Original Article

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Low medication adherence is associated with decline in health-related quality of life: results of a longitudinal analysis among older women and men with hypertension

Erin Peacock[a], Cara Joyce[c], Leslie S. Craig[a], Zachary Lenane[b], Elizabeth W. Holt[d], Paul Muntner[e], and Marie Krousel-Wood[a,f,g]

Objective: The aim of this study was to determine the association of low antihypertensive medication adherence with decline in health-related quality of life (HRQOL) over 1 year.

Methods: We used data from older men and women with hypertension ($n = 1525$) enrolled in the Cohort Study of Medication Adherence among Older Adults. Adherence was measured using the validated self-report four-item Krousel-Wood Medication Adherence Scale (K-Wood-MAS-4) (low adherence = score ≥ 1) and prescription refill-based proportion of days covered (PDC) (low adherence = PDC < 0.80). We defined decline in HRQOL as a decrease in Mental Component Summary (MCS) or Physical Component Summary (PCS) score (from the RAND 36-Item Health Survey 1.0 administered at two time points – at the time of adherence assessment and 1 year later) equivalent to the minimal important difference (MID) for each respective summary score, calculated as the average of MID estimates derived from distribution and anchor-based approaches.

Results: The prevalence of low adherence was 38.6% using the K-Wood-MAS-4 and 23.9% using PDC. On the basis of mean MID estimates of 4.40 for MCS and 5.16 for PCS, 21.8 and 25.2% of participants experienced a decline in MCS and PCS, respectively, over 1 year. Low adherence was associated with a decline in MCS for K-Wood-MAS-4 [prevalence ratio = 1.32, 95% confidence interval (95% CI) 1.08–1.62, $P = 0.008$], but not PDC (prevalence ratio = 1.17, 95% CI 0.94–1.47, $P = 0.168$). Low adherence was not associated with decline in PCS (K-Wood-MAS-4: prevalence ratio = 0.95, 95% CI 0.79–1.16; PDC: prevalence ratio = 1.10, 95% CI 0.90–1.35).

Conclusion: Low self-report medication adherence is associated with decline in mental HRQOL over 1 year in older adults with hypertension.

Keywords: health-related quality of life, hypertension, K-Wood-MAS-4, medication adherence, older adults, proportion of days covered

Abbreviations: BP, blood pressure; CES-D, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; CoSMO, Cohort Study of Medication Adherence among Older Adults; CVD, cardiovascular disease; HRQOL, health-related quality of life; K-Wood-MAS-4, 4-item Krousel-Wood Medication Adherence Scale; MCO, managed care organization; MCS, Mental Component Summary; MID, minimal important difference; PCS, Physical Component Summary; PDC, proportion of days covered; RAND-36, RAND 36-Item Health Survey 1.0; SD, standard deviation; SEM, standard error of measurement

INTRODUCTION

Health-related quality of life (HRQOL) is an indicator of how a health condition and its treatment affect physical, emotional and social well being [1]. Hypertension is an important modifiable risk factor for cardiovascular disease (CVD) [2], which is associated with poor HRQOL [3,4]. Given the growing number of older adults [5] with hypertension and at risk for CVD, there is an increasing concern about declining HRQOL in a growing segment of the USA population [6]. Identifying modifiable factors associated with declining HRQOL among older adults may facilitate efforts to address this concern.

Antihypertensive medications can lower blood pressure (BP) and reduce CVD risk [7]; yet, only about half of adults with hypertension take their medications as prescribed [8]. Although several previous cross-sectional studies have shown

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[a]Tulane University School of Medicine, New Orleans, Louisiana, [b]San Mateo County Behavioral Health and Recovery Services, San Mateo, California, [c]Loyola University Stritch School of Medicine, Chicago, Illinois, [d]Furman University, Greenville, South Carolina, [e]University of Alabama at Birmingham School of Public Health, Birmingham, Alabama, [f]Tulane University School of Public Health and Tropical Medicine, New Orleans, Louisiana and [g]Ochsner Health System, New Orleans, Louisiana, USA

Correspondence to Marie Krousel-Wood, Tulane University School of Medicine, 1430 Tulane Avenue, New Orleans, Louisiana, 70112, USA. Tel: +1 504 988 5397; e-mail: mawood@tulane.edu

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an association between low antihypertensive medication adherence and poor HRQOL [9–13], few data exist on the effect of low adherence on change in HRQOL over time in older adults. A 2016 systematic review and meta-analysis of observational and experimental studies reported that adhering to antihypertensive pharmacotherapy was associated with improved mental, physical and overall HRQOL. However, the generalizability of the results was limited by the small number of studies available, variability in adherence assessments used, lack of information across age, sex and race subgroups, and likelihood of publication bias [14].

To address limitations identified by the 2016 systematic review [14], we determined the association of low medication adherence, using both self-report and pharmacy refill measures, with decline in HRQOL over a 1-year follow-up period among a sample of older women and men with established hypertension, overall and across age, sex and race subgroups. Knowledge of the association between low adherence and subsequent decline in HRQOL may assist healthcare providers and researchers to identify older adults at risk for declining HRQOL.

MATERIALS AND METHODS

Study population and timeline

We conducted a secondary analysis of data from the Cohort Study of Medication Adherence among Older Adults (CoSMO), a prospective cohort study of factors associated with antihypertensive medication adherence and CVD among older adults with hypertension. The CoSMO study design and baseline characteristics have been published previously [15]. In brief, 2194 patients, 65 years of age and older and taking antihypertensive medication were recruited and enrolled from a large managed care organization (MCO) in southeastern Louisiana. Recruitment was conducted from August 2006 to September 2007. A telephonic survey was administered three times at yearly intervals. Data were extracted from health records and administrative databases of the MCO. This analysis used data from first (henceforth, 'Time 1') and second (henceforth, 'Time 2') follow-up surveys when the self-report adherence items and HRQOL were collected. Overall, 1884 participants completed Time 1 and Time 2 surveys. Of these participants, we excluded only 11 who reported their race to be other than white or black, 339 who had missing pharmacy refill or self-report adherence measures at Time 1, and nine who had missing HRQOL data at Time 1 or Time 2, yielding a sample of 1525 for this analysis. The CoSMO study was approved by Institutional Review Board and the privacy board of the MCO. Participants gave verbal informed consent and human subjects procedures were in accordance with institutional guidelines [15].

Study measures

Exposure: Low medication adherence

The primary exposure variable was low self-report medication adherence at Time 1 measured by the four-item Krousel-Wood Medication Adherence Scale (K-Wood-MAS-4). The K-Wood-MAS-4 was developed to predict pharmacy refill adherence in older adults taking antihypertensive medications [16]: using pharmacy refill in the prior year as the reference standard, the four-item scale had moderate discrimination [C statistic of 0.704, 95% confidence interval (95% CI) 0.683–0.714]; had sensitivity and specificity of 67.4 and 67.8%, respectively; and performed comparably to other published tools. Low K-Wood-MAS-4 adherence has been associated with uncontrolled BP (adjusted odds ratio = 1.29, 95% CI 1.01–1.65) and incident CVD (adjusted hazard ratio = 2.29, 95% CI 1.61–3.26) [17]. The tool is composed of four items assessing four aspects of adherence behaviour: forgetfulness, intentionally missing pills when one feels better, medication-taking self-efficacy and physical health limitations. By design, the K-Wood-MAS-4 captures implementation adherence, or the extent to which treated patients continue to take their medication as prescribed [18], and provides a general assessment of adherence behaviour for people with treated, established chronic disease. One point is assigned for each item response indicating suboptimal adherence, low self-efficacy or physical health limitations. The K-Wood-MAS-4 score is calculated as the sum across items; low adherence is defined as K-Wood-MAS-4 score at least 1.

We also assessed adherence using antihypertensive medication refill data from the pharmacy claims database of the MCO. Using all antihypertensive medication prescriptions filled in the year prior to Time 1, proportion of days covered (PDC) was calculated as the number of days with medication available to take divided by the number of days between the first and last pharmacy refills in the time period [19]. As has been previously reported, PDC was calculated for each antihypertensive medication class separately and then averaged across classes to generate an overall PDC for antihypertensive medications [7,17,20]. Low pharmacy refill adherence was defined as PDC less than 0.8 [19].

Outcome: decline in health-related quality of life

The HRQOL outcomes assessed were declines in Mental Component Summary (MCS) and Physical Component Summary (PCS) in the year between Time 1 and Time 2 data capture. HRQOL was captured using the RAND 36-Item Health Survey 1.0 (RAND-36) [21], which includes 36 questions comprising four physical and four mental health subscales. Subscale scores were weighted and aggregated to create MCS and PCS scores, which were standardized to a mean of 50 and standard deviation of 10 in the general USA population [22].

Decline in HRQOL was defined as a decrease in MCS or PCS score between Time 1 and Time 2 (i.e. over 1 year) equivalent to the minimal important difference (MID) for each respective summary score. MID is 'the smallest difference ... that informed patients or informed proxies perceive as important, either beneficial or harmful, and that would lead the patient or clinician to consider a change in the management [23]'. Details on calculation of MID are presented in the Statistical analysis section.

Covariates: sociodemographic, health behaviour, healthcare and clinical factors

Sociodemographic factors, including age, sex, race, marital status and education, and *health behaviour* factors, including smoking status, alcohol consumption and healthy lifestyle modifications for BP control (weight control, salt

reduction and fruit and vegetable consumption) [24] were assessed by self-report. Low hypertension knowledge was defined as scores in the lowest tertile using a validated tool [25]. Depressive symptoms were defined as scores at least 16 using the 20-item Center for Epidemiologic Studies Depression Scale (CES-D) [26]. Low social support was defined as scores in the lowest tertile using the RAND Medical Outcomes Study Social Support Survey [27]. Low coping was defined as a score below the median using a shortened version of the John Henry Active Coping Scale [28].

Healthcare factors, including number of visits to a healthcare provider in the year prior to Time 1 and reduction in medications due to cost, were assessed by self-report. Low satisfaction with healthcare was defined as an average 'poor' or 'fair' rating using the Group Health Association of America Consumer Satisfaction Survey [29].

Clinical factors included self-reported duration of hypertension, height and weight. Comorbid conditions and number of classes of antihypertensive medications filled in the year prior to Time 1 were identified using administrative data. Using data on comorbid conditions, we calculated the Charlson Comorbidity Index [30]. BP was abstracted from electronic health records for the year preceding Time 1 and average SBP and DBP levels were calculated as the mean of all seated measurements. Uncontrolled BP was defined as SBP at least 140 mmHg or DBP at least 90 mm Hg.

Statistical analysis

Pearson's chi-squared tests and Student's *t*-tests were used to test for differences in participant characteristics by adherence status. An overall MID estimate for each summary score was calculated as the average of MID estimates derived from four approaches [31,32]. In distribution-based approaches, MID was defined as 0.5 standard deviation (SD) of Time 1 MCS or PCS score [33]; and standard error of measurement (SEM) of Time 1 MCS or PCS, which was calculated as $\sigma_x(1-\Gamma_{xx})^{1/2}$, where σ_x was SD and Γ_{xx} was Cronbach's α [32,34]. In the cross-sectional anchor-based approach, MID was defined as the difference in mean MCS or PCS score between those who answered that their health now was *somewhat* or *much worse* and those who indicated that their present health was *the same* or *better than* their health 1 year ago on that item in the Time 1 RAND-36 [32]. In the longitudinal anchor-based approach, MID was defined as the difference in mean change in MCS or PCS score from Time 1 to Time 2 between those who indicated that they were *more often* worn out at Time 2 than at Time 1 and those who indicated *no increase* in frequency of being worn out between the two survey administrations using the responses to that RAND-36 item [32]. The percentage of participants with decline in MCS and PCS was summarized for each individual MID estimate as well as for the overall mean MID estimate.

Separate multivariable Poisson regression models with robust standard errors were used to estimate prevalence ratios and 95% CIs for decline in MCS or PCS. Initial models were adjusted for sociodemographic factors, including age, sex, race, marital status, education. Subsequent models were also adjusted for hypertension knowledge, social support, coping, alcohol consumption, healthy lifestyle modifications for BP control and number of visits to a healthcare provider in the past year. To address the possibility of reverse causality (i.e. the potential effect of mental HRQOL on adherence), we also adjusted for Time 1 depressive symptoms. Final models were further adjusted for clinical factors including Charlson Comorbidity Index, BP control and number of classes of antihypertensive medications filled.

Age (<75 versus ≥75 years), sex (men versus women) and race (black versus white) stratified analyses were performed. Effect modification by age, sex and race was tested by including an *adherence x age*, *adherence x sex* or *adherence x race* interaction term in the fully adjusted model for the overall sample. Given that the physical function item of the K-Wood-MAS-4 originated from the RAND-36, we conducted a sensitivity analysis using only three items from the K-Wood-MAS-4 (i.e. excluding the physical function item). We conducted a second sensitivity analysis using four alternative definitions of decline in HRQOL that were based on the individual MID estimates derived from the four approaches. Given the possibility that poor mental HRQOL at Time 1 could affect medication adherence over the following year, a third sensitivity analysis examined decline in MCS or PCS among those without low initial MCS or PCS, respectively. Low MCS and PCS were defined as scores in the lowest tertile of the respective distribution of summary scores [9], which corresponded to cut points of 54.7 and 37.8, respectively. A fourth sensitivity analysis used a composite measure of low adherence: participants were categorized into one of four categories based on their K-Wood-MAS-4 and PDC adherence statuses (i.e. low K-Wood-MAS-4 adherence and low PDC adherence; low K-Wood-MAS-4 adherence and not low PDC adherence; not low K-Wood-MAS-4 adherence and low PDC adherence; not low K-Wood-MAS-4 adherence and not low PDC adherence). In a final sensitivity analysis, we examined the association between low pharmacy refill adherence measured in the one-year interval between Time 1 and Time 2 (rather than in the year prior to Time 1) and decline in MCS and PCS. All analyses were performed using Stata v14.1 (StataCorp, College Station, Texas, USA). Figure 1 was created using R 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Participant characteristics

The mean age of the participants included in the sample was 76.2 years. Approximately 59.7% of participants were women, 27.9% were black and 55.3% were married (Table 1). The prevalence of low medication adherence was 38.6% when measured by K-Wood-MAS-4 and 23.9% when measured by PDC.

Minimal important difference in health-related quality of life

The MID estimates for MCS ranged from 3.13 for the SEM distribution-based approach to 6.15 for the cross-sectional anchor-based approach (Table 2). The MID estimates for PCS ranged from 2.49 for the longitudinal anchor-based approach to 9.68 for the cross-sectional anchor-based

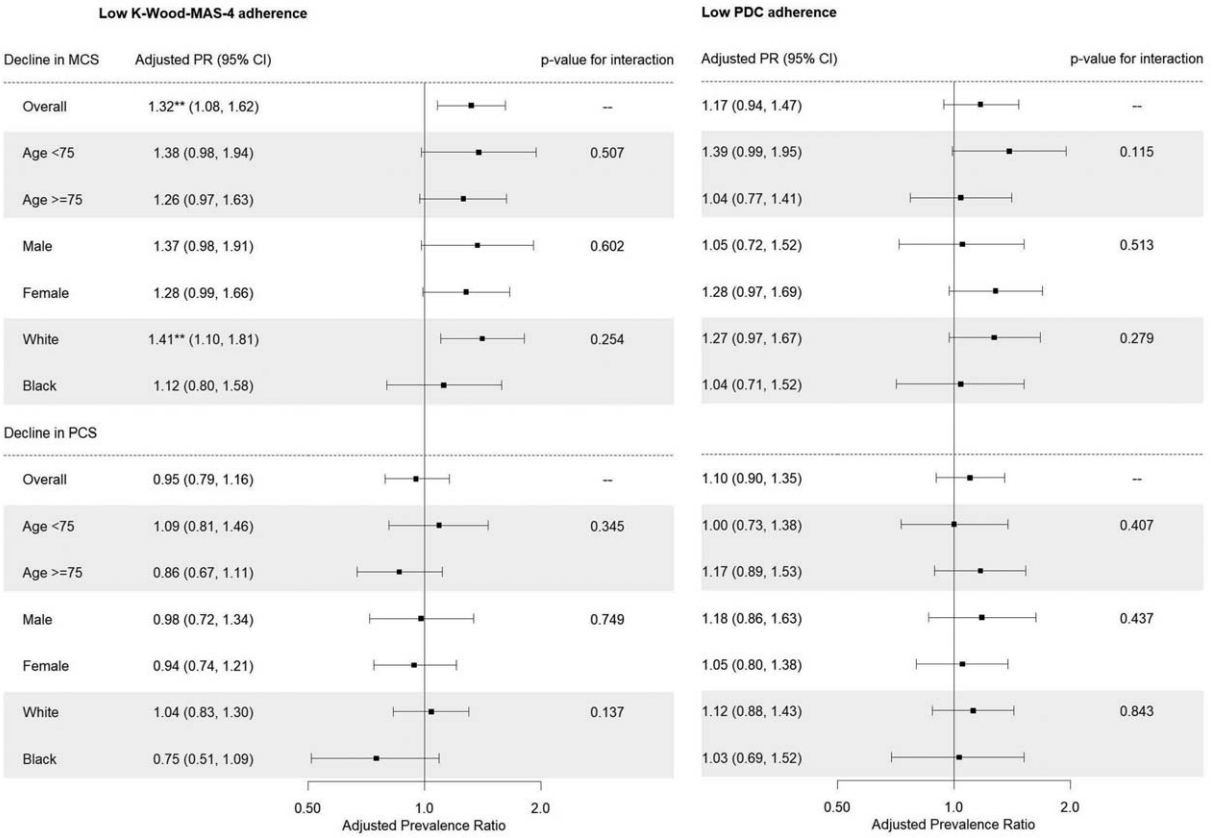

FIGURE 1 Adjusted prevalence ratios and 95% confidence intervals for decline in health-related quality of life (MCS and PCS), overall and stratified by age, sex and race. Reference category for all models: high adherence. CI, confidence interval; K-Wood-MAS-4, Krousel-Wood medication adherence scale; MCS, Mental Component Summary; PCS, Physical Component Summary; PDC, proportion of days covered; PR, prevalence ratio. $^{**}P < 0.01$.

TABLE 1. Participant characteristics

		K-Wood-MAS-4 adherence			PDC adherence		
	Overall $n = 1525$	High $n = 936$	Low $n = 589$	*P*	High $n = 1161$	Low $n = 364$	*P*
Age ≥75 years (%)	56.3	56.4	56.0	0.883	57.5	52.5	0.095
Female (%)	59.7	57.4	63.5	0.018	59.4	61.0	0.577
Black (%)	27.9	24.3	33.6	<0.001	24.6	38.2	<0.001
Married (%)	55.3	55.6	54.8	0.784	55.8	53.6	0.453
High school education or greater (%)	80.6	82.3	77.9	0.037	82.1	75.8	0.008
Low hypertension knowledge (%)	29.6	26.7	34.3	0.002	29.1	31.3	0.421
Depressive symptoms (%)	12.8	8.3	19.9	<0.001	12.2	14.6	0.246
Low social support (%)	34.9	32.1	39.4	0.003	35.1	34.3	0.803
Low coping (%)	47.9	46.5	50.1	0.169	48.7	45.3	0.266
Hypertension duration ≥10 years (%)	63.4	62.9	64.3	0.581	63.5	63.2	0.913
High body mass index (%)	76.0	75.1	77.4	0.313	75.4	78.1	0.283
Charlson Comorbidity Index ≥2 (%)	56.3	52.8	62.0	<0.001	54.4	62.6	0.005
Uncontrolled blood pressure (%)	29.7	27.3	33.5	0.013	27.5	36.9	0.001
Ever smoked (%)	49.9	49.8	50.0	0.935	48.5	54.3	0.054
2+ alcoholic drinks per week (%)	24.0	27.4	18.7	<0.001	24.9	21.2	0.150
2+ health lifestyle modifications (%)	80.3	81.1	79.1	0.329	80.2	80.5	0.916
3+ classes of antihypertensive medications (%)	46.4	44.2	49.8	0.036	46.3	46.7	0.881
Low satisfaction with healthcare (%)	3.7	2.0	6.3	<0.001	3.0	5.8	0.015
6+ visits to healthcare provider in past year (%)	28.4	24.5	34.5	<0.001	26.4	34.7	0.002
Reduced medications due to cost (%)	2.2	1.0	4.1	<0.001	1.1	5.5	<0.001
MCS score (mean, SD)	55.2 (9.1)	56.2 (8.1)	53.6 (10.3)	<0.001	55.5 (8.7)	54.3 (10.2)	0.026
PCS score (mean, SD)	42.3 (10.9)	45.2 (9.5)	37.7 (11.6)	<0.001	42.7 (10.9)	41.2 (11.1)	0.029

K-Wood-MAS-4, Krousel-Wood medication adherence scale; MCS, Mental Component Summary; PCS, Physical Component Summary; PDC, proportion of days covered; SD, standard deviation.

TABLE 2. Distribution- and anchor-based minimal important difference estimates for health-related quality of life (Mental Component Summary and Physical Component Summary) and percentage with decline using each definition

	Distribution-based				Anchor-based					
	0.5 SD		1 SEM		Cross-sectional		Longitudinal		Mean	
Health-related quality of life	MID estimate	% (*n*) with decline	MID estimate	% (*n*) with decline	MID estimate	% (*n*) with decline	MID estimate	% (*n*) with decline	MID estimate	% (*n*) with decline
MCS	4.54	20.7 (316)	3.13	28.5 (435)	6.15	16.0 (244)	3.80	25.9 (395)	4.40	21.8 (332)
PCS	5.47	23.9 (365)	3.02	35.1 (535)	9.68	12.4 (189)	2.49	38.2 (582)	5.16	25.2 (384)

Health-related quality of life (MCS and PCS) measured using RAND 36-Item Health Survey 1.0.
MCS, Mental Component Summary; MID, minimal important difference; PCS, Physical Component Summary; SD, standard deviation; SEM, standard error of measurement.

approach. Using the mean MID across the four approaches of 4.40 for MCS and 5.16 for PCS, 21.8 and 25.2% of participants experienced a decline in MCS and PCS, respectively, over 1 year (i.e. from Time 1 to Time 2). The percentage of respondents experiencing a decline in HRQOL for individual MID estimates ranged from 16.0 to 28.5% for MCS and from 12.4 to 38.2% for PCS.

Decline in health-related quality of life

Mental component summary

Among those with low K-Wood-MAS-4 adherence, 26.0% experienced a decline in MCS compared with 19.1% of those with high K-Wood-MAS-4 adherence. Also, 24.5 and 20.9% of those with a low and high PDC adherence, respectively, experienced a decline in MCS. After adjustment for sociodemographic, health behaviour, healthcare and clinical factors, low adherence at Time 1 was associated with a decline in MCS from Time 1 to Time 2 for K-Wood-MAS-4 (prevalence ratio = 1.32, 95% CI 1.08–1.62, $P = 0.008$), but not PDC (prevalence ratio = 1.17, 95% CI 0.94–1.47, $P = 0.168$), adherence (Table 3, Fig. 1; full model results presented in Table S1 in Supplemental Digital Content, http://links.lww.com/HJH/B424).

Physical component summary

Among those with low K-Wood-MAS-4 adherence, 23.6% experienced a decline in PCS compared with 26.2% of those with high K-Wood-MAS-4 adherence. Among those with low and high PDC adherence, 26.9 and 24.6%, respectively, experienced a decline in PCS. After adjustment for sociodemographic, health behaviour, healthcare and clinical factors, low medication adherence at Time 1 was not associated with a decline in PCS from Time 1 to Time 2 (prevalence ratio = 0.95, 95% CI 0.79–1.16, $P = 0.633$ for K-Wood-MAS-4; prevalence ratio = 1.10, 95% CI 0.90–1.35, $P = 0.362$ for PDC) (Table 3, Fig. 1; full model results presented in Table S1 in Supplemental Digital Content, http://links.lww.com/HJH/B424).

Subgroup analysis

There was no evidence of effect modification by age, sex or race (all P-interaction > 0.05). Results stratified by age, sex and race are presented in Fig. 1. The association between low self-report adherence and decline in MCS was present in whites (prevalence ratio = 1.41, 95% CI 1.10–1.81, $P = 0.007$), but not blacks (prevalence ratio = 1.12, 95% CI 0.80–1.58, $P = 0.505$).

Sensitivity analysis

The prevalence ratio for the association between low adherence and decline in MCS when the physical function item was excluded from the K-Wood-MAS-4 was 1.23 (95% CI 0.99–1.53, $P = 0.060$). There was no association between low adherence and decline in PCS when the physical function item was excluded from the K-Wood-MAS-4 (PR = 1.14, 95% CI 0.93–1.39, $P = 0.214$).

The prevalence ratio for the association between low adherence and decline in MCS as defined by each individual MID estimate ranged from 1.23 (95% CI 1.04–1.46, $P = 0.016$) to 1.53 (95% CI 1.20–1.96, $P = 0.001$) using K-Wood-MAS-4 and from 1.11 (95% CI 0.90–1.35, $P = 0.332$)

TABLE 3. Unadjusted and adjusted prevalence ratios and 95% confidence intervals for a decline in health-related quality of life (Mental Component Summary and Physical Component Summary)

Health-related quality of life	Unadjusted PR (95% CI)	Model 1 PR (95% CI)	Model 2 PR (95% CI)	Model 3 PR (95% CI)
Mental Component Summary (MCS)				
Low K-Wood-MAS-4 adherence	1.36** (1.12–1.64)	1.33** (1.10–1.61)	1.28* (1.05–1.56)	1.32** (1.08–1.62)
Low PDC adherence	1.17 (0.94–1.44)	1.15 (0.93–1.42)	1.13 (0.91–1.41)	1.17 (0.94–1.47)
Physical Component Summary (PCS)				
Low K-Wood-MAS-4 adherence	0.90 (0.75–1.08)	0.92 (0.77–1.10)	0.92 (0.76–1.11)	0.95 (0.79–1.16)
Low PDC adherence	1.09 (0.90–1.33)	1.13 (0.93–1.38)	1.12 (0.92–1.37)	1.10 (0.90–1.35)

Reference category for all models: high adherence.
Model 1 adjusted for age, sex, race, marital status, education.
Model 2 adjusted for Model 1 variables and hypertension knowledge, depressive symptoms, social support, coping, alcohol consumption, healthy lifestyle modifications and number of visits to healthcare provider in past year.
Model 3 adjusted for Model 2 variables and comorbidities, blood pressure control and number of classes of antihypertensive medication.
CI, confidence interval; K-Wood-MAS-4, Krousel-Wood medication adherence scale; PDC, proportion of days covered; PR, prevalence ratio.
*$P < 0.05$.
**$P < 0.01$.

TABLE 4. Adjusted prevalence ratios and 95% confidence intervals for a decline in health-related quality of life (Mental Component Summary and Physical Component Summary) as defined by individual minimal important difference estimates

Health-related quality of life	Minimal important difference estimate			
	0.5 SD	1 SEM	Cross-sectional	Longitudinal
Mental Component Summary (MCS)				
Low K-Wood-MAS-4 adherence	1.35** (1.09–1.66)	1.23* (1.04–1.46)	1.53*** (1.20–1.96)	1.24* (1.03–1.48)
Low PDC adherence	1.17 (0.93–1.47)	1.15 (0.95–1.38)	1.27 (0.97–1.65)	1.11 (0.90–1.35)
Physical Component Summary (PCS)				
Low K-Wood-MAS-4 adherence	0.93 (0.76–.14)	0.92 (0.79–1.07)	0.78 (0.57–1.06)	0.92 (0.80–1.06)
Low PDC adherence	1.10 (0.89–1.36)	0.99 (0.84–1.17)	1.09 (0.79–1.50)	0.98 (0.83–1.15)

Reference category for all models: high adherence.
Models adjusted for age, sex, race, marital status, education, hypertension knowledge, depressive symptoms, social support, coping, alcohol consumption, health lifestyle modifications, number of visits to healthcare provider in past year, comorbidities, blood pressure control, and number of classes of antihypertensive medication
CI, confidence interval; K-Wood-MAS-4, Krousel-Wood medication adherence scale; PDC, proportion of days covered; PR, prevalence ratio; SD, standard deviation; SEM, standard error of measurement.
*$P < 0.05$.
**$P < 0.01$.
***$P < 0.001$.

to 1.27 (95% CI 0.97–1.65, $P = 0.080$) using PDC (Table 4). The prevalence ratio for the association between low adherence and decline in PCS ranged from 0.78 (95% CI 0.57–1.06, $P = 0.117$) to 0.93 (95% CI 0.76–1.14, $P = 0.512$) using K-Wood-MAS-4 and from 0.98 (95% CI 0.83–1.15, $P = 0.796$) to 1.10 (95% CI 0.89–1.36, $P = 0.376$) using PDC.

Among those without low initial MCS, low adherence was associated with decline in MCS (prevalence ratio = 1.43, 95% CI 1.13–1.80, $P = 0.003$ using K-Wood-MAS-4; prevalence ratio = 1.35, 95% CI 1.05–1.73, $P = 0.017$ using PDC). There was no association between low adherence and decline in PCS among those without low initial PCS (prevalence ratio = 1.16, 95% CI 0.94–1.43, $P = 0.172$ using K-Wood-MAS-4; prevalence ratio = 1.07, 95% CI 0.86–1.35, $P = 0.533$ using PDC).

Using the four-category composite adherence measure, having both low K-Wood-MAS-4 and low PDC adherence was associated with a decline in MCS over the following year (prevalence ratio = 1.46, 95% CI 1.08–1.96, $P = 0.013$) (Table 5). Having only low K-Wood-MAS-4 adherence (and not low PDC adherence) was also associated with decline in MCS (prevalence ratio = 1.31, 95% CI 1.04–1.67, $P = 0.025$), while having only low PDC adherence (and not low K-Wood-MAS-4 adherence) was not associated with decline in MCS (prevalence ratio = 1.15, 95% CI = 0.82–1.61, $P = 0.417$). There was no increase in the likelihood of a decline in PCS for any of the adherence categories (prevalence ratio = 1.05, 95% CI 0.79–1.40, $P = 0.726$; prevalence ratio = 0.93, 95% CI 0.74–1.18, $P = 0.566$; prevalence ratio = 1.10, 95% CI 0.83–1.46, $P = 0.507$; respectively).

TABLE 5. Adjusted prevalence ratios and 95% confidence intervals for association between composite adherence measure and a decline in health-related quality of life (Mental Component Summary and Physical Component Summary)

Adherence category	Decline in MCS	Decline in PCS
Low K-Wood-MAS-4 and low PDC	1.46* (1.08–1.96)	1.05 (0.79–1.40)
Low K-Wood-MAS-4 and not low PDC	1.31* (1.04–1.67)	0.93 (0.74–1.18)
Not low K-Wood-MAS-4 and low PDC	1.15 (0.82–1.61)	1.10 (0.83–1.46)
Not low K-Wood-MAS-4 and not low PDC	Ref	Ref

Models adjusted for age, sex, race, marital status, education, hypertension knowledge, depressive symptoms, social support, coping, alcohol consumption, health lifestyle modifications, number of visits to healthcare provider in past year, comorbidities, blood pressure control and number of classes of antihypertensive medication.
CI, confidence interval; K-Wood-MAS-4, Krousel-Wood medication adherence scale; MCS, Mental Component Summary; PCS, Physical Component Summary; PDC, proportion of days covered; PR, prevalence ratio.
*$P < 0.05$.

When low pharmacy fill adherence was measured in the one-year interval between Time 1 and Time 2, low adherence over this period was not associated with decline in MCS (prevalence ratio = 1.19, 95% CI 0.95–1.49, $P = 0.137$) or PCS (prevalence ratio = 1.15, 95% CI 0.93–1.42, $P = 0.204$) from Time 1 to Time 2.

DISCUSSION

Low self-report antihypertensive medication adherence was associated with a decline in mental HRQOL over 1 year among older adults. Low medication adherence was not associated with decline in physical HRQOL. The findings from this longitudinal analysis extend those of previous cross-sectional studies demonstrating an association between low medication adherence and poor HRQOL [9,35]. Moreover, our findings for mental HRQOL are consistent with a 2016 systematic review and meta-analysis of 20 clinical trials and observational studies showing that adhering to medications is associated with improvements in mental HRQOL [14]. The current analysis addressed several limitations common to the studies included in the systematic review. We used two measures of medication adherence, including a validated self-report tool and pharmacy refill-based adherence measure, had a relatively large sample of older adults, and were able to adjust for BP control, a potential cofounder.

There was no evidence of differences in the association between low adherence and decline in HRQOL across age, sex and race subgroups (all P-interaction > 0.05). However, the study was not designed to examine age, sex and race differences and may have been underpowered to detect effect modification, particularly by race given the limited sample of blacks (e.g. $n = 400$ in the fully adjusted model testing the association between low K-Wood-MAS-4 adherence and decline in PCS). Race differences in adherence [36]

and HRQOL [37] warrant further research with larger subgroup samples.

The association between low medication adherence and decline in HRQOL was present for self-report but not pharmacy refill adherence. In the sensitivity analysis using the composite adherence measure, those with both low self-report and low pharmacy refill adherence were most likely to have a decline in MCS, followed by those with only low self-report adherence. In the absence of low self-report adherence, low pharmacy refill adherence was not associated with a decline in MCS. Although pharmacy refill adherence measures reflect the extent to which prescriptions are filled as directed, self-report adherence measures may better reflect actions across the cascade of adherence behaviour, which may have a greater impact on change in HRQOL [7,38]. In addition, the K-Wood-MAS-4 assesses multiple domains influencing adherence behaviour (forgetfulness, intentionally missing pills when one feels better, medication-taking self-efficacy and physical health limitations) [16] and may be a more sensitive indicator of decline in HRQOL than the pharmacy refill measure. Finally, the different results for self-report versus pharmacy refill adherence may also be due to the different effective recall periods for the two measures: in the primary analysis, PDC reflects adherence behaviour averaged over the year preceding Time 1 while the K-Wood-MAS-4, an implementation adherence measure, does not specify a recall period and provides an assessment of general adherence behaviour. Prior work revealed an annual rate of decline of only 4.3% for self-report adherence in a cohort of older patients with established hypertension over 2 years of follow-up [39], suggesting that self-reported implementation adherence is relatively stable in this population. However, it is possible that the K-Wood-MAS-4 is capturing adherence behaviour more proximal to the detection of decline in HRQOL than prescription-based approaches. In the sensitivity analysis, using a more proximal measure of PDC adherence (pharmacy refill data captured between Time 1 and Time 2) yielded qualitatively similar results compared with the main analysis that captured pharmacy refill data in the year prior to Time 1.

Results were qualitatively similar when excluding the physical function item from the self-report measure, suggesting that the physical function item does not entirely explain the association between self-report adherence and decline in HRQOL. Moreover, results were qualitatively similar when decline in HRQOL was defined using individual MID estimates, indicating results are robust to variation in how MID is calculated.

Medication adherence is a complex issue**.** It is possible that the associations observed are due to the effect of mental HRQOL on medication adherence (i.e. reverse causality). Indeed, previous longitudinal studies have demonstrated that poor mental health leads to low adherence [40,41]. To address this possibility, we adjusted for Time 1 depressive symptoms in the models and conducted a sensitivity analysis that included only those with high/moderate initial MCS. Adjustment for depressive symptoms did not attenuate the association between low adherence and decline in MCS and results of the sensitivity analysis were qualitatively similar to those obtained from the primary analysis. We cannot, however, rule out the possibility that, for some participants, the decline in MCS we detected from Time 1 to Time 2 was an extension of an existing downward trend in mental health that preceded the detection of, and contributed to, low adherence at Time 1. Thus, the alternative interpretation of the study results cannot be entirely excluded by the methodological strategies we employed to address reverse causality.

Although the exact mechanism linking low adherence to decline in HRQOL is unknown, it is possible that adherence to antihypertensive medication therapy may prevent decline in HRQOL via better BP control [42,43], or because of its association with nonpharmacological lifestyle changes [15], which are associated with improvements in HRQOL [43]. However, including uncontrolled BP and healthy lifestyle modifications in regression models did not substantially change the association between low adherence and decline in HRQOL. Moreover, controlling for comorbidities, which are associated with both low adherence [36] and low HRQOL [44], did not attenuate the relationship between low adherence and decline in HRQOL. Finally, including number of classes of antihypertensive medications in the models as a measure of medication burden did not change the association between low adherence and decline in HRQOL. Further work is needed to elucidate the mechanism linking adherence behaviour to changes in HRQOL.

This study has several strengths, including the prospective longitudinal design, comprehensive collection of variables with both validated self-report and pharmacy fill adherence measures, multiple assessments of HRQOL and diverse sample of community-dwelling older adults with hypertension. The restriction of our sample to adults in a managed care setting minimizes confounding effects of health insurance, access to medical care and employment status. The K-Wood-MAS-4 is short, simple to use, open access, has been internally validated, and has comparable performance statistics to other widely-used self-report adherence tools [16]. Finally, the use of both distribution and anchor-based approaches to derive MID estimates for decline in summary scores accounts for both clinical relevance and measurement precision and thereby addresses the limitations associated with using either approach in isolation [32].

The results of this analysis should be considered in the context of study limitations. The CoSMO sample was restricted to English-speaking, insured adults in one region of the United States, and results may not be generalizable to other contexts. Participants excluded from this analysis due to loss to follow-up, reporting race to be other than black or white ($n = 11$), or missing adherence or HRQOL measures were more likely than the full CoSMO sample to be black, have lower education and lower hypertension knowledge, have high stress, report low healthcare satisfaction despite more provider visits in the year prior, have higher rates of low PDC adherence and uncontrolled BP, and be less likely to adopt healthy behaviours for BP control. Moreover, given the documented association between poor adherence and mortality risk [45], the Time 1 medication-taking behaviour of participants who could be included in the analysis because they survived to Time 2 may not be reflective of the medication-taking behaviour of all CoSMO participants. Self-report and pharmacy refill adherence are

indirect measures and do not assess whether patients took their medications as prescribed. Nevertheless, previous research demonstrating associations of K-Wood-MAS-4 and pharmacy refill adherence with BP control and incident CVD [16,17] suggests that the measures reflect actual medication-taking behaviour. Although the CoSMO study collected comprehensive data on numerous factors related to medication adherence according to a published conceptual framework [15], it was a nonexperimental study; thus, there is the possibility that unobserved factors that explain the association between low adherence and decline in HRQOL were not captured for inclusion in the model. Finally, though inclusion of Time 1 depressive symptoms in the model did not attenuate the association between low adherence and decline in MCS, and though the results of the sensitivity analysis excluding those with low MCS at Time 1 were qualitatively similar to those from the main analysis, these methodological strategies may have been insufficient to rule out the possibility of reverse causality, that is that the observed association is due to the effect of mental HRQOL on adherence. Thus, this alternative explanation cannot be entirely excluded.

Although the primary goal of hypertension management has traditionally been to prevent CVD and extend life, there is growing attention to evaluating and improving subjective well being for patients [46]. In this context, HRQOL is a key indicator of how hypertension and its treatment affect a patient's life. Understanding the link between medication adherence and HRQOL may provide opportunities to optimize patient-reported outcomes [42]. In the current study, low self-report medication adherence was associated with decline in mental HRQOL over 1 year among older women and men with established hypertension. K-Wood-MAS-4 is a simple self-report tool that is practical to administer in clinical and research settings and may help providers and researchers to identify older adults with low adherence at risk for declining HRQOL. Further work is needed to confirm findings in larger and more diverse populations and to investigate whether improvements in antihypertensive medication adherence are associated with improvements in HRQOL for older adults with hypertension.

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Conflicts of interest

The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

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REFERENCES

1. Cella DF, Bonomi AE. Measuring quality of life: 1995 update. *Oncology (Williston Park)* 1995; 9:47–60.
2. Stanaway JD, Afshin A, Gakidou E, Lim SS, Abate D, Abate KH, *et al.* Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet* 2018; 392:1923–1994.
3. Trevisol DJ, Moreira LB, Kerkhoff A, Fuchs SC, Fuchs FD. Health-related quality of life and hypertension: systematic review and meta-analysis of observational studies. *J Hypertens* 2011; 29:179–188.
4. Djärv T, Wikman A, Lagergren P. Number and burden of cardiovascular diseases in relation to health-related quality of life in a cross-sectional population-based cohort study. *BMJ open* 2012; 2:e001554.
5. Ortman JM, Velkoff VA, Hogan H. *An aging nation: the older population in the United States*. Washington, DC: United States Census Bureau, Economics and Statistics Administration, US Department of Commerce; 2014.
6. Pandya A, Gaziano TA, Weinstein MC, Cutler D. More americans living longer with cardiovascular disease will increase costs while lowering quality of life. *Health Aff (Millwood)* 2013; 32:1706–1714.
7. Krousel-Wood M, Holt E, Joyce C, Ruiz R, Dornelles A, Webber LS, *et al.* Differences in cardiovascular disease risk when antihypertensive medication adherence is assessed by pharmacy fill versus self-report: the Cohort Study of Medication Adherence among Older Adults (CoSMO). *J Hypertens* 2015; 33:412–420.
8. Naderi SH, Bestwick JP, Wald DS. Adherence to drugs that prevent cardiovascular disease: meta-analysis on 376,162 patients. *Am J Med* 2012; 125:882–887; e1.
9. Holt EW, Muntner P, Joyce CJ, Webber L, Krousel-Wood MA. Health-related quality of life and antihypertensive medication adherence among older adults. *Age Ageing* 2010; 39:481–487.
10. Jneid S, Jabbour H, Hajj A, Sarkis A, Licha H, Hallit S, *et al.* Quality of life and its association with treatment satisfaction, adherence to medication, and trust in physician among patients with hypertension: a cross-sectional designed study. *J Cardiovasc Pharmacol Ther* 2018; 23:532–542.
11. Khayyat SM, Mohamed MM, Khayyat SMS, Alhazmi RSH, Korani MF, Allugmani EB, *et al.* Association between medication adherence and quality of life of patients with diabetes and hypertension attending primary care clinics: a cross-sectional survey. *Qual Life Res* 2019; 28:1053–1061.
12. Park NH, Song MS, Shin SY, Jeong Jh, Lee HY. The effects of medication adherence and health literacy on health-related quality of life in older people with hypertension. *Int J Older People Nurs* 2018; 13:e12196.
13. Uchmanowicz B, Chudiak A, Mazur G. The influence of quality of life on the level of adherence to therapeutic recommendations among elderly hypertensive patients. *Patient Prefer Adherence* 2018; 12:2593–2603.
14. Souza ACCd, Borges JWP, Moreira TMM. Quality of life and treatment adherence in hypertensive patients: systematic review with meta-analysis. *Rev Saude Publica* 2016; 50:71.
15. 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; 93:753–769.
16. Krousel-Wood M, Joyce C, Holt EW, Levitan EB, Dornelles A, Webber LS, *et al.* Development and evaluation of a self-report tool to predict low pharmacy refill adherence in elderly patients with uncontrolled hypertension. *Pharmacotherapy* 2013; 33:798–811.
17. Krousel-Wood M, Peacock E, Joyce C, Li S, Frohlich E, Re R, *et al.* A hybrid 4-item Krousel-Wood Medication Adherence Scale predicts cardiovascular events in older hypertensive adults. *J Hypertens* 2019; 37:851–859.
18. Vrijens B, De Geest S, Hughes DA, Przemyslaw K, Demonceau J, Ruppar T, *et al.* A new taxonomy for describing and defining adherence to medications. *Br J Clin Pharmacol* 2012; 73:691–705.

19. Choudhry NK, Shrank WH, Levin RL, Lee JL, Jan SA, Brookhart MA, *et al*. Measuring concurrent adherence to multiple related medications. *Am J Manag Care* 2009; 15:457–464.
20. Basak R, McCaffrey I, David J, Bentley JP, Przybyla SM, West-Strum D, Banahan BF. Adherence to multiple medications prescribed for a chronic disease: a methodological investigation. *J Manag Care Spec Pharm* 2014; 20:815–823.
21. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992; 30:473–483.
22. Laucis NC, Hays RD, Bhattacharyya T. Scoring the SF-36 in orthopaedics: a brief guide. *J Bone Joint Surg Am* 2015; 97:1628–1634.
23. Schunemann HJ, Puhan M, Goldstein R, Jaeschke R, Guyatt GH. Measurement properties and interpretability of the Chronic respiratory disease questionnaire (CRQ). *Copd* 2005; 2:81–89.
24. Centers for Disease Control and Prevention (CDC), National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey Questionnaire. Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 2003–2004.
25. Williams MV, Baker DW, Parker RM, Nurss JR. Relationship of functional health literacy to patients' knowledge of their chronic disease. A study of patients with hypertension and diabetes. *Arch Intern Med* 1998; 158:166–172.
26. Radloff LS. The CES-D Scale: a self-report depression scale for research in the general population. *Appl Psychol Measure* 1977; 1:385–401.
27. Sherbourne CD, Stewart AL. The MOS social support survey. *Soc Sci Med* 1991; 32:705–714.
28. Fernander AF, Duran RE, Saab PG, Llabre MM, Schneiderman N. Assessing the reliability and validity of the John Henry Active Coping Scale in an urban sample of African Americans and white Americans. *Ethn Health* 2003; 8:147–161.
29. Davies AR, Ware JE. *GHAA's consumer satisfaction survey and user's manual*. Washington, DC: Group Health Association of America; 1991
30. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; 40:373–383.
31. Swigris JJ, Brown KK, Behr J, du Bois RM, King TE, Raghu G, *et al*. The SF-36 and SGRQ: validity and first look at minimum important differences in IPF. *Respir Med* 2010; 104:296–304.
32. Jayadevappa R, Malkowicz SB, Wittink M, Wein AJ, Chhatre S. Comparison of distribution-and anchor-based approaches to infer changes in health-related quality of life of prostate cancer survivors. *Health Serv Res* 2012; 47:1902–1925.
33. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. *Med Care* 2003; 41:582–592.
34. Wyrwich KW, Tierney WM, Wolinsky FD. Further evidence supporting an SEM-based criterion for identifying meaningful intra-individual changes in health-related quality of life. *J Clin Epidemiol* 1999; 52:861–873.
35. Montiel-Luque A, Núñez-Montenegro AJ, Martín-Aurioles E, Canca-Sánchez JC, Toro-Toro MC, González-Correa JA, *et al*. Medication-related factors associated with health-related quality of life in patients older than 65 years with polypharmacy. *PLoS One* 2017; 12:e0171320.
36. Williams LG, Peacock E, Joyce C, Bazzano LA, Sarpong D, Whelton PK, *et al*. Risk factors for low pharmacy refill adherence among older hypertensive men and women by race. *Am J Med Sci* 2018; 356:464–475.
37. Singh JA, Bharat A, Khanna D, Aquino-Beaton C, Persselin JE, Duffy E, *et al*. Racial differences in health-related quality of life and functional ability in patients with gout. *Rheumatology (Oxford)* 2017; 56:103–112.
38. Steiner JF. Rethinking adherence. *Ann Intern Med* 2012; 157:580–585.
39. Krousel-Wood M, Joyce C, Holt E, Muntner P, Webber LS, Morisky DE, *et al*. Predictors of decline in medication adherence: results from the cohort study of medication adherence among older adults. *Hypertension* 2011; 58:804–810.
40. 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; 40:248–257.
41. Holvast F, Wouters H, Hek K, Schellevis F, Voshaar RO, van Dijk L, *et al*. Nonadherence to cardiovascular drugs in older patients with depression: a population-based cohort study. *Int J Cardiol* 2019; 274:366–371.
42. Degl'Innocenti A, Elmfeldt D, Hofman A, Lithell H, Olofsson B, Skoog I, *et al*. Health-related quality of life during treatment of elderly patients with hypertension: results from the Study on COgnition and Prognosis in the Elderly (SCOPE). *J Hum Hypertens* 2004; 18:239–245.
43. Grimm RH, Grandits GA, Cutler JA, Stewart AL, McDonald RH, Svendsen K, *et al*. Relationships of quality-of-life measures to long-term lifestyle and drug treatment in the Treatment of Mild Hypertension Study. *Arch Intern Med* 1997; 157:638–648.
44. Fortin M, Lapointe L, Hudon C, Vanasse A, Ntetu AL, Maltais D. Multimorbidity and quality of life in primary care: a systematic review. *Health Qual Life Outcomes* 2004; 2:51.
45. Corrao G, Rea F, Compagnoni MM, Merlino L, Mancia G. Protective effects of antihypertensive treatment in patients aged 85 years or older. *J Hypertens* 2017; 35:1432–1441.
46. Sullivan M. The new subjective medicine: taking the patient's point of view on healthcare and health. *Soc Sci Med* 2003; 56:1595–1604.