improve adherence have been met with mixed results, and those that have achieved success have done so at significant cost and by complex means (50). In a recent update of a Cochrane review on the subject across many conditions, even the most effective interventions did not lead

**Table 1—Characteristics of included studies in the meta-analysis**

| Reference | Study type | Treatment group (no participants) | Adherence measures | Threshold for good adherence | Prevalence of poor adherence | Follow-up | Location |
|---|---|---|---|---|---|---|---|
| Gibson et al., 2010 (32) | Retrospective cohort study (administrative claims data) | T2D on at least one OHA (96,734) | PDC | PDC ≥80%; PDC <80% | 25.5% | 24 months | U.S. |
| Zhu et al., 2015 (39) | Retrospective cohort study (Indiana Network for Patient Care) | T2D on at least one OHA (24,067) | PDC | PDC ≥80%; PDC <80% | 90.6% | 12 months | U.S. |
| Hong and Kang, 2011 (33) | Retrospective cohort study (administrative claims data) | T2D on at least one OHA (40,082) | MPR | MPR ≥80%; MPR <80% | 70.6% | 24 months | South Korea |
| Ho et al., 2006 (38) | Retrospective cohort study (Kaiser Permanente diabetes register) | Diabetes including diet controlled, those on OHAs and insulin (11,532) | PDC for OHAs, antihypertensives and statins | PDC ≥80%; PDC <80% | 21.3% | 16 months | U.S. |
| Encinosa et al., 2010 (34) | Retrospective cohort study (administrative claims data) | T2D on at least one OHA (12,046) | PDC | PDC 100%; PDC <50% | 47.5% | 12 months | U.S. |
| Jha et al., 2012 (35) | Retrospective cohort study (administrative claims data–Medco database) | Diabetes on at least one OHA but not insulin (81,807) | MPR | MPR ≥80%; MPR <80% | 24.8% | 12 months | U.S. |
| Lau and Nau, 2004 (36) | Retrospective cohort study (administrative claims data) | T2D on at least one OHA but not insulin (900) | MPR | MPR ≥80%; MPR <80% | 28.8% | 12 months | U.S. |
| White et al., 2004 (37) | Retrospective cohort study (administrative claims data) | Diabetes on at least one OHA (50,957) | MPR | MPR ≥75%; MPR <75% | 32.8% | 12 months | U.S. |

MPR, medication possession ratio; PDC, percentage of days covered; T2D, type 2 diabetes.

**Table 2—Outcomes by adherence of included studies in the meta-analysis**

| | | | CVD, events/participants, *n* (%) | | All-cause mortality, events/participants, *n* (%) | | All-cause hospitalization, events/participants, *n* (%) | |
|---|---|---|---|---|---|---|---|---|
| Reference | Adjustment | Adjusted estimates | Good adherence | Poor adherence | Good adherence | Poor adherence | Good adherence | Poor adherence |
| Gibson et al., 2010 (32) | Amputation, MI, cerebrovascular disease, neuropathy, PAD, renal events, retinopathy | Good adherence: OR MI 0.29 (95% CI 0.22–0.84), *P* = 0.014; OR cerebrovascular disease 0.83 (95% CI 0.55–1.24), *P* = 0.679 | 6,918/72,067 (9.6)* | 3,478/24,667 (14.1)* | | | | |
| Zhu et al., 2015 (39) | Age, sex, race, hypertension, ischemic heart disease, stroke, renal disease | Poor adherence: OR mortality 1.21 (95% CI 1.12–1.31), *P* = NS | | | 25/2,269 (1.1) | 294/21,798 (1.3) | | |
| Hong and King, 2011 (33) | No adjusted estimates provided | N/A | | | | | 377/2,269 (16.6) | 3,945/21,798 (18.1) |
| Ho et al., 2006 (38) | Age, sex, hypertension, MI, CAD, PAD, cerebrovascular disease, CCF, renal insufficiency, retinopathy | Poor adherence: OR mortality 1.39 (95% CI 1.07–1.82), *P* = NS | | | 86/11,800 (0.7) | 276/28,282 (1.0) | | |
| Encinosa et al., 2010 (34) | No adjusted estimates provided | N/A | | | | | 1,456/11,800 (13.1) | 3,714/28,282 (13.1) |
| Jha et al., 2012 (35) | No adjusted estimates provided | N/A | | | 363/9,076 (4.0) | 145/2,456 (5.9) | | |
| Lau and Nau, 2004 (36) | Age, sex, number of OHA therapies, Charlson comorbidity index, prior hospitalization | Poor adherence: OR hospitalization 2.53 (95% CI 1.38–4.64), *P* = NS | | | | | 1,743/9,076 (19.2) | 570/2,456 (23.2) |
| White et al., 2004 (37) | Age, sex, Charlson comorbidity index | Poor adherence: OR hospitalization 1.31 (95% CI 1.24–1.38) | | | | | 847/6,322 (13.4) | 784/5,724 (13.7) |

CAD, coronary artery disease; CCF, congestive cardiac failure; MI, myocardial infarction; OR, odds ratio; PAD, peripheral artery disease. *Cerebrovascular disease and acute myocardial infarction.

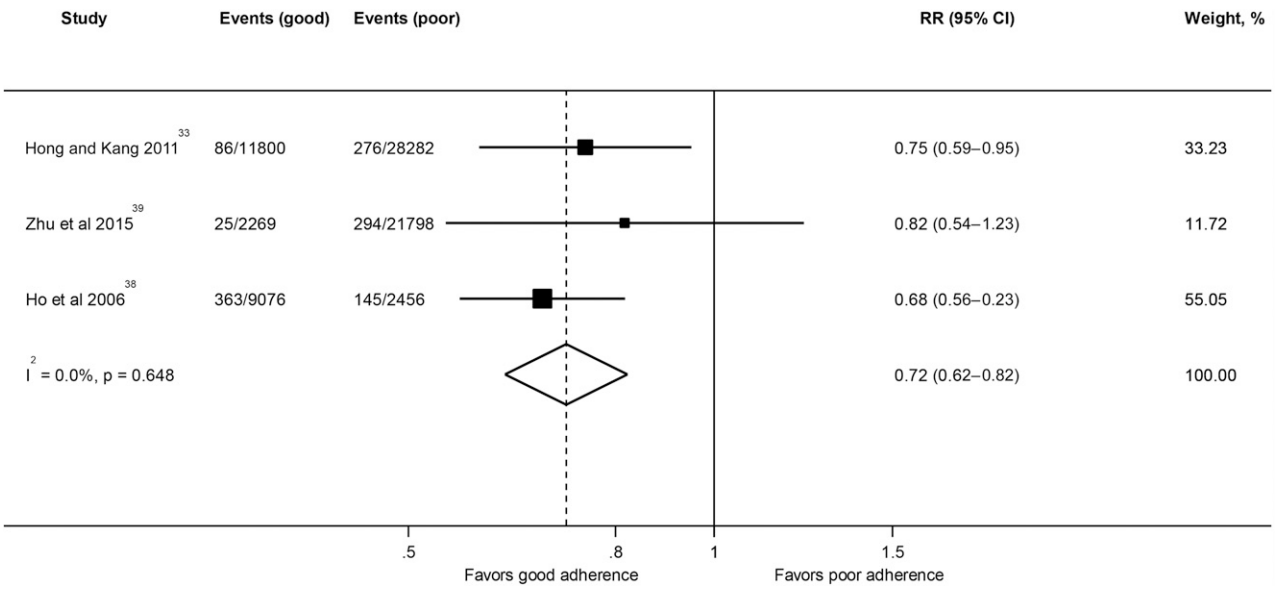


**Figure 2—**Association between medication adherence and all-cause mortality in type 2 diabetes.

to large improvements in adherence (50). Adherence has been called the "next frontier in quality improvement" (51), and without effective strategies to improve it on a population level, progress in clinical outcomes in type 2 diabetes achieved over recent decades may plateau, in spite of improvements in conventional quality of care indicators and the range of therapies available.

Despite limited success in preventing or delaying complications of type 2 diabetes in high-income countries, the rapid escalation in numbers of those affected in developing countries is of great concern. In developed countries, the burden of diabetes is thought to account for ~5–14% of health care spending (52,53), yet less than a quarter of this cost is related to the management of diabetes itself; the treatment of complications of the disease accounts for the remaining budget (52). In developing countries, where prevalence is rising most quickly and 80% of diabetes case subjects live (54), expenditure on diabetes as a proportion of total health budget is currently low and the cost of treating complications alone has the potential to absorb a large proportion of existing health care budgets (53). The

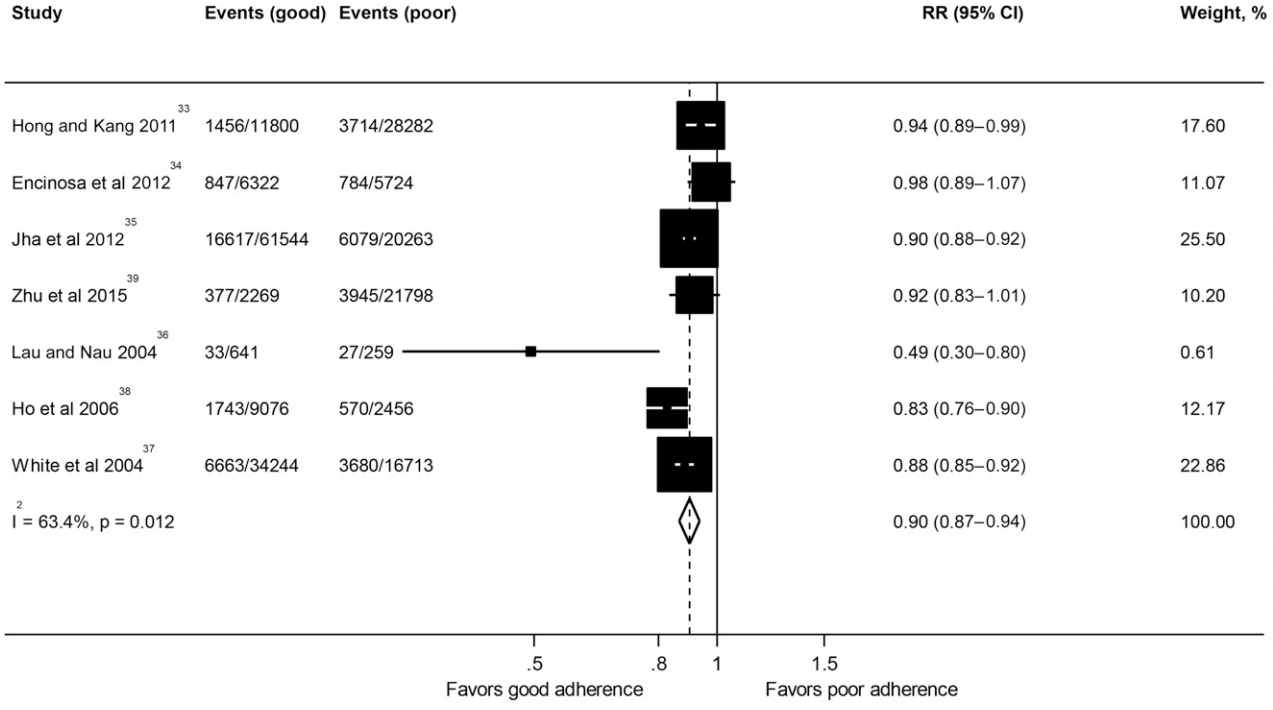


**Figure 3—**Association between medication adherence and all-cause hospitalization in type 2 diabetes.

estimates presented in this study suggest that efforts to improve adherence may help to reduce the frequency of hospitalization in type 2 diabetes, with possible implications for cost savings on a population level. It should be reiterated that our findings do not imply causation; however, it is plausible that efforts to improve adherence may prevent unplanned hospital visits and help to divert resources toward preventive medicine, which should be the cornerstone of any successful public health policy in diabetes.

Our findings add to calls for high quality studies on interventions to improve adherence in type 2 diabetes in clinical practice settings. Further investigation with access to individual participant data is required to establish the mechanisms behind the protective effect of adherence and to guide strategies for improving adherence. In particular, the absence of any clinical trial data in the present analyses suggests a systematic failure to report outcomes in subgroups stratified by adherence. Some 66 studies identified in our search reported on the prevalence of poor adherence or a mean adherence rate but failed to report on outcomes as a function of adherence and were therefore excluded from our analyses. Given the placebo-controlled nature of many clinical trials, an opportunity to study the healthy adherer effect was lost. Unresolved questions relate to whether the improvement in clinical outcomes observed in people with good adherence is due to improved control of modifiable risk, a healthy adherer effect, or other as yet unmeasured factors. Whether good adherence is associated with benefits for the prevention of diabetes-specific complications also merits further consideration, as they carry significant morbidity and mortality and account for a disproportionate share of overall health care expenditure.

A key strength of the current study is the size of included studies. The pooled cohorts for all-cause mortality and hospitalization outcomes involved 119,569 and 265,279 person-years of follow-up, respectively. There are certain limitations with this study. First, and common to all meta-analyses that lack individual participant data, the RRs presented are not adjusted for potential confounding variables. Meta-analyses of crude estimates from observational studies may be subject to residual confounding. We were unable to produce any estimates using adherence on a continuous scale as all included studies reported on outcomes in binary groups (good vs. poor adherence). The cohorts studied differed between, and within, studies in their baseline characteristics. Given the limited number of studies, we were unable to assess the associations by relevant subgroups, including by medication class and other important clinical factors, such as duration of diabetes. Despite conducting a detailed literature search, we found only a single study meeting our eligibility requirements that reported on cardiovascular events separately among groups with good and poor adherence. We were therefore unable to assess the association with adherence beyond its findings. There are a wide range of measures of adherence; the most commonly encountered methods were medication possession ratios and percentage of days covered. The variety of adherence measures is problematic for comparisons across studies, and consensus for a uniform methodology of reporting adherence in clinical trials and observational studies is needed. Although direct measures of adherence that record the level of medication or its metabolite in the blood, for example, are considered more robust than indirect methods such as pill counting, these are not practical in routine clinical practice or for large epidemiological studies. Poor adherence in clinical trials also poses problems for power calculations as an assumed treatment effect may be attenuated by missed doses or persistence failure (55). In the absence of a gold-standard measure and threshold for good adherence, we took a pragmatic approach to define good adherence as 80%, which is common in the literature. Again, individual participant data linking numerical values for adherence with outcome may have yielded greater precision in our estimates. The limited number of studies precluded the ability to investigate the possibility of publication bias in greater detail. Last, with the exception of one study that considered adherence across three classes of medications, all studies reported adherence rates to antihyperglycemic therapy only. In a real-world setting, patients with type 2 diabetes are frequently prescribed a range of medication classes to modify cardiovascular risk, including blood pressure treatments and statins. We were unable to differentiate the impact of adherence to other medications apart from antihyperglycemic agents.

In this meta-analysis, better adherence to medication in adults with type 2 diabetes is associated with reduced rates of all-cause mortality and hospitalization. In conjunction with previous studies, these data should encourage health care professionals to routinely assess adherence in clinical practice and make efforts to improve it where it falls below 80%. In addition, our findings should serve to reinforce to patients the importance of taking medications as prescribed, in order to avoid premature death and preventable admissions to the hospital. We identified no randomized controlled trial reporting on outcomes stratified by adherence, suggesting a systematic failure to publish this important information. Efforts should be made to report on subgroups by adherence where possible in the clinical trial setting. Finally, high quality studies examining the effectiveness of interventions to improve adherence in chronic disease are needed to guide international efforts to curb the effects of the diabetes epidemic.

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**Author Contributions.** K.K. conceived and designed the study, provided oversight for the statistical analysis, and drafted the manuscript. S.S., S.K., and M.D. conceived the study and critically

appraised the manuscript. All authors read and approved the final manuscript.

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