Published in final edited form as:

Intern Med J. 2018 April ; 48(4): 414–421. doi:10.1111/imj.13687.

Barriers to Medication Adherence and Links to Cardiovascular Disease Risk Factor Control: The Framingham Heart Study

Rachel Hennein, BS^{1,2} [Post-baccalaureate research fellow], Shih-Jen Hwang, PhD^{1,2} [Biostatistician], Rhoda Au, PhD^{4,6} [Professor], Daniel Levy, MD^{1,2} [Director], Paul Muntner, PhD³ [Professor], Caroline S. Fox, MD, MPH^{1,2,4} [Medical Officer], and Jiantao Ma, MBBS, PhD^{1,2} [Post-doctoral research fellow]

¹Framingham Heart Study, Framingham, Massachusetts, USA

²Population Sciences Branch, Division of Intramural Research, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland, USA

³Department of Epidemiology, University of Alabama at Birmingham, Birmingham, Alabama

⁴Department of Neurology, Boston University School of Medicine, Boston, Massachusetts

⁵Division of Endocrinology and Metabolism, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts

⁶Department of Anatomy & Neurobiology, Boston University School of Medicine and Department of Epidemiology, Boston University School of Public Health

Abstract

Background—In the elderly, impaired cognition may weaken medication adherence and compromise treatment for cardiovascular disease (CVD).

Aims—We examined risk factors for medication adherence and the relationship between adherence and levels of CVD risk factors among older participants with hypertension, dyslipidemia, and diabetes in the Framingham Heart Study.

Methods—The four-item Morisky Medication Adherence Scale was administered to 1,559 participants, median age 70 years, 53% women. We created an adherence score, ranging from 0–4, with low adherence defined as a score ≤ 2 . CVD risk factors were assessed using standard protocols. Cognition was measured using the Mini-Mental State Examination (MMSE) and depressive symptoms were measured using the Center for Epidemiologic Studies of Depression (CES-D) scale.

Results—Among participants who self-reported taking antihypertensive, lipid-lowering, and/or hyperglycemic medication(s), 12% (n=191) had low medication adherence. The risk of low

Corresponding Author: Rachel Hennein, BS, NHLBI's Framingham Heart Study and Population Sciences Branch, 73 Mt. Wayte Avenue, Suite 2, Framingham, Massachusetts 01702, rachel.hennein@nih.gov, Phone: (508) 935-3442, Fax: (508) 872-2678.

NHLBI disclaimer statement: The views expressed in this manuscript are those of the authors and do not necessarily represent the views of the National Heart, Lung, and Blood Institute; the National Institutes of Health; or the U.S. Department of Health and Human Services."

Disclosures: None

adherence increased by 45% (9%CI: 25-68%, $P<0.001$) per five-unit increase in CES-D score. In participants taking antihypertensive medication ($n=1,017$), low adherence was associated with higher mean diastolic blood pressure (73 mmHg, 95%CI: 71-75 vs. 71 mmHg, 95%CI: 70-71; $P=0.04$) after adjusting for covariates. Among participants taking lipid-lowering medication ($n=937$), low adherence was associated with higher mean low-density lipoprotein cholesterol (92 mg/dL, 95%CI: 87-96 vs. 86 mg/dL, 95%CI: 84-88; $P=0.03$). Low adherence was not associated with fasting plasma glucose ($P=0.10$) or hemoglobin A1c ($P=0.68$) in the subgroup of participants ($n=192$) taking hypoglycemic medication.

Conclusions—Depressive symptoms might act as a barrier for medication adherence, which exacerbates CVD risk factors in older-aged adults.

Keywords

Medication adherence; Cardiovascular Diseases; Hypertension; Cholesterol; Diabetes Mellitus; Type 2

Introduction

Medication adherence is vital for long-term healthcare expenditure.^{1, 2} Low medication adherence may account for up to \$300 billion of annual healthcare costs in the United States.³ It has been estimated that up to 50% of patients do not adhere to prescribed medications, defined as taking fewer doses than prescribed or discontinuing treatment.⁴⁻⁷ Low medication adherence may compromise the effectiveness of treatment for cardiovascular conditions such as hypertension,^{8, 9} dyslipidemia,^{10,11} and hyperglycemia.^{12,13} However, a systematic review of randomized controlled trials of medication adherence interventions concluded that most strategies aimed at improving medication adherence have not been successful in improving adherence and clinical outcomes for cardiovascular diseases (CVD) and associated risk factors.¹⁴ This highlights the need to identify risk factors contributing to low medication adherence, and how low adherence affects CVD risk among high-risk populations.¹⁵

Older adults constitute a high-risk population for poor medication adherence; as the population ages, chronic coexisting conditions coupled with decreased cognitive functioning might lead to decreased adherence.^{7, 16, 17} A recent systematic review of 15 studies concluded that individuals with cognitive impairment had lower rates of medication adherence compared to those without cognitive impairment.¹⁷ Further, the Cohort Study of Medication Adherence among Older Adults (CoSMO), a prospective cohort study of 2,194 older adults with hypertension, examined the barriers to antihypertensive adherence and clinical outcomes.¹⁶ Participants with low compared with high cognitive functioning were 2.71 times more likely to have low medication adherence and 1.20 times more likely to have uncontrolled blood pressure.¹⁶ However, a large gap of knowledge exists regarding risk factors for poor medication adherence and the clinical implications of medication nonadherence on chronic diseases in older adults, particularly those at risk for cognitive decline.⁷

The objectives of the present study were to: 1) examine risk factors (demographic, socio-economic, lifestyle, and cognitive factors) associated with medication adherence, and 2) study the cross-sectional associations between medication adherence and levels of CVD risk factors among participants with hypertension, dyslipidemia, and diabetes in a sample of older adult participants enrolled in a large community-based cohort. Our hypothesis was that low medication adherence would be common and associated with adverse CVD risk factor profiles.

Methods

Study sample

Framingham Heart Study (FHS) participants who attended the ninth examination (2011 to 2014) in the Offspring cohort were included. This cohort has been described elsewhere.^{18,19} Data were collected during a physician interview, a physical examination, and by standard laboratory tests for CVD risk factors. The four-item Morisky Medication Adherence Scale²⁰ was administered to the 2,430 participants who attended the ninth examination. The use of hypertensive, lipid-lowering, and/or hypoglycemic medication(s) was determined by self-report. After excluding 537 participants who did not report taking at least one of the three studied medications (antihypertensive, lipid-lowering, or hypoglycemic), 245 participants with missing responses to the Morisky Medication Adherence Scale, and 89 participants with missing information to covariate assessment(s), a sample including 1,559 participants was available for analysis. The first analysis aimed to study risk factors for low medication adherence. The second analysis studied the associations between medication adherence and CVD risk profiles in 1,017 participants taking hypertensive medications, 937 participants taking lipid-lowering medication, and 192 participants taking hypoglycemic medication, with each condition analyzed separately. The FHS protocols and procedures were approved by the Institutional Review Board for Human Research at Boston University Medical Center and all participants provided written informed consent.

Medication adherence assessment

Medication adherence was assessed using the four-item Morisky Medication Adherence Scale, which has been used to study adherence for hypertension,²⁰ diabetes,^{21,22} and CVD²³ medications. The four questions included: 1) Did you ever forget to take your medicine? 2) Are you careless at times about taking your medicine? 3) When you feel better do you stop taking your medicine? 4) Sometimes if you feel worse when you take the medicine, do you stop taking it? Response options to these four questions were either yes or no, and were assigned the values of 1 or 0, respectively. The values were summed to create an adherence score, ranging from 0 to 4, with higher scores indicating poorer medication adherence. Participants with an adherence score of ≤ 2 were defined as having low medication adherence, which is consistent with prior studies.^{21,22}

Cardiovascular disease risk factors assessment

At the study examination visit in the FHS research clinic, systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting plasma glucose (FPG), and hemoglobin A1c (HbA1c) were measured in accordance with standard protocols.²⁴ SBP and DBP were

measured twice by the same physician, and the average of the two measurements was used. Hypertension (HTN) was defined as SBP $\geq$ 140 mmHg, DBP $\geq$ 90 mmHg, or the use of antihypertensive medication. HTN control was defined as SBP <140 mmHg and DBP <90 mmHg among participants with HTN. Low density lipoprotein cholesterol (LDLc) was estimated using the Friedewald equation.²⁵ LDLc control was defined as LDLc <100 mg/dL (2.59 mmol/L) if participants had prevalent CVD or type 2 diabetes or <130 mg/dL (3.36 mmol/L) otherwise.

Anthropometry and covariate assessment

Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Participants who reported that they smoked regularly (on average one cigarette or more per day) in the past year were categorized as current smokers. Alcohol consumption was estimated by self-reported intake of beer, wine, liquor, and spirits. A physical activity score was calculated using responses to a questionnaire on the intensity of and time spent performing physical activity per day.²⁶ Employment status (employed, self-employed, or retired from usual occupation vs. unemployed or laid off) and marital status (married, living as married, or living with partner vs. single, never married, separated, divorced, or widowed) were derived from a standard questionnaire. The Mini-Mental State Examination (MMSE), a brief dementia-screening questionnaire, was implemented to assess participant's cognitive function.²⁷ The MMSE, which has a maximum score of 30, included 16 individual questions to assess functions for orientation, registration, attention and calculation, recall, and language and praxis. The Center for Epidemiologic Studies of Depression (CES-D) scale was administered to assess depressive symptoms.²⁸ The CES-D scale, ranging from 0 to 60, consisted of 20 items evaluating depressive affect, somatic complaints, positive affect, and interpersonal relations.

Statistical analysis

The characteristics of participants were calculated by level of adherence, low (adherence score $\geq$ 2) or high (score <2), and compared using student's *t*-test or chi-square test. To assess factors associated with low medication adherence, a multiple regression model was implemented with the outcome of low medication adherence. Factors examined included sex, age, BMI, alcohol consumption, current smoking status, physical activity score, employment status, marital status, MMSE score, and CES-D score.

Two models were used to examine the associations between low medication adherence and CVD risk factors for each of the self-reported medication groups (antihypertensive, lipid-lowering, and hypoglycemia, separately). Covariates in model 1 were sex and age, while model 2 adjusted for sex, age, and variables that were significant in the above analysis for risk factors of low medication adherence. Among participants who reported taking antihypertensive medication, the associations between medication adherence and SBP, DBP, and HTN control were analyzed. In participants who reported taking lipid-lowering medication, the associations between medication adherence and LDLc and LDLc control were analyzed. In participants who reported taking hypoglycemic medication, the associations between medication adherence and FPG, HbA1c, and diabetes control were analyzed. Multivariable-adjusted linear regression models were used for continuous

outcomes, while Poisson regression models with robust standard errors were used to calculate relative risk (RR) for dichotomized disease control as the prevalence was high.²⁹

A secondary analysis was conducted to examine whether age modified the observed association between medication adherence and CVD risk factors. A cross-product term of age (< 70 years or ≥70 years) and medication adherence was included in the fully adjusted model. An age of 70 years was chosen as it was the median age of the overall study sample. All statistical analyses were conducted using SAS statistical software (version 9.3; SAS Institute, Cary, North Carolina). A two-tailed $P < 0.05$ value was considered statistically significant.

Results

Participant characteristics

Among the 1,559 participants (median age 70 years, 53% women) with complete responses to the Morisky Medication Adherence Scale and covariate assessments, 695 (45%) participants reported that they had forgotten to take medicine; 158 (10%) participants reported that they had been careless at times about taking medicine; 45 (3%) participants reported that they had stopped taking medicine when they felt better; and 116 (7%) participants reported that they had stopped taking medicine when they felt worse. Overall, 191 (12%) participants had low medication adherence, defined as adherence score ≤ 2. Among the participants in the low medication adherence group, 181 (95%) reported that they had forgotten to take medicine; 136 (71%) reported that they had been careless at times about taking medicine; 31 (16%) reported that they had stopped taking medicine when they felt better; and 73 (38%) reported that they had stopped taking medicine when they felt worse. The prevalence of myocardial infarction and stroke was similar in participants with low medication adherence compared with those with better adherence, 8.4% ($n=16$) vs. 8.0% ($n=175$). Participants with low medication adherence had a higher CES-D score (Table 1; $P < 0.001$).

Potential risk factors for low medication adherence

As presented in Table 2, higher CES-D scores, indicating more depressive symptoms, were associated with an increased likelihood of low medication adherence; the odds ratio (OR) for having an adherence score ≤ 2 was 1.44 (95%CI: 1.23-1.67, $P < 0.001$) for every five-unit increase in CES-D score after adjustment for multiple covariates (Table 2).

In a post hoc analysis, we categorized participants by CES-D score using cut-off values of 16 and 22. We employed a multiple regression analysis that adjusted for all other potential risk factors shown in Table 2. We observed a dose-response relationship between CES-D score and medication adherence. Using participants with a CES-D score below 16 as reference, the OR of low medication adherence was 1.29 (95%CI: 0.91, 1.85) in participants who had a CES-D score of 16 to 21, while the OR of low medication adherence was 3.03 (95%CI: 1.94, 4.73) in participants who had a CES-D of 22 or above (indicating more severe depression), $P\text{-trend} < 0.001$.

Participants taking antihypertensive medication (n=1,017)

Compared with participants who had high medication adherence (n=918, 90%), those with low medication adherence (n=99, 10%) had higher DBP after adjustment for sex, age, and CES-D score (73 mmHg, 95%CI: 71-75 vs. 71 mmHg, 95%CI: 70-71; $P=0.04$) (Table 3, top panel). No association was present between medication adherence and SBP or medication adherence and HTN control (Table 3, top panel).

Participants taking lipid-lowering medication (n=937)

Compared with participants who had high medication adherence (n=825, 88%), those with low medication adherence (n=112, 12%) had higher LDLc (92 mg/dL, 95%CI: 87-96 vs. 86 mg/dL, 95%CI: 84-88; $P=0.03$), after adjustment for sex, age, and CES-D score (Table 3, middle panel). Participants with low medication adherence were also 11% more likely to have uncontrolled LDLc levels compared to their counterparts in the high medication adherence group (RR: 1.11, 95%CI: 1.02-1.22; $P=0.02$) (Table 3, middle panel).

Participants taking hypoglycemic medication (n=192)

Compared with the high medication adherence group (n=169, 88%), participants with low medication adherence (n=23, 12%) showed no statistically significant differences in FPG, HbA1c, or diabetes control (Table 3, bottom panel).

Secondary analysis

Age-specific analyses for the association between adherence and cardiovascular risk factors and disease control are presented in Tables S1 and S2, respectively. The p-value for interaction between age and medication adherence was greater than 0.05 for all outcomes except LDLc control and FPG. High adherence was associated with lower LDLc and LDLc control among participants ≤ 70 years but not among those >70 years (p -interaction=0.007; Table S2, middle panel). Additionally, the p -interaction was 0.05 for FPG (Table S1, bottom panel); however, there was no statistically significant association between medication adherence and FPG levels in either age group.

Discussion

Principle findings

Among older adults in the current analysis, 12% were categorized as having low medication adherence. A higher CES-D score (i.e. more depressive symptoms) was associated with low medication adherence. Further, low adherence was associated with higher DBP in participants using antihypertensive medication and higher and uncontrolled LDLc in participants using lipid-lowering medications.

In the context of the current literature

The prevalence of low medication adherence in our study sample (12%) is lower compared to several other cohort studies.¹⁶ Nevertheless, our findings are in line with many studies, which have shown that low medication adherence may hinder the effectiveness of treatment for various conditions^{8-14, 30, 31}. For example, low medication adherence is one of the key

risk factors for poor hypertension control,¹⁶ and may account for up to half of resistant hypertension cases.³⁰ CoSMO, including 2,194 adults with hypertension, assessed the determinants of medication adherence using the medication possession ratio and a validated self-report adherence scale. The analyses showed that adherence, measured by both metrics, was associated with uncontrolled blood pressure.¹⁶ It should be noted that high SBP is particularly prevalent among adults in FHS,³² which might have decreased the power for the association between SBP and medication adherence. Additionally, a retrospective cohort study of 1,066 patients receiving statin medication found that the risk of not achieving the LDLc reduction goal in patients who had intermediate and low adherence increased by 31% and 88% respectively compared with those with high adherence.³³ Although the present study did not find an association between medication adherence and glycemic control, potentially due to the small sample size of participants using hypoglycemic medication (n=192), other studies have reported an association. In a systematic review of adherence and glycemic control determined by HbA1c, there was a direct association between low medication adherence, which was assessed by self-report and pharmacy fills, and worse glycemic control.¹²

Many intervention studies have been designed, but failed to improve either medication adherence or associated clinical outcomes through improvements in adherence.¹⁴ Interventions specifically designed to improve medication adherence barriers in individuals at-risk for poor adherence could lead to better clinical outcomes.^{6, 15} For example, the observation from the present study that a higher CES-D score could constitute a barrier for adherence is consistent with other studies.^{12, 34-39} To target depression as a barrier to medication adherence for comorbid conditions, studies have analyzed the extent to which integrated care could be effective in treating both disease outcomes. A randomized trial in 64 individuals with hypertension and depression showed that integrated care, focused on treating hypertension and depression simultaneously, improved adherence to antihypertensive medications and resulted in lower blood pressure.⁴⁰ However, a randomized controlled trial that examined individual cognitive therapies in 94 outpatients with diabetes and comorbid depression found that glycemic control was not improved even though depressive symptoms were reduced.⁴¹ Thus, future intervention studies tailored to older adults with depression and CVD are warranted to improve medication adherence and clinical outcomes.

It should be noted that other factors in addition to depression may be barriers to achieving high medication adherence. As shown in the present analyses, adjustment for depressive symptoms did not substantially change the association between low medication adherence and increased CVD risk. Cognitive impairment and memory may have a role in medication adherence among the elderly. MMSE score ceiling effects resulted in no statistically significant association between cognitive functioning and low medication adherence in the present study. The MMSE alone may not be effective in diagnosing mild cognitive impairment.⁴² Nevertheless, a small pre-post intervention study found that reminder devices improved medication adherence in older adults with mild cognitive impairment.⁴³ Thus, additional well-designed studies with larger sample sizes are needed to identify the role of cognitive decline in medication adherence, as well as the relationship between reduction of these factors and control of chronic diseases in the elderly population.¹⁷

Implications

Many studies have shown that medication adherence is an important factor associated with CVD risk.^{8, 14} Although the observed association is relatively weak, our findings do support that improving medication adherence may benefit control for CVD risk factors. This is particularly important for the elderly population since older adults constitute a high-risk population for poor medication adherence due to decreased cognitive function. The finding that depressive symptoms may act as a risk factor for medication nonadherence in older adults should be considered in future intervention studies and clinical practice.

Strengths and limitations

This study used the comprehensive data collected from FHS, which has been a hallmark in identifying CVD risk factors among free-living adults.⁴⁴ However, due to the observational and cross-sectional nature of this study and relatively weak observed association between medication adherence and CVD risk factors, a causal relationship could not be ascertained. No gold standard definition exists for long-term medication adherence.⁴⁵ Defining low medication adherence as two or more positive responses to the Morisky Medication Adherence Scale is somewhat arbitrary, and primarily focuses on participants' attitudes toward their medications rather than their behaviors. The self-reported questionnaire also has the potential to introduce response bias into the study. In addition, the Morisky Medication Adherence Scale does not assess other factors that may contribute to low medication adherence, such as the general healthcare system.⁴⁶ We could not validate medication adherence assessed by the questionnaire with medication possession ratios or provider data in our study sample. Further, since only one medication adherence questionnaire was implemented, we cannot test the association of current CES-D score to remote medication adherence. The use of MMSE to measure cognitive functioning might not have been sufficient to identify those with mild cognitive impairment, especially because previous studies have found that cognitive impairment significantly impacts medication adherence.^{7, 16} The secondary age interaction analyses were also limited due to the small subgroup sample sizes. Finally, all study participants were Caucasian, which may limit the generalizability to populations of different racial and/or ethnic backgrounds.

In conclusion, low medication adherence was associated with adverse CVD risk profiles, including uncontrolled LDLc and higher DBP and LDLc, in a group of older adults in the community. Having more depressive symptoms was associated with low medication adherence. Future intervention studies are warranted to examine if integrating care for depression and CVD risk factors could improve medication adherence and clinical outcomes in the elderly.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding: This work was conducted in part using resources and data from the Framingham Heart Study (FHS) of the National Heart, Lung and Blood Institute (NHLBI) of the National Institute of Health and Boston University

School of Medicine. This work was supported by the NHLBI contract [HHSN2682015000011]. Several of the authors (RH, JM, SJH, DL, CJF) were NIH employees when this manuscript was prepared.

References

1. Iuga AO, Mcguire MJ. Adherence and health care costs. *Risk Manag Healthc Policy*. 2014; 7:35–44. [PubMed: 24591853]
2. Viswanathan M, Golin CE, Jones CD, et al. Interventions to improve adherence to self-administered medications for chronic diseases in the United States: a systematic review. *Ann Intern Med*. 2012; 157(11):785–95. [PubMed: 22964778]
3. Dimatteo MR. Variations in patients' adherence to medical recommendations: a quantitative review of 50 years of research. *Med Care*. 2004; 42(3):200–9. [PubMed: 15076819]
4. Kripalani S, Yao X, Haynes RB. Interventions to enhance medication adherence in chronic medical conditions: a systematic review. *Arch Intern Med*. 2007; 167(6):540–50. [PubMed: 17389285]
5. Haynes RB, Mckibbin KA, Kanani R. Systematic review of randomised trials of interventions to assist patients to follow prescriptions for medications. *Lancet*. 1996; 348(9024):383–6. [PubMed: 8709739]
6. Conn VS, Ruppar TM, Enriquez M, Cooper P. Medication adherence interventions that target subjects with adherence problems: Systematic review and meta-analysis. *Res Social Adm Pharm*. 2016; 12(2):218–46. [PubMed: 26164400]
7. Gellad WF, Grenard JL, Marcum ZA. A systematic review of barriers to medication adherence in the elderly: looking beyond cost and regimen complexity. *Am J Geriatr Pharmacother*. 2011; 9(1): 11–23. [PubMed: 21459305]
8. Krousel-wood M, Thomas S, Muntner P, Morisky D. Medication adherence: a key factor in achieving blood pressure control and good clinical outcomes in hypertensive patients. *Curr Opin Cardiol*. 2004; 19(4):357–62. [PubMed: 15218396]
9. Abegaz TM, Shehab A, Gebreyohannes EA, Bhagavathula AS, Elnour AA. Nonadherence to antihypertensive drugs: A systematic review and meta-analysis. *Medicine (Baltimore)*. 2017; 96(4):e5641. [PubMed: 28121920]
10. Frolkis JP, Pearce GL, Nambi V, Minor S, Sprecher DL. Statins do not meet expectations for lowering low-density lipoprotein cholesterol levels when used in clinical practice. *Am J Med*. 2002; 113(8):625–9. [PubMed: 12505111]
11. Penning-van beest FJ, Termorshuizen F, Goettsch WG, Klungel OH, Kastelein JJ, Herings RM. Adherence to evidence-based statin guidelines reduces the risk of hospitalizations for acute myocardial infarction by 40%: a cohort study. *Eur Heart J*. 2007; 28(2):154–9. [PubMed: 17158123]
12. Doggrell SA, Warot S. The association between the measurement of adherence to anti-diabetes medicine and the HbA1c. *Int J Clin Pharm*. 2014; 36(3):488–97. [PubMed: 24710953]
13. De vries mcclintock HF, Morales KH, Small DS, Bogner HR. Patterns of Adherence to Oral Hypoglycemic Agents and Glucose Control among Primary Care Patients with Type 2 Diabetes. *Behav Med*. 2016; 42(2):63–71. [PubMed: 24673362]
14. Nieuwlaat R, Wilczynski N, Navarro T, Hobson N, Jeffery R, Keenanasseril A, et al. Interventions for enhancing medication adherence. *Cochrane Database Syst Rev*. 2014; 11 CD000011.
15. Seabury SA, Gupta CN, Philipson TJ, Henkhaus LE. Understanding and overcoming barriers to medication adherence: a review of research priorities. *J Manag Care Spec Pharm*. 2014; 20(8): 775–83. [PubMed: 25062070]
16. Krousel-wood MA, Muntner P, Islam T, Morisky DE, Webber LS. Barriers to and determinants of medication adherence in hypertension management: perspective of the cohort study of medication adherence among older adults. *Med Clin North Am*. 2009; 93(3):753–69. [PubMed: 19427503]
17. Smith D, Lovell J, Weller C, et al. A systematic review of medication non-adherence in persons with dementia or cognitive impairment. *PLoS ONE*. 2017; 12(2):e0170651. [PubMed: 28166234]
18. Dawber TR, Meadors GF, Moore FE. Epidemiological approaches to heart disease: the Framingham Study. *Am J Public Health Nations Health*. 1951; 41(3):279–81. [PubMed: 14819398]

19. Dallmeier D, Larson MG, Wang N, Fontes JD, Benjamin EJ, Fox CS. Addition of inflammatory biomarkers did not improve diabetes prediction in the community: the Framingham heart study. *J Am Heart Assoc.* 2012; 1(4):e000869. [PubMed: 23130155]
20. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. *Med Care.* 1986; 24(1):67–74. [PubMed: 3945130]
21. Walker EA, Shmukler C, Ullman R, Blanco E, Scollan-koliopoulus M, Cohen HW. Results of a successful telephonic intervention to improve diabetes control in urban adults: a randomized trial. *Diabetes Care.* 2011; 34(1):2–7. [PubMed: 21193619]
22. Cohen HW, Shmukler C, Ullman R, Rivera CM, Walker EA. Measurements of medication adherence in diabetic patients with poorly controlled HbA(1c). *Diabet Med.* 2010; 27(2):210–6. [PubMed: 20546266]
23. Shalansky SJ, Levy AR, Ignaszewski AP. Self-reported Morisky score for identifying nonadherence with cardiovascular medications. *Ann Pharmacother.* 2004; 38(9):1363–8. [PubMed: 15238622]
24. Preis SR, Pencina MJ, Hwang SJ, D'Agostino RB Sr, Savage PJ, Levy D. Trends in cardiovascular disease risk factors in individuals with and without diabetes mellitus in the Framingham Heart Study. *Circulation.* 2009; 120(3):212–20. [PubMed: 19581493]
25. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem.* 1972; 18(6):499–502. [PubMed: 4337382]
26. Kannel WB, Belanger A, D'agostino R, Israel I. Physical activity and physical demand on the job and risk of cardiovascular disease and death: the Framingham Study. *Am Heart J.* 1986; 112(4): 820–5. [PubMed: 3766383]
27. Rovner BW, Folstein MF. Mini-mental state exam in clinical practice. *Hosp Pract (Off Ed).* 1987; 22:99, 103, 106, 110.
28. Radloff L. The CES-D Scale: a self-report depression scale for research in the general population. *Appl Psychol Methods.* 1977; 1(3):385–401.
29. Lovasi GS, Underhill LJ, Jack D, Richards C, Weiss C, Rundle A. At Odds: Concerns Raised by Using Odds Ratios for Continuous or Common Dichotomous Outcomes in Research on Physical Activity and Obesity. *Open Epidemiol J.* 2012; 5:13–17. [PubMed: 23002407]
30. Burnier M. Managing 'resistance': is adherence a target for treatment? *Curr Opin Nephrol Hypertens.* 2014; 23(5):439–43. [PubMed: 25036746]
31. Kolandaivelu K, Leiden BB, O'gara PT, Bhatt DL. Non-adherence to cardiovascular medications. *Eur Heart J.* 2014; 35(46):3267–76. [PubMed: 25265973]
32. Vasan RS, Larson MG, Leip EP, Kannel WB, Levy D. Assessment of frequency of progression to hypertension in nonhypertensive participants in the Framingham Heart Study: a cohort study. *Lancet.* 2001; 358(9294):1682–86. [PubMed: 11728544]
33. Vupputuri S, Joski PJ, Kilpatrick R, Woolley JM, Robinson BE, Farkouh ME, et al. LDL cholesterol response and statin adherence among high-risk patients initiating treatment. *Am J Manag Care.* 2016; 22(3):e106–15. [PubMed: 26978237]
34. Lewis LM. Factors associated with medication adherence in hypertensive blacks: a review of the literature. *J Cardiovasc Nurs.* 2012; 27(3):208–19. [PubMed: 21760525]
35. Gentil L, Vasiliadis HM, Prévile M, Bossé C, Berbiche D. Association between depressive and anxiety disorders and adherence to antihypertensive medication in community-living elderly adults. *J Am Geriatr Soc.* 2012; 60(12):2297–301. [PubMed: 23110563]
36. Caughey GE, Preiss AK, Vitry AI, Gilbert AL, Ryan P, Shakib S, et al. Does antidepressant medication use affect persistence with diabetes medicines? *Pharmacoepidemiol Drug Saf.* 2013; 22(6):615–22. [PubMed: 23447430]
37. Osborn CY, Egede LE. The relationship between depressive symptoms and medication nonadherence in type 2 diabetes: the role of social support. *Gen Hosp Psychiatry.* 2012; 34(3): 249–53. [PubMed: 22401705]
38. Krousel-wood M, Islam T, Muntner P, Holt E, Joyce C, Morisky DE, et al. Association of depression with antihypertensive medication adherence in older adults: cross-sectional and longitudinal findings from CoSMO. *Ann Behav Med.* 2010; 40(3):248–57. [PubMed: 20703839]

39. Gonzalez JS, Safren SA, Delahanty LM, Cagliero E, Wexler DJ, Meigs JB, et al. Symptoms of depression prospectively predict poorer self-care in patients with Type 2 diabetes. *Diabet Med*. 2008; 25(9):1102–7. [PubMed: 19183315]
40. Bogner HR, De vries HF. Integration of depression and hypertension treatment: a pilot, randomized controlled trial. *Ann Fam Med*. 2008; 6(4):295–301. [PubMed: 18626028]
41. Tovote KA, Fleer J, Snippe E, Peeters AC, Emmelkamp PM, Sanderman R, et al. Individual mindfulness-based cognitive therapy and cognitive behavior therapy for treating depressive symptoms in patients with diabetes: results of a randomized controlled trial. *Diabetes Care*. 2014; 37(9):2427–34. [PubMed: 24898301]
42. Devenney E, Hodges JR. The Mini-Mental State Examination: pitfalls and limitations. *Pract Neurol*. 2017; 17(1):79–80. [PubMed: 27903765]
43. Kamimura T, Ishiwata R, Inoue T. Medication reminder device for the elderly patients with mild cognitive impairment. *Am J Alzheimers Dis Other Dement*. 2012; 27(4):238–42. [PubMed: 22739031]
44. Chen G, Levy D. Contributions of the Framingham Heart Study to the Epidemiology of Coronary Heart Disease. *JAMA Cardiol*. 2016; 1(7):825–830. [PubMed: 27464224]
45. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med*. 2005; 353(5):487–97. [PubMed: 16079372]
46. Briesacher BA, Gurwitz JH, Soumerai SB. Patients at-risk for cost-related medication nonadherence: a review of the literature. *J Gen Intern Med*. 2007; 22(6):864–71. [PubMed: 17410403]

Table 1

Participant characteristics by self-reported medication adherence (n=1559)

	High medication adherence	Low medication adherence [†]	p-value
n (%)	1368 (88)	191 (12)	
Age, <i>years</i>	71 ± 8	70 ± 9	0.10
Women, <i>n (%)</i>	712 (52)	111 (58)	0.12
Body mass index, <i>kg/m²</i>	29 ± 5	29 ± 6	0.46
Alcohol, <i>servings/week</i>	5 ± 8	5 ± 7	0.42
Current smokers, <i>n (%)</i>	87 (6)	14 (7)	0.61
Physical activity score	35 ± 6	35 ± 5	0.67
Employment [‡] , <i>n (%)</i>	615 (45)	82 (43)	0.60
Marital status [§] , <i>n (%)</i>	405 (30)	70 (37)	0.05
MMSE score	29 ± 2	29 ± 2	0.30
CES-D [¶] score	15 ± 4	17 ± 5	<0.001***

Numbers in the table are mean ± standard deviation or proportion (counts)

[†]Low medication adherence was defined as Morisky Medication Adherence Scale score of ≤ 2[‡]Employment status: % unemployed or laid off[§]Marital status: % single, never married, separated, divorced, or widowed^{||}MMSE: Mini-Mental State Examination[¶]CES-D: The Center for Epidemiologic Studies of Depression

Table 2

Odds ratios for low medication adherence in 1559 Framingham Heart Study participants

Multiple Regression [†]		
	Odds ratio (95%CI)	p-value
Women	1.07 (0.77-1.50)	0.68
Age [‡]	0.86 (0.69-1.06)	0.16
MMSE score [§]	1.03 (0.93-1.13)	0.61
BMI	1.00 (0.98-1.03)	0.78
CES-D score	1.44 (1.23-1.67)	<.0001
Marital status [¶]	1.34 (0.96-1.88)	0.09
Unemployed [#]	0.96 (0.69-1.33)	0.79
Alcohol intake	1.00 (0.97-1.02)	0.72
Physical activity score	1.00 (0.97-1.03)	0.98
Current smoking status	1.02 (0.56-1.89)	0.94

Numbers in the table are odds ratios (95%CI)

Low medication adherence was defined as Morisky Medication Adherence Scale score of 2

[†] Multiple regression model adjusted for sex, age, and CES-D score[‡] Per 10-year increase in age[§] MMSE: Mini-Mental State Examination^{||} Per 5-unit increased in the Center for Epidemiologic Studies of Depression (CES-D) score[¶] Marital status: % single, never married, separated, divorced, or widowed[#] Employment status: % unemployed or laid off

Table 3

Cardiovascular risk factors and disease control by self-reported medication adherence

		High medication adherence	Low medication adherence [†]	p-value
Individuals using antihypertensive medication (n=1017)				
n (%)		918 (90)	99 (10)	
SBP [‡] (mmHg)	Model 1	129 (128, 130)	131 (128, 134)	0.37
	Model 2	129 (128, 130)	131 (128, 134)	0.37
DBP [§] (mmHg)	Model 1	71 (70, 71)	73 (71, 75)	0.03*
	Model 2	71 (70, 71)	73 (71, 75)	0.04*
HTN control (%)	Model 1	Ref.	1.02 (0.91, 1.15)	0.75
	Model 2	Ref.	1.02 (0.91, 1.15)	0.73
Individuals using lipid-lowering medication (n=937)				
n (%)		825 (88)	112 (12)	
LDLc [¶] (mg/dL)	Model 1	86 (84, 88)	91 (87, 96)	0.04
	Model 2	86 (84, 88)	92 (87, 96)	0.03
LDLc [¶] control (%)	Model 1	Ref.	1.12 (1.02, 1.22)	0.01**
	Model 2	Ref.	1.11 (1.02, 1.22)	0.02*
Individuals using hypoglycemic medication (n=192)				
n (%)		169 (88)	23 (12)	
FPG [#] (mg/dL)	Model 1	134 (128, 139)	143 (128, 158)	0.24
	Model 2	133 (128, 138)	147 (132, 162)	0.10
HbA1c ^{††} (%)	Model 1	6.7 (6.6, 6.9)	6.8 (6.4, 7.2)	0.91
	Model 2	6.7 (6.6, 6.9)	6.8 (6.4, 7.2)	0.68
Diabetes control (%)	Model 1	Ref.	0.87 (0.69, 1.10)	0.24
	Model 2	Ref.	0.86 (0.67, 1.12)	0.27

Numbers in the table are least squares mean and 95% confidence interval for continuous variables (SBP, DBP, LDLc, FPG, and HbA1c) and relative risk and 95% confidence interval using Poisson regression with robust standard errors for disease control.

Model 1 covariates: age and sex

Model 2 covariates: age, sex, and CES-D score

[†] Low medication adherence was defined as Morisky Medication Adherence Scale score of ≤ 2

[‡] SBP: systolic blood pressure

[§] DBP: diastolic blood pressure

^{||} HTN: hypertension

[¶] LDLc: low density lipoprotein cholesterol

[#] FPG: fasting plasma glucose

^{††} HbA1c: hemoglobin A1c