ORIGINAL RESEARCH

Combined Effect of Income and Medication Adherence on Mortality in Newly Treated Hypertension: Nationwide Study of 16 Million Person-Years

Hokyou Lee, MD; Jong Heon Park, MD, PhD; James S. Floyd, MD; Sungha Park, MD, PhD; Hyeon Chang Kim, MD, PhD

***Background*—**Low socioeconomic status and poor medication adherence are known to be associated with increased morbidity and mortality among patients with hypertension, but their combined effects have not been studied. We therefore evaluated the joint association of household income and medication adherence with death and cardiovascular disease in patients newly treated for hypertension.

***Methods and Results*—**This was a nationwide cohort study using the Korean National Health Insurance database. We included 1 651 564 individuals, aged 30 to 80 years, with newly treated hypertension and no prior cardiovascular disease and followed them for 10 years. Main exposures were household income in quintiles and adherence to antihypertensive medication, estimated by medication possession ratio: good (≥0.8), moderate (0.5 to <0.8), or poor (<0.5). The primary outcomes were all-cause and cardiovascular deaths. Higher mortality risk was observed in patients with low income (adjusted hazard ratio=1.50, 99% CI= 1.46-1.53; lowest versus highest quintile) and poor medication adherence (adjusted hazard ratio=1.66, 99% CI=1.63-1.68; poor versus good adherence). When compared with the highest-income and good-adherence group, adjusted hazard ratio (99% CI) of death was 1.56 (1.52-1.61) for highest-income poor-adherers, 1.46 (1.41-1.51) for lowest-income good-adherers, and 2.46 (2.38-2.54) for lowest-income poor-adherers (*P* for interaction <0.001).

***Conclusions*—**Low socioeconomic status and poor adherence to antihypertensive medication are associated with increased mortality and cardiovascular disease risks, but patients with low income are subject to larger excess risks by nonadherence. This highlights the potential importance of promoting medication adherence for risk reduction, especially in low-income patients with hypertension. **(*J Am Heart Assoc*. 2019;8:e013148. DOI: 10.1161/JAHA.119.013148.)**

Key Words: health disparities • hypertension • income • medication adherence • mortality • real-world data

High blood pressure is the leading risk factor for death and cardiovascular disease (CVD) globally.[1] Despite effective blood pressure-lowering treatments available, populations of low socioeconomic status often have poor awareness and control.[2-4] Accruing evidence suggests that socioeconomic deprivation is associated with increased risk for death and CVD.[5] However, among patients newly treated for hypertension, there are scarce data on mortality according to income gradient or on which factors can be improved to lower poverty-related death in these patients.

Previous studies have reported an association between adherence to antihypertensive medication and cardiovascular events.[6,7] Medication adherence is an important clinical and public health issue, given that nonadherence is a major risk factor for adverse outcome and increased medical cost.[8] Although nonadherence is prevalent among low-income patients, it is unclear whether its effect on clinical outcome varies according to socioeconomic gradient because the combined effect of income and medication adherence has not been fully studied. Therefore, in a large primary prevention population, we investigated the risks for death and CVD hospitalizations according to combination of household

From the Departments of Preventive Medicine (H.L., H.C.K.) and Internal Medicine (H.L., S.P., H.C.K.), Graduate School (H.L.), and Division of Cardiology, Severance Cardiovascular Hospital and Cardiovascular Research Institute (S.P.), Yonsei University College of Medicine, Seoul, Korea; Big Data Steering Department, National Health Insurance Service, Wonju, Korea (J.H.P., H.C.K.); Departments of Medicine (J.S.F.) and Epidemiology (J.S.F.), University of Washington, Seattle, WA.

Accompanying Tables S1 through S7 and Figures S1 through S7 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.013148

Correspondence to: Hyeon Chang Kim, MD, PhD, FAHA, Department of Preventive Medicine, Yonsei University College of Medicine, 50 Yonsei-ro, Seodaemun-gu, Seoul 03722, Republic of Korea. E-mail: hckim@yuhs.ac

Received May 1, 2019; accepted July 24, 2019.

Clinical Perspective

What Is New?

- Both low income and poor medication adherence are associated with higher mortality, but their joint association is more potent than each risk factor individually.
- The excess risk by poor medication adherence is greater in individuals with low socioeconomic status, but even with good medication adherence, low-income patients are still at increased mortality risk.

What Are the Clinical Implications?

- Measures to improve medication adherence should be sought to reduce mortality in low-income patients with hypertension, and management of poverty-driven cardiovascular risk factors should accompany these measures.
- Because socioeconomic information is readily available from existing data, future research may identify uniquely vulnerable patients for evidence-based interventions to optimize pharmacologic therapy and improve medication adherence.

income and medication adherence in patients who started hypertension treatment.

Methods

Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers may be sent to the National Health Insurance Service (NHIS) at https://nhiss.nhis.or.kr/bd/ab/bdaba000eng.do

Data Source

We used a nationwide electronic database provided by the NHIS, which includes deidentified claim records of the entire Korean population. The NHIS is the single provider of universal healthcare coverage in South Korea. The NHIS database encompasses both insurance programs: health insurance program covering 97% of the population, and medical aid program covering the remaining 3% with financial needs or under special provisions (eg, national meritorious individuals). The database contains sociodemographic details, reimbursement claims with *International Classification of Disease*, *Tenth Edition* (*ICD-10*) coding, general health checkup results, and death information.[9] Description of the data source has been done in previous studies.[10] The study protocol was approved by the Institutional Review Board of Severance Hospital, Yonsei University Health System, Seoul, Korea (Approval No. 4-2017-0322). Informed consent was not required, as this is a retrospective study of deidentified administrative data.

Study Population

We identified 1 977 432 individuals, aged 30 to 80, newly treated for primary hypertension (*ICD-10* code I10 with antihypertensive medication; Table S1) from January 1, 2004 to December 31, 2007. Identification of treated hypertension followed the protocol developed by the Korean Society of Hypertension.[10,11] We excluded patients with prior diagnosis or medication for any hypertensive disease, prior myocardial infarction (MI), heart failure, or stroke (Table S2), or fewer than 2 prescriptions during the first year of treatment (Figure S1). To minimize the effect of reverse causality, we also excluded individuals who died or had a CVD event within 2 years following the index date (N=88 830). Those with incomplete income information, including medical aid beneficiaries, were also omitted from the analysis (N=237 038). The final 1 651 564 individuals were followed until death, migration from the database, or censoring date (10 years from the index date), whichever came first.

Sociodemographic Information and Covariates

As a proxy for household income we used insurance premium, determined by government assessment of salary and assets, rather than self-report. Household insurance premiums were grouped into quintiles among all households in Korea at the index year. Medical aid beneficiaries do not pay insurance premiums; their economic statuses are heterogeneous and are not included in the income quintiles. We therefore excluded medical aid from the study. Working status was categorized into either employed or self-/unemployed. The Charlson Comorbidity Index was calculated using *ICD-10* codes[12,13] claimed during the 2 years before the index date.

Assessment of Medication Adherence

Antihypertensive adherence was determined by medication possession ratio, which is the number of days' medication supplied divided by the number of days in a time period.[14] The medication possession ratio is among the best available methods using retrospective data[15] and correlates well with other adherence measures.[16] We calculated the medication possession ratio for the first 2 years after index date and classified it into 3 levels: good ($\geq$0.8), moderate ($\geq$0.5 and $<$0.8), or poor ($<$0.5) adherence, as done in previous studies.[7,17,18] We capped the medication possession ratio at 1.0 to discard days oversupplied.

Outcomes

The primary outcomes were all-cause and cardiovascular deaths. All deaths and their causes were ascertained by linkage to the Statistics Korea database via resident registration numbers. Cardiovascular death was defined as death due to CVD (*ICD-10*, I00-I99) by certificate. The secondary outcomes were atherosclerotic CVD, a composite of MI and/or stroke, MI, stroke, and heart failure, defined as the first hospitalization with the corresponding condition as the main diagnosis (Table S2).

Statistical Analyses

Baseline characteristics were reported as frequency and percentage or median and interquartile range. We used a Cox proportional hazards model to calculate hazard ratio (HR) and 99% CI for each outcome according to household income, medication adherence, and the combination of the 2 (15 levels: 5 levels of income by 3 levels of adherence). Multivariable Cox regression was adjusted for age, sex, employment status, household income, Charlson Comorbidity Index, use of glucose-lowering drugs, use of lipid-lowering drugs, antihypertensive drug class, and medication adherence. We further stratified our analyses by sex, given that health-related behaviors, medication adherence, and mortality may differ by sex. Interactions of sex with income and adherence and interaction between the income and adherence interaction within each sex were tested as continuous terms in the full model. The proportionality of hazards was checked graphically by log-minus-log plot and by Schoenfeld residuals. The assumption of proportional hazards was not violated.

Several additional analyses were done on different subsets or inclusion of data. First, monotherapy initiators (N=923 664, excluding first-line β-blockers) and combination therapy initiators (N=572 445) were analyzed separately. Second, given our operational definition excluding individuals with only 1 prescribing visit for stricter identification of treated hypertension, we performed sensitivity analyses including those without further visits (total N=2 163 335) to ensure that excluding these individuals did not alter the association between adherence and mortality. Finally, because our main analysis did not account for lifestyle or clinical parameters, we performed additional analyses on 643 026 individuals with health checkup results closest to, and within the past 2 years from, the index date (median 7.3 months). We added cigarette smoking (never, past, or current), alcohol consumption (none, 1-2 times/wk, ≥3 times/wk), physical exercise (none, 1-2 times/wk, ≥3 times/wk), body mass index, systolic blood pressure, fasting glucose, and total cholesterol in this model. Details of health screening variables are described elsewhere.[19] All analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC) and R version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria) with *survival* package.

Results

Baseline Characteristics

A total of 1 651 564 individuals were followed for 15 956 805 person-years. Baseline characteristics by income levels are summarized in Table 1. Median age was 53 (interquartile range 46-63) years, and 47.5% were women. Age was comparable across income levels, and female sex and employed status were more prevalent in the lowest income group. Individuals with lower income were more likely to be on multiple antihypertensive agents. For the initial regimen, diuretics, beta-blockers, or calcium channel blockers were more common in lower income groups, whereas angiotensin II receptor blockers were more frequently used in higher income groups. Distribution of Charlson Comorbidity Index was comparable across the groups, but patients with lower income had marginally fewer documented comorbidities.

During the first 2 years of treatment, 742 387 (45.0%) patients showed good adherence, 348 236 (21.1%) moderate adherence, and 560 941 (34.0%) poor adherence to antihypertensive medication. Medication adherence tended to be positively associated with household income. Further descriptive statistics stratified by level of adherence are summarized in Table S3.

Death and CVD Hospitalizations According to Income and Medication Adherence

During 15 956 805 person-years, 136 287 deaths were observed. Mortality rates were higher in individuals with lower household income (1010.9 versus 779.1 per 100 000 person-years; lowest versus highest income). Lower household income was independently associated with increased mortality, even after adjustment for age, sex, employment, comorbidities, antihypertensive medications, and adherence. The HR (99% CI) for all-cause and cardiovascular death were 1.64 (1.59-1.68) and 1.75 (1.64-1.87) in men and 1.31 (1.27-1.36) and 1.38 (1.29-1.47) in women, when lowest-income group was compared with highest-income group (Table 2). Poor medication adherence was also associated with greater risk for all-cause and cardiovascular death—HR (99% CI), 1.70 (1.66-1.73) and 1.95 (1.86-2.05) in men and 1.56 (1.52-1.60) and 1.74 (1.64-1.83) in women—when compared with good adherence and adjusted for covariates (Table 2). There were significant

Table 1. Baseline Characteristics by Household Income

	Household Income, Quintile				
	Q5, Highest	Q4	Q3	Q2	Q1, Lowest
	(N=470 609)	(N=371 434)	(N=297 474)	(N=240 613)	(N=271 434)
Age, y	54 [46-64]	53 [45-63]	53 [45-61]	53 [46-61]	55 [47-63]
Sex					
Female	212 709 (45.2%)	170 661 (45.9%)	137 849 (46.3%)	117 620 (48.9%)	145 660 (53.7%)
Male	257 900 (54.8%)	200 773 (54.1%)	159 625 (53.7%)	122 993 (51.1%)	125 774 (46.3%)
Employment status					
Employed workers	107 543 (22.9%)	69 086 (18.6%)	56 082 (18.9%)	49 733 (20.7%)	93 535 (34.5%)
Self- or unemployed	363 066 (77.1%)	302 348 (81.4%)	241 392 (81.1%)	190 880 (79.3%)	177 899 (65.5%)
Initial antihypertensive agent*					
Diuretics	123 885 (26.3%)	102 736 (27.7%)	84 339 (28.4%)	69 269 (28.8%)	78 558 (28.9%)
β-blockers	99 990 (21.2%)	81 707 (22.0%)	66 773 (22.4%)	54 863 (22.8%)	61 236 (22.6%)
Calcium channel blockers	262 915 (55.9%)	215 554 (58.0%)	175 943 (59.1%)	144 130 (59.9%)	163 669 (60.3%)
ACE inhibitors	58 650 (12.5%)	47 909 (12.9%)	38 161 (12.8%)	30 340 (12.6%)	34 068 (12.6%)
Angiotensin II receptor blockers	112 559 (23.9%)	78 138 (21.0%)	60 241 (20.3%)	46 758 (19.4%)	51 299 (18.9%)
Others	3643 (0.8%)	2589 (0.7%)	2004 (0.7%)	1610 (0.7%)	1818 (0.7%)
Number of antihypertensive class					
1	314 312 (66.8%)	243 264 (65.5%)	192 307 (64.6%)	154 550 (64.2%)	174 686 (64.4%)
2	125 283 (26.6%)	102 261 (27.5%)	83 115 (27.9%)	68 000 (28.3%)	76 719 (28.3%)
≥3	31 014 (6.6%)	25 909 (7.0%)	22 052 (7.4%)	18 063 (7.5%)	20 029 (7.4%)
Use of glucose-lowering drugs	79 180 (16.8%)	64 529 (17.4%)	52 405 (17.6%)	42 794 (17.8%)	48 045 (17.7%)
Use of lipid-lowering drugs	66 642 (14.2%)	47 198 (12.7%)	35 768 (12.0%)	27 490 (11.4%)	30 420 (11.2%)
Charlson Comorbidity Index					
0	231 950 (49.3%)	185 006 (49.8%)	151 885 (51.1%)	124 890 (51.9%)	142 041 (52.3%)
1	89 736 (19.1%)	71 188 (19.2%)	55 936 (18.8%)	45 156 (18.8%)	53 196 (19.6%)
2	81 841 (17.4%)	63 871 (17.2%)	50 237 (16.9%)	39 405 (16.4%)	42 729 (15.7%)
≥3	67 082 (14.3%)	51 369 (13.8%)	39 416 (13.3%)	31 162 (13.0%)	33 468 (12.3%)
Medication possession ratio	0.78 [0.37-0.95]	0.75 [0.32-0.94]	0.72 [0.29-0.93]	0.71 [0.27-0.92]	0.73 [0.30-0.93]
Medication adherence					
Good	225 169 (47.8%)	167 883 (45.2%)	128 731 (43.3%)	101 928 (42.4%)	118 676 (43.7%)
Moderate	97 682 (20.8%)	78 119 (21.0%)	63 202 (21.2%)	51 511 (21.4%)	57 722 (21.3%)
Poor	147 758 (31.4%)	125 432 (33.8%)	105 541 (35.5%)	87 174 (36.2%)	95 036 (35.0%)

Data are presented as median [interquartile range] or frequency (percent). ACE indicates angiotensin-converting-enzyme.
*Counted with duplicates for combination therapy.

interactions of sex with both income and adherence in association with all outcomes ($P<0.005$) except for myocardial infarction ($P>0.1$).

When stratified by the combination of income and adherence, poor medication adherence was associated with higher risk for all-cause and cardiovascular death across all income groups. However, the absolute risks and their difference by adherence gradually increased toward lower household income, especially in men. In lowest-income men, cumulative death rates were 1714.7 versus 1064.8 per 100 000 person-years for poor versus good adherers, whereas in highest-income men, rates were 1110.1 versus 694.9 per 100 000 person-years for poor versus good adherers. After adjustment for covariates, excess risk for all-cause death associated with poor medication adherence was 117% in lowest-income men and 59% in highest-income

Table 2. All-Cause and Cardiovascular Death According to Household Income and Medication Adherence

Variables	People	All-Cause Death				Cardiovascular Death			
		Events	Rate*	HR (95% CI)		Events	Rate*	HR (95% CI)	
				Model 1	Model 2			Model 1	Model 2
Total	1 651 564	136 287	854.1			27 195	170.4		
Income, quintile									
5, highest	470 609	35 544	779.1	1.00 (reference)	1.00 (reference)	6974	152.9	1.00 (reference)	1.00 (reference)
4	371 434	29 156	810.5	1.16 (1.13-1.18)	1.14 (1.12-1.17)	5838	162.3	1.21 (1.16-1.27)	1.19 (1.13-1.24)
3	297 474	23 888	831.0	1.29 (1.26-1.32)	1.26 (1.23-1.29)	4681	162.8	1.34 (1.27-1.40)	1.29 (1.23-1.35)
2	240 613	21 365	921.7	1.46 (1.42-1.49)	1.41 (1.38-1.44)	4274	184.4	1.53 (1.46-1.61)	1.46 (1.39-1.54)
1, lowest	271 434	26 334	1010.9	1.54 (1.51-1.58)	1.50 (1.46-1.53)	5428	208.4	1.63 (1.56-1.71)	1.55 (1.48-1.63)
Adherence									
Good	742 387	49 451	683.6	1.00 (reference)	1.00 (reference)	9374	129.6	1.00 (reference)	1.00 (reference)
Moderate	348 236	29 140	866.5	1.35 (1.32-1.37)	1.30 (1.28-1.33)	5883	174.9	1.43 (1.37-1.49)	1.41 (1.35-1.47)
Poor	560 941	57 696	1076.4	1.70 (1.67-1.73)	1.66 (1.63-1.68)	11 938	222.7	1.84 (1.78-1.91)	1.88 (1.81-1.95)
Men	867 065	85 811	1032.1			15 198	182.8		
Income, quintile									
5, highest	257 900	21 290	854.9	1.00 (reference)	1.00 (reference)	3589	144.1	1.00 (reference)	1.00 (reference)
4	200 773	18 669	966.7	1.20 (1.17-1.23)	1.18 (1.15-1.21)	3353	173.6	1.29 (1.21-1.37)	1.26 (1.18-1.34)
3	159 625	15 624	1020.7	1.35 (1.31-1.38)	1.31 (1.27-1.34)	2743	179.2	1.42 (1.33-1.52)	1.36 (1.27-1.45)
2	122 993	14 139	1207.0	1.58 (1.54-1.63)	1.53 (1.48-1.57)	2589	221.0	1.75 (1.63-1.87)	1.65 (1.54-1.76)
1, lowest	125 774	16 089	1351.4	1.70 (1.66-1.75)	1.64 (1.59-1.68)	2924	245.6	1.87 (1.75-1.99)	1.75 (1.64-1.87)
Adherence									
Good	389 003	30 735	815.2	1.00 (reference)	1.00 (reference)	5191	137.7	1.00 (reference)	1.00 (reference)
Moderate	180 554	17 823	1029.5	1.36 (1.33-1.40)	1.31 (1.28-1.34)	3139	181.3	1.43 (1.35-1.51)	1.40 (1.32-1.49)
Poor	297 508	37 253	1324.4	1.77 (1.73-1.80)	1.70 (1.66-1.73)	6868	244.2	1.93 (1.84-2.02)	1.95 (1.86-2.05)
Women	784 499	50 476	660.5			11 997	157.0		
Income, quintile									
5, highest	212 709	14 254	688.0	1.00 (reference)	1.00 (reference)	3385	163.4	1.00 (reference)	1.00 (reference)
4	170 661	10 487	629.5	1.10 (1.07-1.14)	1.10 (1.06-1.13)	2485	149.2	1.15 (1.07-1.23)	1.13 (1.05-1.21)
3	137 849	8264	615.0	1.21 (1.17-1.25)	1.19 (1.15-1.24)	1938	144.2	1.26 (1.17-1.36)	1.23 (1.14-1.32)
2	117 620	7226	630.2	1.27 (1.22-1.32)	1.24 (1.20-1.29)	1685	147.0	1.31 (1.22-1.42)	1.26 (1.17-1.37)
1, lowest	145 660	10 245	724.3	1.34 (1.30-1.39)	1.31 (1.27-1.36)	2504	177.0	1.44 (1.34-1.54)	1.38 (1.29-1.47)
Adherence									
Good	353 384	18 716	540.3	1.00 (reference)	1.00 (reference)	4183	120.8	1.00 (reference)	1.00 (reference)
Moderate	167 682	11 317	693.6	1.30 (1.26-1.34)	1.27 (1.24-1.31)	2744	168.2	1.39 (1.31-1.48)	1.38 (1.30-1.47)
Poor	263 433	20 443	802.6	1.57 (1.53-1.61)	1.56 (1.52-1.60)	5070	199.1	1.70 (1.61-1.80)	1.74 (1.64-1.83)

Model 1 included either income or adherence as the primary independent variable and was adjusted for age, sex, and employment status. Model 2 included both income and adherence as independent variables and was adjusted for age, sex, employment status, Charlson Comorbidity Index, use of glucose-lowering drugs, use of lipid-lowering drugs, and antihypertensive drug class. HR indicates hazard ratio.

*Per 100 000 person-years.

men (Figure 1). Similarly, excess risks for cardiovascular death associated with poor adherence were 178% versus 84% in lowest- versus highest-income men, respectively (Figure 1). There were significant interactions between income and adherence in association with all-cause and cardiovascular death ($P<0.001$ and 0.020). In women, the difference in mortality risk by income was also present but was not as prominent as in men. Excess risks associated with poor

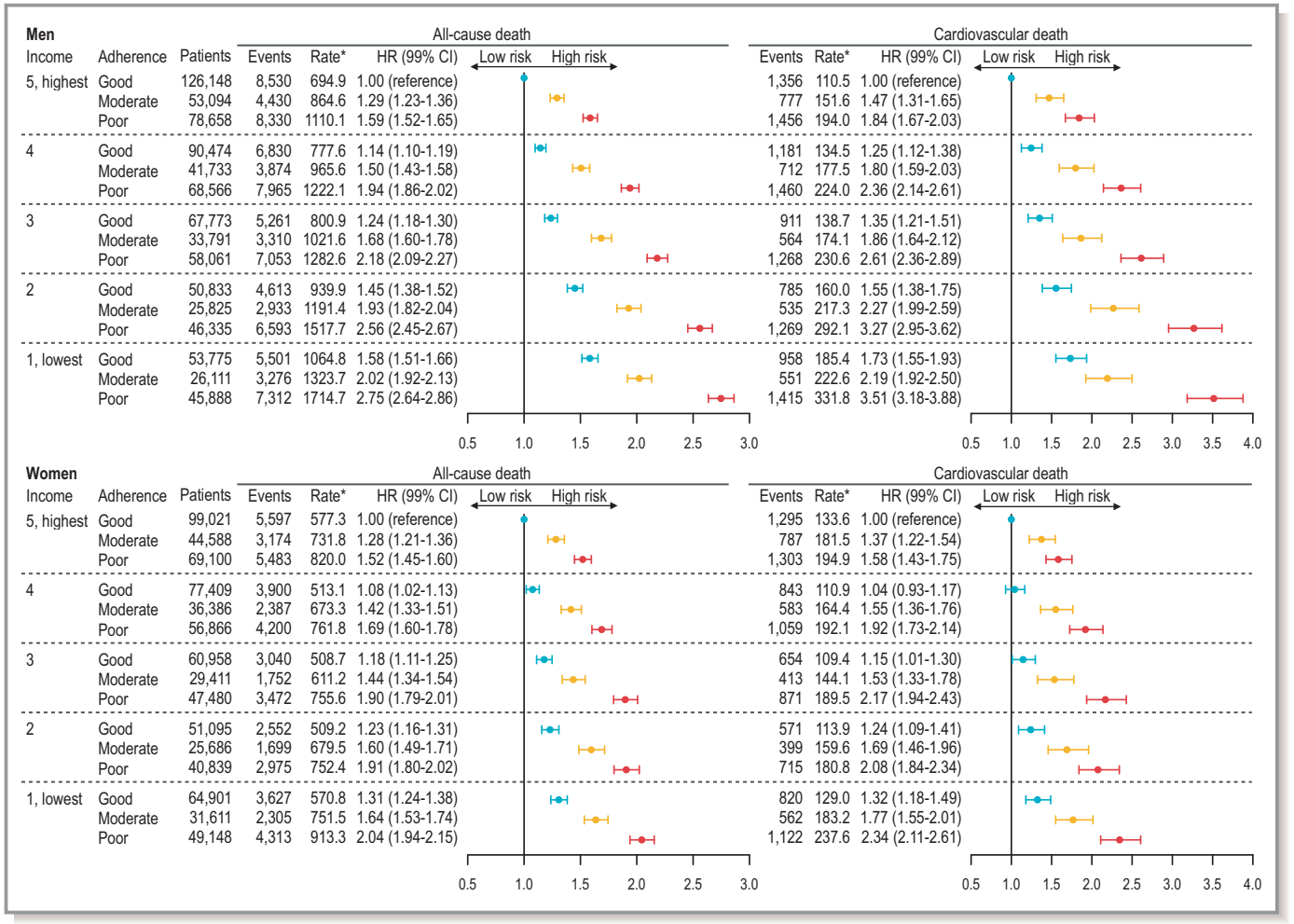


Figure 1. Combined effect of income and adherence on all-cause and cardiovascular death in men and women. Multivariate Cox regression adjusted for age, employment status, Charlson Comorbidity Index, use of glucose-lowering drugs, use of lipid-lowering drugs, and antihypertensive drug class. *P* for interaction between income and adherence in men and women was <0.001 and 0.454 for all-cause death and 0.020 and 0.187 for cardiovascular death, respectively. HR indicates hazard ratio. *Per 100 000 person-years.

adherence in lowest- versus highest-income women were 73% versus 52% for all-cause death and 102% versus 58% for cardiovascular death (Figure 1). Income-adherence interaction did not reach statistical significance in women ($P>0.1$). Kaplan-Meier curves for all-cause and cardiovascular death showed that both income and adherence were individually associated with survival, but the impact of low income on survival was much less in women than in men (Figure 2). Associations with CVD hospitalizations showed similar joint effects of income and adherence, but interactions between income and adherence did not reach statistical significance for nonfatal outcomes ($P>0.1$) except for stroke in women (Figures S2, S3, and Tables S4, S5).

Additional Analyses

We performed several additional analyses on different subsets or inclusion criteria. First, when monotherapy and combination therapy initiators were analyzed separately, the income-adherence joint associations with mortality and its sex difference were consistently observed in both groups (Figures S4 and S5). Second, when patients with fewer than 2 visits were added as sensitivity analyses, the HRs were marginally attenuated, but the joint income-adherence associations with mortality and the sex difference remained (Figure S6). Finally, we performed an additional analysis on 643 026 individuals with health examination results. Overall mortality rates in health examinees were lower than in the entire study patients (685.3 per 100 000 person-years). We observed consistent joint associations of income and adherence with death and CVD, as described in the main analysis, but with attenuated HRs when further adjustment was made for cigarette smoking, alcohol consumption, physical exercise, body mass index, systolic blood pressure, fasting glucose, and total cholesterol (Figure 3 and Tables S6 and S7). Income-adherence interaction did not reach

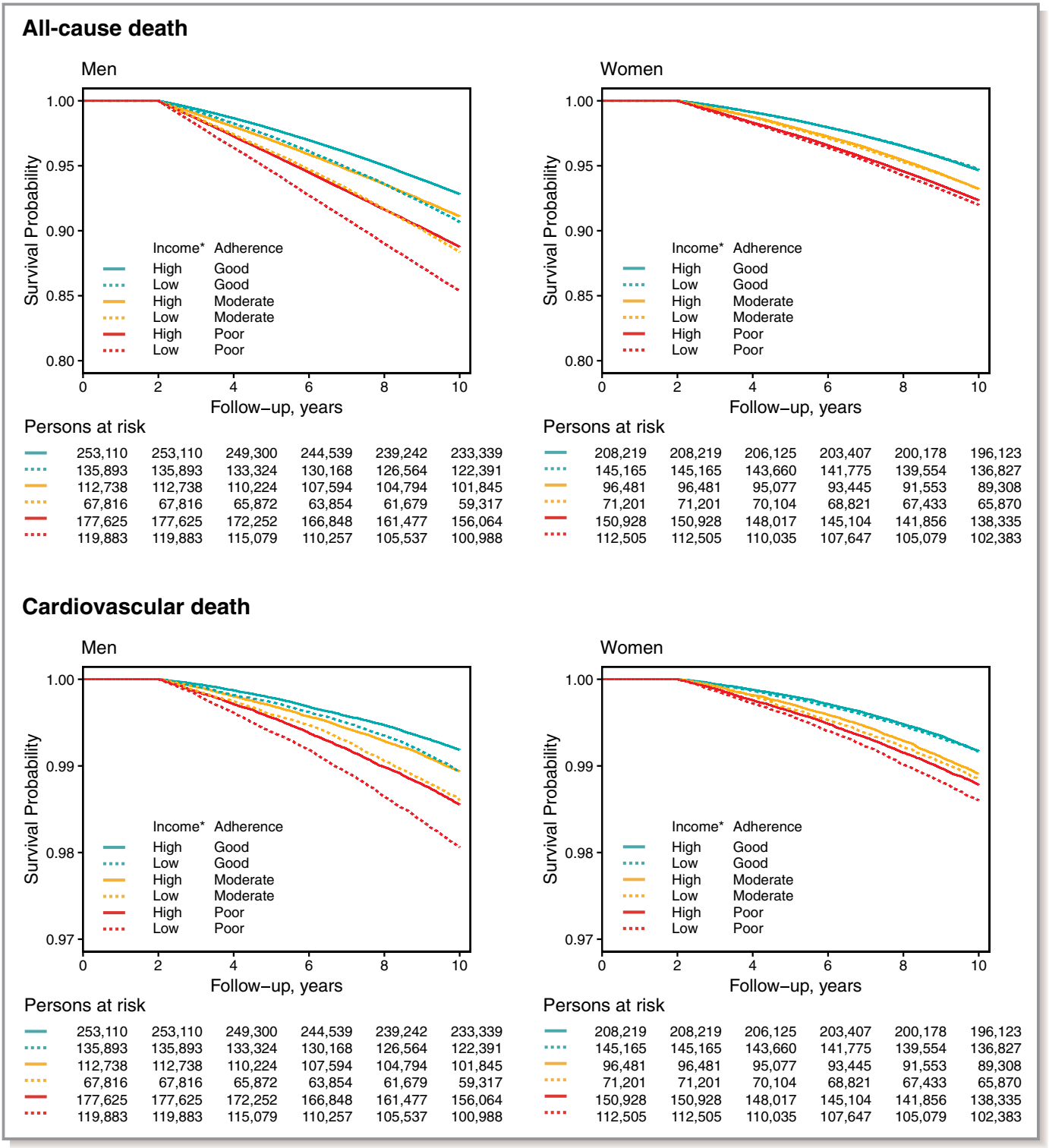


Figure 2. Kaplan-Meier curves for all-cause and cardiovascular death stratified by income and adherence in men and women. *Income was dichotomized into high (upper 50%) and low (lower 50%).

statistical significance in this analysis. A fraction of these participants underwent a repeated examination within 2 to 4 years after index date (median 2.8 years, N=466 103). On follow-up, individuals with poor medication adherence had smaller blood pressure reduction than those with good adherence (Figure S7). This trend was comparable across all income groups and after adjustment for baseline systolic blood pressure and other risk factors.

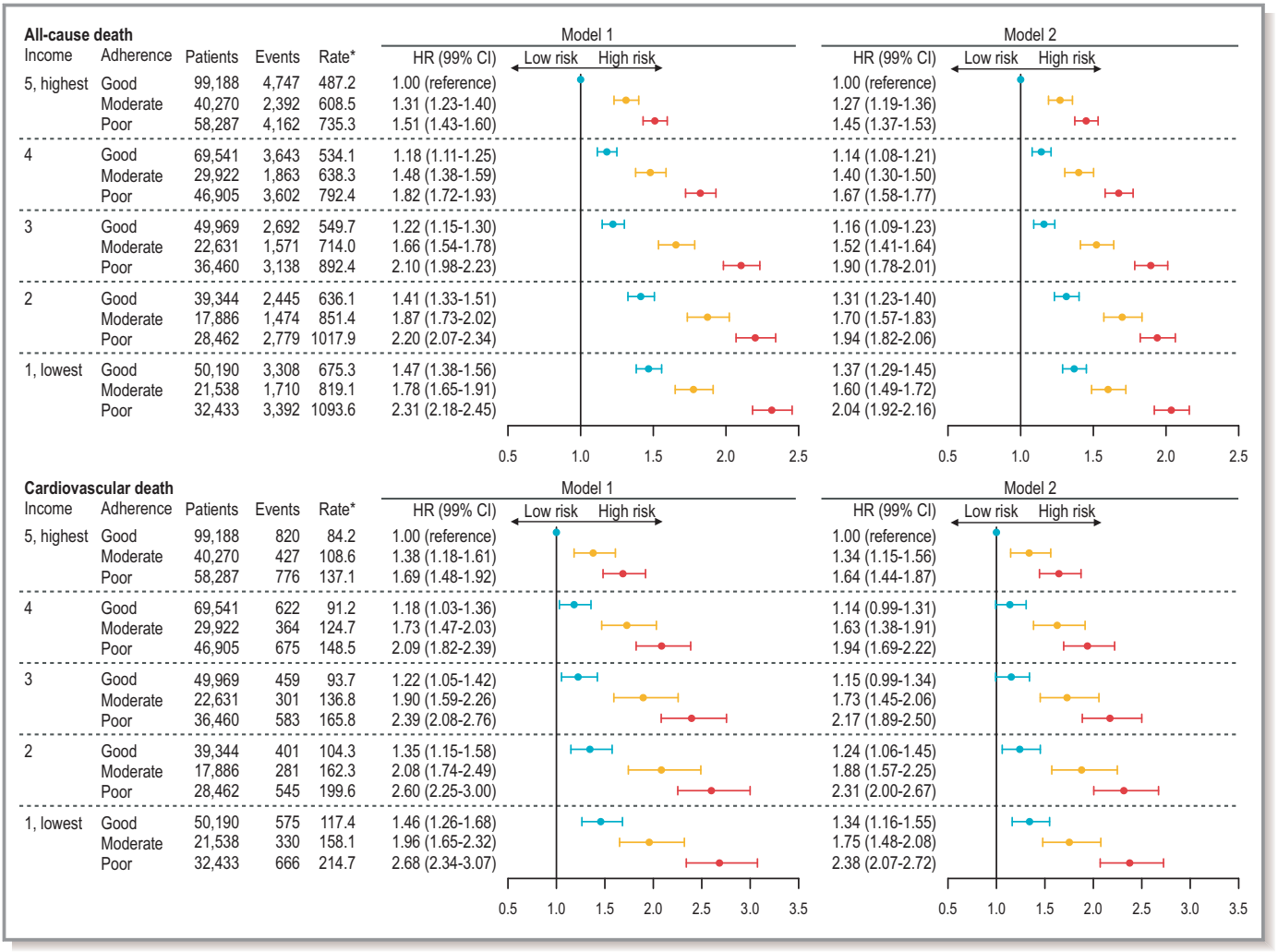


Figure 3. Combined effect of income and adherence on all-cause and cardiovascular death in health examinees. Multivariate Cox regression with model 1 adjusted for age, sex, employment status, Charlson Comorbidity Index, use of glucose-lowering drugs, use of lipid-lowering drugs, and antihypertensive drug class; model 2 further adjusted for cigarette smoking, alcohol consumption, physical exercise, body mass index, systolic blood pressure, fasting glucose, and total cholesterol. *P* for interaction between income and adherence in model 1 and model 2 was 0.173 and 0.385 for all-cause death and 0.144 and 0.192 for cardiovascular death, respectively. HR indicates hazard ratio. *Per 100 000 person-years.

Discussion

In this nationwide study of newly treated hypertension, we found that low income and poor adherence to antihypertensive medication were associated with increased mortality, and the excess risk by poor adherence was greater in individuals with low socioeconomic status. People with lower household income were not only more likely to be nonadherent but were also at higher risk for death when they were not adherent to antihypertensive medication. From this excess risk from poor versus good medication adherence in our study, we project an absolute risk reduction over 500 per 100 000 person-years for an intervention that would promote medication adherence in the lowest income group, assuming causality between nonadherence and mortality. Of note, Koreans have a high rate of healthcare utilization due to universal health insurance coverage, as evident by the largest number of doctor visits per capita among Organisation for Economic Cooperation and Development countries,[20] and a high participation rate in the national general health screening program (eg, 77.7% in 2016).[21] Therefore, the finding of a significant differential income effect under such a highly accessible healthcare system is unexpected and noteworthy.

Socioeconomic status has long been implicated as a major risk factor for death and CVD.[22] Low-income countries as well as low-income subpopulations within developed countries have higher CVD prevalence and mortality rates.[23] However, there is limited evidence of which modifiable risk factor should be targeted for intervention in low-income patients with hypertension. Previous studies have reported that poor

medication adherence is associated with morbidity and mortality in individuals with hypertension.[6,7] Our findings suggest that low income and medication nonadherence are important risk factors for mortality and CVD among initiators of hypertension treatment, and the joint association of income and adherence appears to be even more potent than each risk factor individually. Because these measures are readily available from existing data, it may be possible to identify uniquely vulnerable patients for evidence-based interventions that seek to optimize pharmacologic therapy and to improve medication adherence.

Determinants of medication adherence may be multifactorial, including demographics, comorbidities, and socioeconomic status.[24] In our study good medication adherence was associated with older age, female sex, higher income, employed status, concurrent uses of glucose-lowering and lipid-lowering drugs, and single-pill combination antihypertensive therapy, although further study is needed because only a limited number of predictors could be assessed. Use of single-pill combinations may promote adherence and reduce cost simultaneously.[17,25] Optimal visit schedules or follow-up strategies to maximize adherence in low-income patients should be further studied, and policies should tackle socioeconomic barriers to healthcare access in patients with low income or other social deprivations.

There are several explanations how nonadherence-related adverse outcome could be affected by income gradient. Despite universal health insurance coverage in Korea, relative poverty and its implication in health disparity require attention.[26] In the KNHANES (Korean National Health and Nutrition Examination Survey), patients with low income were more likely to experience unmet healthcare needs and to have uncontrolled hypertension or comorbidities.[27,28] Limited access to healthcare services in a low-income population may lead to more masked or undocumented comorbidities.[29] Clinical severity and unhealthy lifestyle are also associated with low socioeconomic status and, in turn, with adverse outcome.[30] A high proportion of low-income patients in our study were prescribed 3 or more antihypertensive agents, reflecting greater likelihood of their having severe or uncontrolled hypertension. Furthermore, prevalence of other metabolic abnormalities may also be higher in low-income individuals.[31] In our additional analysis with adjustments for smoking, drinking, exercise, body mass index, systolic blood pressure, fasting glucose, and total cholesterol, the joint association of income and adherence with mortality was attenuated but still remained. Moreover, residual risk by low income in good medication adherers is still unexplained after full adjustments. Therefore, further study is needed on some other contributing factors. Notably, Koreans have higher sodium consumption (4.5 g/d) than global average or WHO recommendations, and sodium intake is even higher in individuals with low socioeconomic status or with other poor health behaviors.[32] Job strain is another important risk factor for higher prevalence and worse control of hypertension associated with low socioeconomic status.[33] Although we did not specify job types, we observed higher proportions of employed workers in lower income groups, where job strain may have contributed to difficult blood pressure control and worse cardiovascular outcome.

The reason for sex difference in poverty-related mortality in our study is not clear. Because overall mortality rate and cardiovascular risk are much lower in women, the impact of socioeconomic status may not be as conspicuous as in men. In our study, medication adherence was marginally higher, and the difference by income was smaller, in women than in men. This is in line with another study reporting higher health literacy in women and smaller gradient of health literacy by income in women compared with men.[34] Differences in social and occupational positions by sex may also provide some explanations. Fewer than 10% of women in our study were employed workers, and conversely, the vast majority of women were dependent family members who may have had less exposure to work-related risk factors and better access to healthcare services, compared with employed workers. Moreover, household income may have a weaker association with health-related behaviors in family dependents, whose individual economic status are not directly represented. Further study is needed to investigate these matters.

Our study has several strengths. We utilized a nationwide longitudinal database that covers the entire Korean population. Hence, we captured nearly all patients who started antihypertensive treatment, allowing a large sample size and long follow-up despite strict identification criteria. Because of this large inception cohort design, detailed stratified analyses by sociodemographic factors were also possible. Furthermore, main exposure variables were derived from objective data rather than from self-report. Especially, NHIS premium is levied according to comprehensive assessment of income and assets and is thus a reliable measure of household socioeconomic status. However, we acknowledge that our study also has some limitations. First, the NHIS cohort is based on secondary administrative data in which all medical information had been collected by healthcare professionals but not strictly controlled for research purposes. In this regard the operational definitions of hypertension and CVD may be prone to misdiagnoses and require further validations in future studies. Nonetheless, diagnosis of hypertension using claims has been well reviewed, and its agreement with medical records has been reported.[15,35] Generally accepted identification criteria include case exclusion for the previous $\geq$6 months and availability of data for $\geq$12 months following index date with $\geq$2 prescriptions.[15] We used similar standards

but a longer window period—24 months before and 24 months following index date—to allow stricter case definition and assessment of comorbidity. However, individuals with high blood pressure but with no records of healthcare utilization would not have been identified. Because people with low income have lower rates of awareness and treatment for hypertension,[2-4] excess risk for mortality with low income may have been underestimated in our study. Second, the household income quintile may not equate to an individual family member's income or a sex-specific or within-study income quintile. However, it is unlikely that this measurement error would distort the income-mortality association observed in our study. Third, we arbitrarily chose the first 2 years of treatment for calculating medication adherence. Although considering a longer period of time could provide a more inclusive measure of medication adherence, it may also be more prone to reverse causality or overestimation of adherence.[36] In a clinical setting, attainment of early treatment compliance is often challenging. An Italian population-based study reported almost 50% cumulative incidence of discontinuation of antihypertensive medication at 2 years after initiation.[37] Association of early discontinuation with cardiovascular events was also reported.[38] Therefore, early-treatment nonadherence would be a reasonable representation of high-risk behaviors associated with adverse outcome. Fourth, lifestyle and some risk factors were not universally available in our data. Thus, we performed additional analyses on a subgroup with health examination results and found similar results. However, information on sodium intake, education level, or a distinction between self- and unemployed individuals was not available. Therefore, some residual and unmeasured confounding may exist. Finally, our study was based on Korean adults under universal health insurance and should be interpreted with caution when applied to different populations or different healthcare systems.

In conclusion, both low household income and poor medication adherence are associated with higher risk for death and CVD hospitalization in individuals newly treated for hypertension, but those with low income are subject to greater increase of risk attributable to poor adherence. Therefore, monitoring adherence is crucial when treating hypertension in low-income patients, and policies should focus on promoting medication adherence in populations of low socioeconomic status.

Sources of Funding

This work was partially supported by a grant of the Korea Health Technology R&D Project through the KHIDI (Korea Health Industry Development Institute), funded by the Ministry of Health and Welfare, Republic of Korea (grant no. HI13C0715). Lee was supported by the Physician-Scientist Fellowship Program, Yonsei University College of Medicine, Seoul, Korea.

Author Contributions

Lee and Kim conceived and designed the study. Lee performed statistical analyses; Lee and Kim interpreted the findings. Lee drafted the manuscript. J. H. Park, Floyd, S. Park, and Kim made critical revision of the manuscript for key intellectual content. All authors approved the final manuscript. Kim is the guarantor of this work and, as such, had full access to the data and takes responsibility for their integrity and accuracy.

Disclosures

Dr Floyd has consulted for Shionogi Inc. The remaining authors have no disclosures to report.

References

1. Global Burden of Disease 2016 Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet*. 2017;390:1345–1422.
2. Chow CK, Teo KK, Rangarajan S, Islam S, Gupta R, Avezum A, Bahonar A, Chifamba J, Dagenais G, Diaz R, Kazmi K, Lanas F, Wei L, Lopez-Jaramillo P, Fanghong L, Ismail NH, Puoane T, Rosengren A, Szuba A, Temizhan A, Wielgosz A, Yusuf R, Yusufali A, McKee M, Liu L, Mony P, Yusuf S; PURE Study Investigators. Prevalence, awareness, treatment, and control of hypertension in rural and urban communities in high-, middle-, and low-income countries. *JAMA*. 2013;310:959–968.
3. Lloyd-Sherlock P, Beard J, Minicuci N, Ebrahim S, Chatterji S. Hypertension among older adults in low- and middle-income countries: prevalence, awareness and control. *Int J Epidemiol*. 2014;43:116–128.
4. Palafox B, McKee M, Balabanova D, AlHabib KF, Avezum AJ, Bahonar A, Ismail N, Chifamba J, Chow CK, Corsi DJ, Dagenais GR, Diaz R, Gupta R, Iqbal R, Kaur M, Khatib R, Kruger A, Kruger IM, Lanas F, Lopez-Jaramillo P, Minfan F, Mohan V, Mony PK, Oguz A, Palileo-Villanueva LM, Perel P, Poirier P, Rangarajan S, Rensheng L, Rosengren A, Soman B, Stuckler D, Subramanian SV, Teo K, Tsolekile LP, Wielgosz A, Yaguang P, Yeates K, Yongzhen M, Yusoff K, Yusuf R, Yusufali A, Zatonska K, Yusuf S. Wealth and cardiovascular health: a cross-sectional study of wealth-related inequalities in the awareness, treatment and control of hypertension in high-, middle- and low-income countries. *Int J Equity Health*. 2016;15:199.
5. Niessen LW, Mohan D, Akuoku JK, Mirelman AJ, Ahmed S, Koehlmoos TP, Trujillo A, Khan J, Peters DH. Tackling socioeconomic inequalities and non-communicable diseases in low-income and middle-income countries under the sustainable development agenda. *Lancet*. 2018;391:2036–2046.
6. Mazzaglia G, Ambrosioni E, Alacqua M, Filippi A, Sessa E, Immordino V, Borghi C, Brignoli O, Caputi AP, Cricelli C, Mantovani LG. Adherence to antihypertensive medications and cardiovascular morbidity among newly diagnosed hypertensive patients. *Circulation*. 2009;120:1598–1605.
7. Kim S, Shin DW, Yun JM, Hwang Y, Park SK, Ko YJ, Cho B. Medication adherence and the risk of cardiovascular mortality and hospitalization among patients with newly prescribed antihypertensive medications. *Hypertension*. 2016;67:506–512.
8. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med*. 2005;353:487–497.
9. Seong SC, Kim YY, Khang YH, Park JH, Kang HJ, Lee H, Do CH, Song JS, Bang JH, Ha S, Lee EJ, Shin SA. Data resource profile: the National Health Information Database of the National Health Insurance Service in South Korea. *Int J Epidemiol*. 2017;46:799–800.
10. Lee H, Park S, Kim HC. Temporal and geospatial trends of hypertension management in Korea: a nationwide study 2002–2016. *Korean Circ J*. 2019;49:e36.

11. Kim HC, Cho M-C. Korea hypertension fact sheet 2018. *Clin Hypertens*. 2018;24:1–4.
12. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, Saunders LD, Beck CA, Feasby TE, Ghali WA. Coding algorithms for defining comorbidities in *ICD-9-CM* and *ICD-10* administrative data. *Med Care*. 2005;43:1130–1139.
13. Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P, Januel JM, Sundararajan V. Updating and validating the Charlson Comorbidity Index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol*. 2011;173:676–682.
14. Hess LM, Raebel MA, Conner DA, Malone DC. Measurement of adherence in pharmacy administrative databases: a proposal for standard definitions and preferred measures. *Ann Pharmacother*. 2006;40:1280–1288.
15. Halpern MT, Khan ZM, Schmier JK, Burnier M, Caro JJ, Cramer J, Daley WL, Gurwitz J, Hollenberg NK. Recommendations for evaluating compliance and persistence with hypertension therapy using retrospective data. *Hypertension*. 2006;47:1039–1048.
16. Steiner JF, Prochazka AV. The assessment of refill compliance using pharmacy records: methods, validity, and applications. *J Clin Epidemiol*. 1997;50:105–116.
17. Wang TD, Chen YH, Huang CH, Chen WJ, Chen MF. Bidirectional adherence changes and associated factors in patients switched from free combinations to equivalent single-pill combinations of antihypertensive drugs. *Hypertension*. 2014;63:958–967.
18. Krousel-Wood M, Holt E, Joyce C, Ruiz R, Dornelles A, Webber LS, Morisky DE, Frohlich ED, Re RN, He J, Whelton PK, Muntner P. 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.
19. Seong SC, Kim YY, Park SK, Khang YH, Kim HC, Park JH, Kang HJ, Do CH, Song JS, Lee EJ, Ha S, Shin SA, Jeong SL. Cohort profile: the National Health Insurance Service-National Health Screening Cohort (NHIS-HEALS) in Korea. *BMJ Open*. 2017;7:e016640.
20. OECD. Doctors' consultations (indicator). 2018. Available at: https://doi.org/10.1787/173dcf26-en. Accessed September 13, 2018.
21. National Health Insurance Service. *2016 National Health Screening Statistical Yearbook*. Wonju: National Health Insurance Service; 2017.
22. Clark AM, DesMeules M, Luo W, Duncan AS, Wielgosz A. Socioeconomic status and cardiovascular disease: risks and implications for care. *Nat Rev Cardiol*. 2009;6:712–722.
23. Modesti PA, Agostoni P, Agyemang C, Basu S, Benetos A, Cappuccio FP, Ceriello A, Del Prato S, Kalyesubula R, O'Brien E, Kilama MO, Perlini S, Picano E, Reboldi G, Remuzzi G, Stuckler D, Twagirumukiza M, Van Bortel LM, Watfa G, Zhao D, Parati G; European Society of Hypertension Working Group on Hypertension and Cardiovascular Risk in Low Resource Settings. Cardiovascular risk assessment in low-resource settings: a consensus document of the European Society of Hypertension Working Group on Hypertension and Cardiovascular Risk in Low Resource Settings. *J Hypertens*. 2014;32:951–960.
24. Ho PM, Bryson CL, Rumsfeld JS. Medication adherence: its importance in cardiovascular outcomes. *Circulation*. 2009;119:3028–3035.
25. Sherrill B, Halpern M, Khan S, Zhang J, Panjabi S. Single-pill vs free-equivalent combination therapies for hypertension: a meta-analysis of health care costs and adherence. *J Clin Hypertens (Greenwich)*. 2011;13:898–909.
26. Khang YH, Lee SI. Health inequalities policy in Korea: current status and future challenges. *J Korean Med Sci*. 2012;27(suppl):S33–S40.
27. Kim S, Lee B, Park M, Oh S, Chin HJ, Koo H. Prevalence of chronic disease and its controlled status according to income level. *Medicine (Baltimore)*. 2016;95:e5286.
28. Hwang J. Understanding reasons for unmet health care needs in Korea: what are health policy implications? *BMC Health Serv Res*. 2018;18:557.
29. Devaux M. Income-related inequalities and inequities in health care services utilisation in 18 selected OECD countries. *Eur J Health Econ*. 2015;16:21–33.
30. Bowry AD, Lewey J, Dugani SB, Choudhry NK. The burden of cardiovascular disease in low- and middle-income countries: epidemiology and management. *Can J Cardiol*. 2015;31:1151–1159.
31. Huh JH, Kang DR, Jang JY, Shin JH, Kim JY, Choi S, Cho EJ, Park JS, Sohn IS, Jo SH, Sung KC, Koh KK. Metabolic syndrome epidemic among Korean adults: Korean survey of cardiometabolic syndrome (2018). *Atherosclerosis*. 2018;277:47–52.
32. Hong JW, Noh JH, Kim DJ. Factors associated with high sodium intake based on estimated 24-hour urinary sodium excretion: the 2009–2011 Korea National Health and Nutrition Examination Survey. *Medicine (Baltimore)*. 2016;95:e2864.
33. Grotto I, Huerta M, Sharabi Y. Hypertension and socioeconomic status. *Curr Opin Cardiol*. 2008;23:335–339.
34. Lee HY, Lee J, Kim NK. Gender differences in health literacy among Korean adults: do women have a higher level of health literacy than men? *Am J Mens Health*. 2015;9:370–379.
35. Bullano MF, Kamat S, Willey VJ, Barlas S, Watson DJ, Brenneman SK. Agreement between administrative claims and the medical record in identifying patients with a diagnosis of hypertension. *Med Care*. 2006;44:486–490.
36. Andrade SE, Kahler KH, Frech F, Chan KA. Methods for evaluation of medication adherence and persistence using automated databases. *Pharmacoepidemiol Drug Saf*. 2006;15:565–574.
37. Corrao G, Zambon A, Parodi A, Poluzzi E, Baldi I, Merlino L, Cesana G, Mancia G. Discontinuation of and changes in drug therapy for hypertension among newly-treated patients: a population-based study in Italy. *J Hypertens*. 2008;26:819–824.
38. Corrao G, Zambon A, Parodi A, Merlino L, Mancia G. Incidence of cardiovascular events in Italian patients with early discontinuations of antihypertensive, lipid-lowering, and antidiabetic treatments. *Am J Hypertens*. 2012;25:549–555.

Supplemental Material

Table S1. Index drug codes.

Drug class	ATC code*
Diuretics	C03A, C03B, C03C, C03D, C03E
Beta-blockers	C07
Calcium channel blockers	C08
ACE inhibitors	C09A, C09B
Angiotensin II receptor blockers	C09C, C09D
Others	C02A, C02C, C02D, C02L

*Including subcodes.
ACE, angiotensin-converting-enzyme; ATC, Anatomical Therapeutic Chemical classification.

Table S2. Hospital diagnosis codes.

Diagnosis	ICD-10 code*
Primary hypertension	I10 and antihypertensive medication
Any hypertensive disease (for exclusion)	I10-I13, I15 or antihypertensive medication
Myocardial infarction	I21-I23
Heart failure	I50
Stroke	I60-I64
Cardiovascular death	I00-I99

*Including subcodes.
ICD-10, International Classification of Disease, 10th edition.

Table S3. Baseline characteristics by medication adherence.

Variables	Medication adherence		
	Good (N=742,387)	Moderate (N=348,236)	Poor (N=560,941)
Age, yr	55 [47-63]	53 [46-63]	52 [44-62]
Sex			
Female	353,384 (47.6%)	167,682 (48.2%)	263,433 (47.0%)
Male	389,003 (52.4%)	180,554 (51.8%)	297,508 (53.0%)
Household income, quintile			
5, highest	225,169 (30.3%)	97,682 (28.1%)	147,758 (26.3%)
4	167,883 (22.6%)	78,119 (22.4%)	125,432 (22.4%)
3	128,731 (17.3%)	63,202 (18.1%)	105,541 (18.8%)
2	101,928 (13.7%)	51,511 (14.8%)	87,174 (15.5%)
1, lowest	118,676 (16.0%)	57,722 (16.6%)	95,036 (16.9%)
Employment status			
Employed workers	178,942 (24.1%)	77,744 (22.3%)	119,293 (21.3%)
Self- or non-employed	563,445 (75.9%)	270,492 (77.7%)	441,648 (78.7%)
Initial antihypertensive agent*			
Diuretics	201,016 (27.1%)	96,758 (27.8%)	161,013 (28.7%)
Beta-blockers	152,823 (20.6%)	75,183 (21.6%)	136,563 (24.3%)
Calcium channel blockers	459,464 (61.9%)	205,924 (59.1%)	296,823 (52.9%)
ACE inhibitors	95,696 (12.9%)	46,386 (13.3%)	67,046 (12.0%)
ARBs	173,857 (23.4%)	74,762 (21.5%)	100,376 (17.9%)
Others	3,104 (0.4%)	2,093 (0.6%)	6,467 (1.2%)
Number of drug classes			
1	465,491 (62.7%)	224,131 (64.4%)	389,497 (69.4%)
2	217,481 (29.3%)	98,464 (28.3%)	139,433 (24.9%)
≥3	59,415 (8.0%)	25,641 (7.4%)	32,011 (5.7%)
Use of glucose-lowering drugs	130,753 (17.6%)	67,687 (19.4%)	88,513 (15.8%)
Use of lipid-lowering drugs	97,451 (13.1%)	43,893 (12.6%)	66,174 (11.8%)
Charlson Comorbidity Index			
0	394,445 (53.1%)	175,640 (50.4%)	265,687 (47.4%)
1	139,405 (18.8%)	67,814 (19.5%)	107,993 (19.3%)
2	119,432 (16.1%)	57,726 (16.6%)	100,925 (18.0%)
≥3	89,105 (12.0%)	47,056 (13.5%)	86,336 (15.4%)
Medication possession ratio	0.95 [0.89-1.00]	0.67 [0.59-0.74]	0.16 [0.06-0.33]

*Counted with duplicates for combination therapy.
Data are presented as median [interquartile range] or frequency (percent). ACE, angiotensin-converting-enzyme; ARB, angiotensin II receptor blocker.

Table S4. Hospitalizations for ASCVD and heart failure according to household income and medication adherence.

Variables	Persons	ASCVD (MI and/or stroke)				Heart failure			
		Events	Rate*	HR (99% CI)		Events	Rate*	HR (99% CI)	
				Model 1	Model 2			Model 1	Model 2
Total	1,651,564	78,701	501.0			8,736	54.8		
Income, quintile									
5, highest	470,609	20,760	461.7	1.00 (reference)	1.00 (reference)	2,335	51.2	1.00 (reference)	1.00 (reference)
4	371,434	17,152	484.1	1.11 (1.08-1.14)	1.09 (1.07-1.12)	1,871	52.1	1.15 (1.06-1.25)	1.14 (1.05-1.23)
3	297,474	14,184	501.3	1.21 (1.17-1.24)	1.17 (1.14-1.20)	1,483	51.7	1.25 (1.15-1.36)	1.22 (1.12-1.33)
2	240,613	12,158	533.3	1.30 (1.26-1.34)	1.25 (1.21-1.28)	1,331	57.5	1.40 (1.28-1.53)	1.35 (1.24-1.48)
1, lowest	271,434	14,447	564.5	1.36 (1.32-1.40)	1.30 (1.26-1.33)	1,716	66.0	1.48 (1.36-1.61)	1.43 (1.32-1.56)
Adherence									
Good	742,387	28,519	399.2	1.00 (reference)	1.00 (reference)	3,171	43.9	1.00 (reference)	1.00 (reference)
Moderate	348,236	17,158	518.6	1.37 (1.33-1.40)	1.35 (1.32-1.39)	1,944	57.9	1.38 (1.28-1.49)	1.35 (1.25-1.46)
Poor	560,941	33,024	628.4	1.71 (1.67-1.74)	1.75 (1.71-1.79)	3,621	67.7	1.66 (1.56-1.77)	1.67 (1.57-1.78)
Men	867,065	46,456	568.9			3,767	45.4		
Income, quintile									
5, highest	257,900	12,030	490.6	1.00 (reference)	1.00 (reference)	972	39.1	1.00 (reference)	1.00 (reference)
4	200,773	10,281	541.5	1.14 (1.10-1.18)	1.11 (1.08-1.15)	816	42.3	1.15 (1.02-1.30)	1.13 (1.00-1.28)
3	159,625	8,710	579.5	1.25 (1.20-1.29)	1.20 (1.16-1.25)	687	44.9	1.30 (1.14-1.47)	1.26 (1.10-1.43)
2	122,993	7,398	644.4	1.37 (1.32-1.42)	1.30 (1.26-1.36)	589	50.3	1.45 (1.26-1.66)	1.39 (1.21-1.59)
1, lowest	125,774	8,037	689.9	1.43 (1.38-1.49)	1.35 (1.30-1.41)	703	59.1	1.63 (1.43-1.85)	1.56 (1.37-1.77)
Adherence									
Good	389,003	16,776	451.3	1.00 (reference)	1.00 (reference)	1,327	35.2	1.00 (reference)	1.00 (reference)
Moderate	180,554	9,863	580.2	1.36 (1.32-1.41)	1.34 (1.30-1.39)	800	46.3	1.42 (1.27-1.60)	1.39 (1.24-1.56)
Poor	297,508	19,817	720.7	1.73 (1.68-1.77)	1.77 (1.72-1.81)	1,640	58.4	1.82 (1.65-2.00)	1.83 (1.66-2.01)
Women	784,499	32,245	427.6			4,969	65.1		
Income, quintile									
5, highest	212,709	8,730	427.0	1.00 (reference)	1.00 (reference)	1,363	65.9	1.00 (reference)	1.00 (reference)
4	170,661	6,871	417.9	1.09 (1.05-1.14)	1.08 (1.03-1.12)	1,055	63.4	1.16 (1.05-1.29)	1.15 (1.03-1.28)
3	137,849	5,474	412.7	1.17 (1.12-1.22)	1.14 (1.09-1.19)	796	59.3	1.22 (1.09-1.37)	1.20 (1.07-1.34)
2	117,620	4,760	420.6	1.23 (1.17-1.29)	1.18 (1.13-1.24)	742	64.8	1.37 (1.22-1.54)	1.33 (1.18-1.50)
1, lowest	145,660	6,410	459.7	1.31 (1.25-1.37)	1.26 (1.20-1.31)	1,013	71.7	1.41 (1.27-1.58)	1.37 (1.23-1.53)
Adherence									
Good	353,384	11,743	342.7	1.00 (reference)	1.00 (reference)	1,844	53.3	1.00 (reference)	1.00 (reference)
Moderate	167,682	7,295	453.4	1.36 (1.31-1.41)	1.35 (1.30-1.40)	1,144	70.2	1.33 (1.21-1.47)	1.31 (1.19-1.44)
Poor	263,433	13,207	527.2	1.66 (1.60-1.71)	1.70 (1.65-1.76)	1,981	77.9	1.54 (1.42-1.68)	1.54 (1.41-1.67)

Model 1 was adjusted for age, sex, and employment status.
Model 2 was further adjusted for household income, Charlson Comorbidity Index, use of glucose-lowering drugs, use of lipid-lowering drugs, antihypertensive drug class, and medication adherence.
*Rate per 100,000 person-years. ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; HR, hazard ratio; MI, myocardial infarction.

Table S5. Hospitalizations for myocardial infarction and stroke according to household income and medication adherence.

Variables	Persons	Myocardial infarction				Stroke			
		Events	Rate*	HR (99% CI)		Events	Rate*	HR (99% CI)	
				Model 1	Model 2			Model 1	Model 2
Total	1,651,564	15,811	99.4			64,098	406.8		
Income, quintile									
5, highest	470,609	4,260	93.7	1.00 (reference)	1.00 (reference)	16,810	372.8	1.00 (reference)	1.00 (reference)
4	371,434	3,494	97.4	1.09 (1.03-1.16)	1.09 (1.02-1.15)	13,911	391.5	1.12 (1.09-1.15)	1.10 (1.06-1.13)
3	297,474	2,935	102.4	1.19 (1.11-1.26)	1.17 (1.10-1.24)	11,479	404.5	1.22 (1.18-1.25)	1.17 (1.14-1.21)
2	240,613	2,394	103.6	1.22 (1.14-1.30)	1.19 (1.12-1.27)	9,942	434.8	1.32 (1.28-1.37)	1.26 (1.22-1.30)
1, lowest	271,434	2,728	105.1	1.24 (1.16-1.32)	1.20 (1.13-1.28)	11,956	465.7	1.40 (1.35-1.44)	1.32 (1.28-1.37)
Adherence									
Good	742,387	6,363	88.2	1.00 (reference)	1.00 (reference)	22,583	315.2	1.00 (reference)	1.00 (reference)
Moderate	348,236	3,528	105.3	1.25 (1.19-1.32)	1.24 (1.17-1.31)	13,880	418.2	1.39 (1.35-1.43)	1.38 (1.34-1.42)
Poor	560,941	5,920	110.8	1.35 (1.29-1.41)	1.39 (1.33-1.46)	27,635	524.2	1.80 (1.76-1.84)	1.84 (1.80-1.89)
Men	867,065	11,171	134.9			36,092	440.1		
Income, quintile									
5, highest	257,900	3,055	123.2	1.00 (reference)	1.00 (reference)	9,191	373.4	1.00 (reference)	1.00 (reference)
4	200,773	2,478	128.8	1.07 (0.99-1.14)	1.06 (0.99-1.14)	7,967	417.9	1.15 (1.11-1.20)	1.13 (1.08-1.17)
3	159,625	2,124	139.4	1.17 (1.08-1.25)	1.15 (1.07-1.24)	6,749	447.1	1.27 (1.22-1.33)	1.22 (1.17-1.27)
2	122,993	1,675	143.6	1.19 (1.10-1.29)	1.17 (1.08-1.26)	5,835	506.0	1.43 (1.37-1.49)	1.35 (1.29-1.41)
1, lowest	125,774	1,839	155.3	1.26 (1.17-1.36)	1.23 (1.14-1.33)	6,350	542.4	1.50 (1.43-1.56)	1.40 (1.34-1.46)
Adherence									
Good	389,003	4,545	121.0	1.00 (reference)	1.00 (reference)	12,500	335.0	1.00 (reference)	1.00 (reference)
Moderate	180,554	2,446	141.9	1.22 (1.14-1.30)	1.20 (1.13-1.28)	7,596	444.9	1.41 (1.36-1.47)	1.39 (1.34-1.45)
Poor	297,508	4,180	149.3	1.31 (1.24-1.38)	1.34 (1.27-1.42)	15,996	579.1	1.87 (1.82-1.93)	1.91 (1.85-1.97)
Women	784,499	4,640	60.8			28,006	370.8		
Income, quintile									
5, highest	212,709	1,205	58.3	1.00 (reference)	1.00 (reference)	7,619	372.0	1.00 (reference)	1.00 (reference)
4	170,661	1,016	61.1	1.19 (1.07-1.33)	1.18 (1.06-1.32)	5,944	360.9	1.08 (1.03-1.13)	1.06 (1.02-1.11)
3	137,849	811	60.5	1.28 (1.14-1.45)	1.26 (1.12-1.42)	4,730	356.0	1.15 (1.10-1.21)	1.12 (1.07-1.18)
2	117,620	719	62.8	1.38 (1.22-1.56)	1.34 (1.19-1.52)	4,107	362.3	1.21 (1.15-1.27)	1.16 (1.11-1.22)
1, lowest	145,660	889	63.0	1.33 (1.19-1.49)	1.30 (1.16-1.46)	5,606	401.3	1.31 (1.25-1.37)	1.25 (1.20-1.31)
Adherence									
Good	353,384	1,818	52.6	1.00 (reference)	1.00 (reference)	10,083	293.8	1.00 (reference)	1.00 (reference)
Moderate	167,682	1,082	66.4	1.29 (1.17-1.43)	1.28 (1.16-1.42)	6,284	389.9	1.36 (1.30-1.42)	1.35 (1.29-1.41)
Poor	263,433	1,740	68.4	1.40 (1.28-1.52)	1.45 (1.33-1.58)	11,639	463.7	1.70 (1.64-1.76)	1.74 (1.68-1.80)

Model 1 was adjusted for age, sex, and employment status.
Model 2 was further adjusted for household income, Charlson Comorbidity Index, use of glucose-lowering drugs, use of lipid-lowering drugs, antihypertensive drug class, and medication adherence.
*Rate per 100,000 person-years. CI, confidence interval; HR, hazard ratio.

Table S6. All-cause and cardiovascular death according to household income and medication adherence in health examinees.

Variables		Persons	All-cause death				Cardiovascular death			
			Events	Rate*	HR (99% CI)		Events	Rate*	HR (99% CI)	
					Model 1	Model 2			Model 1	Model 2
Total		643,026	42,918	685.3			7,825	124.9		
Income, quintile										
5, highest		197,745	11,301	584.5	1.00 (reference)	1.00 (reference)	2,023	104.6	1.00 (reference)	1.00 (reference)
4		146,368	9,108	637.6	1.18 (1.14-1.22)	1.14 (1.10-1.18)	1,661	116.3	1.22 (1.12-1.33)	1.17 (1.07-1.27)
3		109,060	7,401	697.3	1.30 (1.25-1.35)	1.23 (1.18-1.27)	1,343	126.5	1.33 (1.22-1.46)	1.25 (1.14-1.37)
2		85,692	6,698	806.5	1.43 (1.38-1.49)	1.33 (1.27-1.38)	1,227	147.7	1.46 (1.33-1.60)	1.34 (1.22-1.48)
1, lowest		104,161	8,410	833.6	1.47 (1.41-1.52)	1.36 (1.31-1.41)	1,571	155.7	1.50 (1.37-1.64)	1.37 (1.26-1.50)
Adherence										
Good		308,232	16,835	557.4	1.00 (reference)	1.00 (reference)	2,877	95.2	1.00 (reference)	1.00 (reference)
Moderate		132,247	9,010	700.1	1.29 (1.24-1.33)	1.25 (1.21-1.29)	1,703	132.3	1.44 (1.33-1.56)	1.40 (1.30-1.52)
Poor		202,547	17,073	873.1	1.57 (1.53-1.62)	1.50 (1.45-1.54)	3,245	165.9	1.81 (1.70-1.94)	1.75 (1.64-1.88)
Income and Adherence										
5, highest	Good	99,188	4,747	487.2	1.00 (reference)	1.00 (reference)	820	84.2	1.00 (reference)	1.00 (reference)
	Moderate	40,270	2,392	608.5	1.31 (1.23-1.40)	1.27 (1.19-1.36)	427	108.6	1.38 (1.18-1.61)	1.34 (1.15-1.56)
	Poor	58,287	4,162	735.3	1.51 (1.43-1.60)	1.45 (1.37-1.53)	776	137.1	1.69 (1.48-1.92)	1.64 (1.44-1.87)
4	Good	69,541	3,643	534.1	1.18 (1.11-1.25)	1.14 (1.08-1.21)	622	91.2	1.18 (1.03-1.36)	1.14 (0.99-1.31)
	Moderate	29,922	1,863	638.3	1.48 (1.38-1.59)	1.40 (1.30-1.50)	364	124.7	1.73 (1.47-2.03)	1.63 (1.38-1.91)
	Poor	46,905	3,602	792.4	1.82 (1.72-1.93)	1.67 (1.58-1.77)	675	148.5	2.09 (1.82-2.39)	1.94 (1.69-2.22)
3	Good	49,969	2,692	549.7	1.22 (1.15-1.30)	1.16 (1.09-1.23)	459	93.7	1.22 (1.05-1.42)	1.15 (0.99-1.34)
	Moderate	22,631	1,571	714.0	1.66 (1.54-1.78)	1.52 (1.41-1.64)	301	136.8	1.90 (1.59-2.26)	1.73 (1.45-2.06)
	Poor	36,460	3,138	892.4	2.10 (1.98-2.23)	1.90 (1.78-2.01)	583	165.8	2.39 (2.08-2.76)	2.17 (1.89-2.50)
2	Good	39,344	2,445	636.1	1.41 (1.33-1.51)	1.31 (1.23-1.40)	401	104.3	1.35 (1.15-1.58)	1.24 (1.06-1.45)
	Moderate	17,886	1,474	851.4	1.87 (1.73-2.02)	1.70 (1.57-1.83)	281	162.3	2.08 (1.74-2.49)	1.88 (1.57-2.25)
	Poor	28,462	2,779	1017.9	2.20 (2.07-2.34)	1.94 (1.82-2.06)	545	199.6	2.60 (2.25-3.00)	2.31 (2.00-2.67)
1, lowest	Good	50,190	3,308	675.3	1.47 (1.38-1.56)	1.37 (1.29-1.45)	575	117.4	1.46 (1.26-1.68)	1.34 (1.16-1.55)
	Moderate	21,538	1,710	819.1	1.78 (1.65-1.91)	1.60 (1.49-1.72)	330	158.1	1.96 (1.65-2.32)	1.75 (1.48-2.08)
	Poor	32,433	3,392	1093.6	2.31 (2.18-2.45)	2.04 (1.92-2.16)	666	214.7	2.68 (2.34-3.07)	2.38 (2.07-2.72)

Model 1 was adjusted for age, sex, employment status, household income, Charlson Comorbidity Index, use of glucose-lowering drugs, use of lipid-lowering drugs, antihypertensive drug class, and medication adherence.
Model 2 was further adjusted for cigarette smoking, alcohol consumption, physical exercise, body mass index, systolic blood pressure, fasting glucose, and total cholesterol.
*Rate per 100,000 person-years. CI, confidence interval; HR, hazard ratio.

Table S7. Hospitalizations for ASCVD and heart failure according to household income and medication adherence in health examinees.

Variables		Persons	ASCVD (MI and/or stroke)				Heart failure			
			Events	Rate*	HR (99% CI)		Events	Rate*	HR (99% CI)	
					Model 1	Model 2			Model 1	Model 2
Total		643,026	26,934	436.1			2,696	43.1		
Income, quintile										
5, highest		197,745	7,604	398.4	1.00 (reference)	1.00 (reference)	702	36.3	1.00 (reference)	1.00 (reference)
4		146,368	5,922	420.2	1.10 (1.05-1.15)	1.06 (1.02-1.11)	541	37.9	1.14 (0.98-1.32)	1.11 (0.96-1.29)
3		109,060	4,651	444.5	1.15 (1.10-1.21)	1.10 (1.05-1.15)	503	47.4	1.44 (1.24-1.67)	1.39 (1.20-1.62)
2		85,692	3,916	478.7	1.21 (1.15-1.27)	1.14 (1.08-1.20)	412	49.7	1.40 (1.20-1.65)	1.35 (1.15-1.59)
1, lowest		104,161	4,841	487.4	1.22 (1.16-1.28)	1.15 (1.09-1.20)	538	53.4	1.46 (1.26-1.71)	1.41 (1.21-1.64)
Adherence										
Good		308,232	10,675	357.5	1.00 (reference)	1.00 (reference)	1,014	33.6	1.00 (reference)	1.00 (reference)
Moderate		132,247	5,792	456.8	1.33 (1.27-1.38)	1.31 (1.25-1.37)	602	46.8	1.40 (1.22-1.60)	1.37 (1.20-1.57)
Poor		202,547	10,467	544.7	1.64 (1.58-1.70)	1.63 (1.57-1.69)	1,080	55.3	1.65 (1.47-1.85)	1.59 (1.42-1.79)
Income and Adherence										
5, highest	Good	99,188	3,214	333.4	1.00 (reference)	1.00 (reference)	295	30.3	1.00 (reference)	1.00 (reference)
	Moderate	40,270	1,621	418.0	1.32 (1.22-1.43)	1.30 (1.20-1.41)	149	37.9	1.29 (1.00-1.68)	1.27 (0.98-1.64)
	Poor	58,287	2,769	497.2	1.59 (1.49-1.70)	1.59 (1.49-1.71)	258	45.6	1.50 (1.20-1.87)	1.44 (1.16-1.80)
4	Good	69,541	2,362	350.2	1.09 (1.02-1.17)	1.06 (0.99-1.14)	198	29.1	1.04 (0.82-1.31)	1.01 (0.80-1.29)
	Moderate	29,922	1,240	430.9	1.42 (1.30-1.55)	1.36 (1.25-1.48)	119	40.8	1.51 (1.14-1.99)	1.45 (1.09-1.92)
	Poor	46,905	2,320	518.9	1.79 (1.66-1.92)	1.72 (1.61-1.85)	224	49.3	1.85 (1.47-2.33)	1.74 (1.38-2.19)
3	Good	49,969	1,720	355.2	1.10 (1.02-1.19)	1.06 (0.98-1.14)	181	37.0	1.33 (1.04-1.70)	1.29 (1.01-1.65)
	Moderate	22,631	1,006	464.2	1.52 (1.38-1.67)	1.43 (1.30-1.57)	121	55.1	2.05 (1.55-2.70)	1.95 (1.47-2.57)
	Poor	36,460	1,925	557.2	1.93 (1.79-2.08)	1.83 (1.70-1.97)	201	57.2	2.21 (1.74-2.80)	2.06 (1.62-2.61)
2	Good	39,344	1,465	385.8	1.20 (1.11-1.30)	1.14 (1.05-1.23)	156	40.6	1.44 (1.11-1.85)	1.38 (1.07-1.79)
	Moderate	17,886	872	512.0	1.61 (1.46-1.77)	1.50 (1.36-1.65)	82	47.4	1.61 (1.17-2.22)	1.52 (1.10-2.10)
	Poor	28,462	1,579	589.1	1.93 (1.79-2.09)	1.82 (1.68-1.97)	174	63.8	2.21 (1.73-2.84)	2.05 (1.60-2.63)
1, lowest	Good	50,190	1,914	395.7	1.21 (1.12-1.31)	1.14 (1.06-1.23)	184	37.6	1.28 (1.00-1.64)	1.23 (0.96-1.57)
	Moderate	21,538	1,053	512.6	1.59 (1.45-1.75)	1.48 (1.35-1.62)	131	62.9	2.07 (1.57-2.71)	1.95 (1.48-2.56)
	Poor	32,433	1,874	616.4	1.98 (1.83-2.13)	1.85 (1.72-2.00)	223	72.0	2.36 (1.87-2.98)	2.19 (1.74-2.77)

Model 1 was adjusted for age, sex, employment status, household income, Charlson Comorbidity Index, use of glucose-lowering drugs, use of lipid-lowering drugs, antihypertensive drug class, and medication adherence.
Model 2 was further adjusted for cigarette smoking, alcohol consumption, physical exercise, body mass index, systolic blood pressure, fasting glucose, and total cholesterol.
*Rate per 100,000 person-years. ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; HR, hazard ratio; MI, myocardial infarction.

Figure S1. Flowchart of inclusion and exclusion criteria.

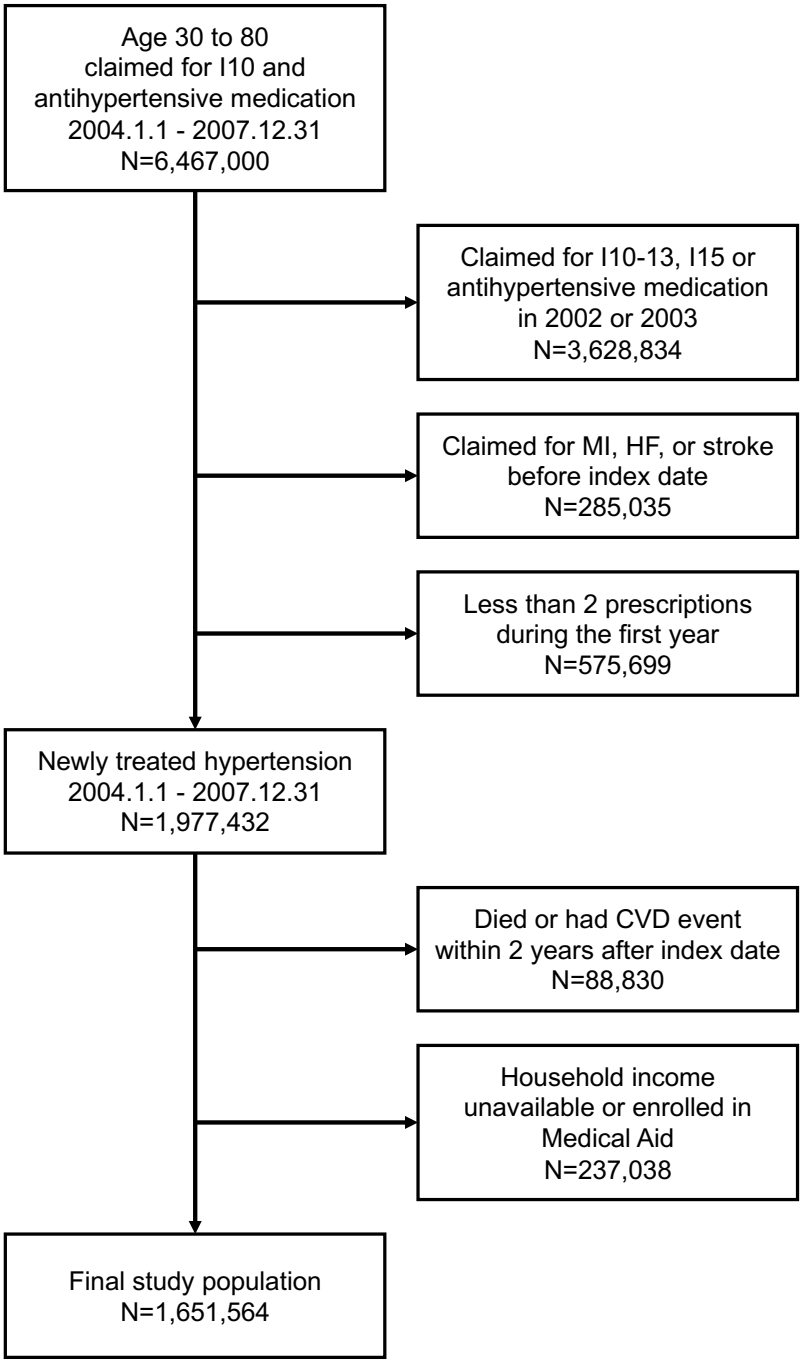
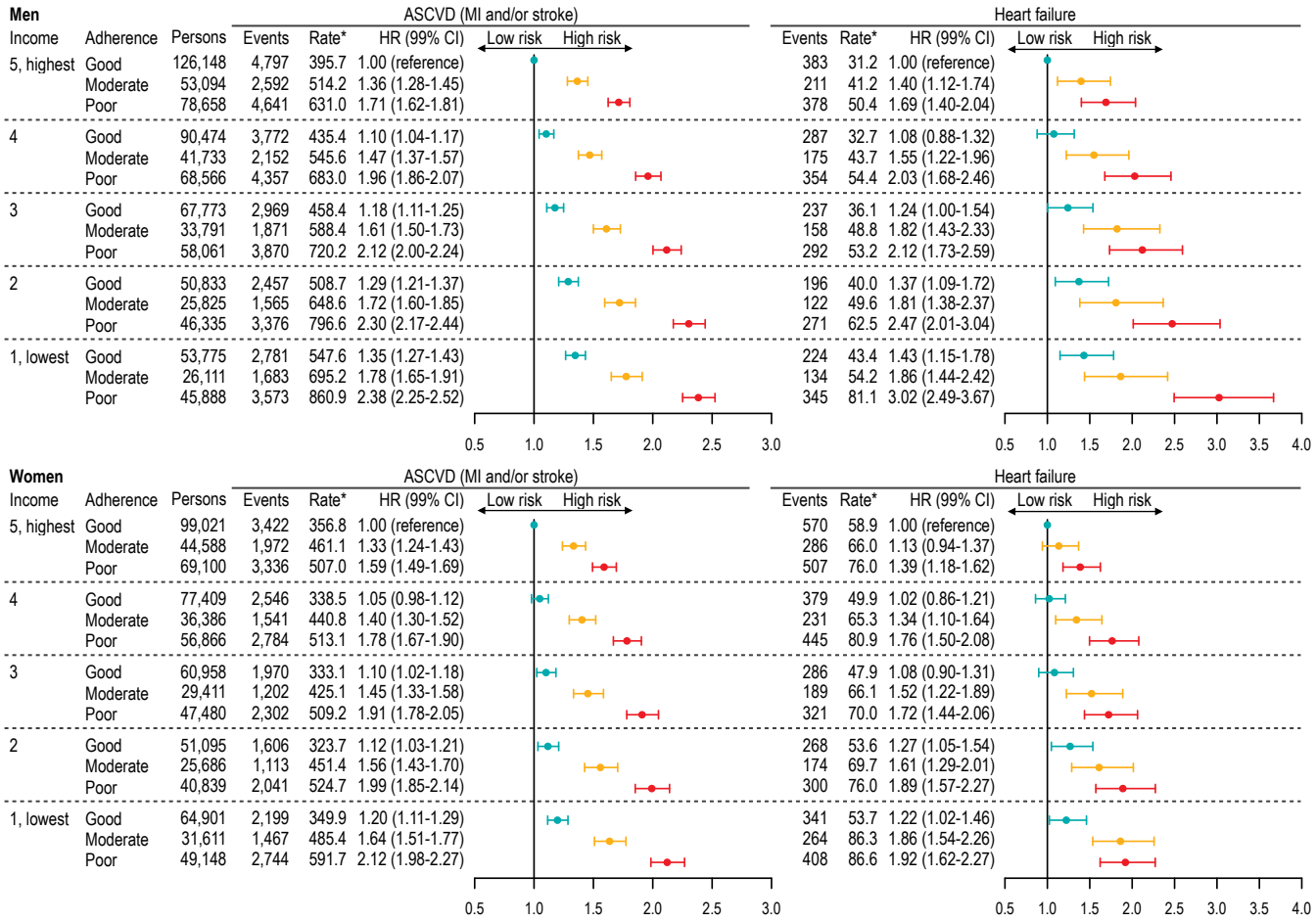
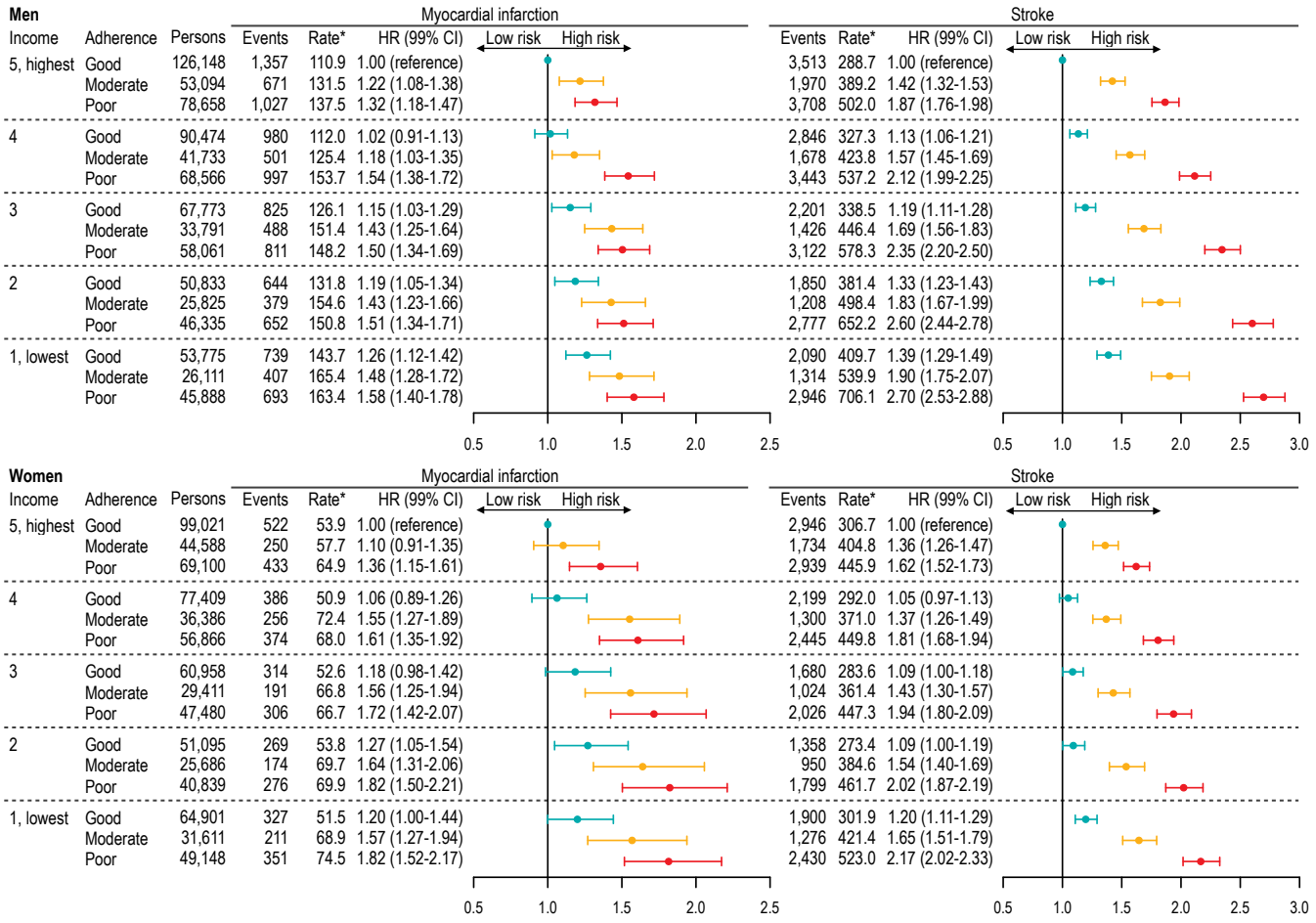


Figure S2. Combined effect of household income and medication adherence on hospitalizations for ASCVD and heart failure in men and women.



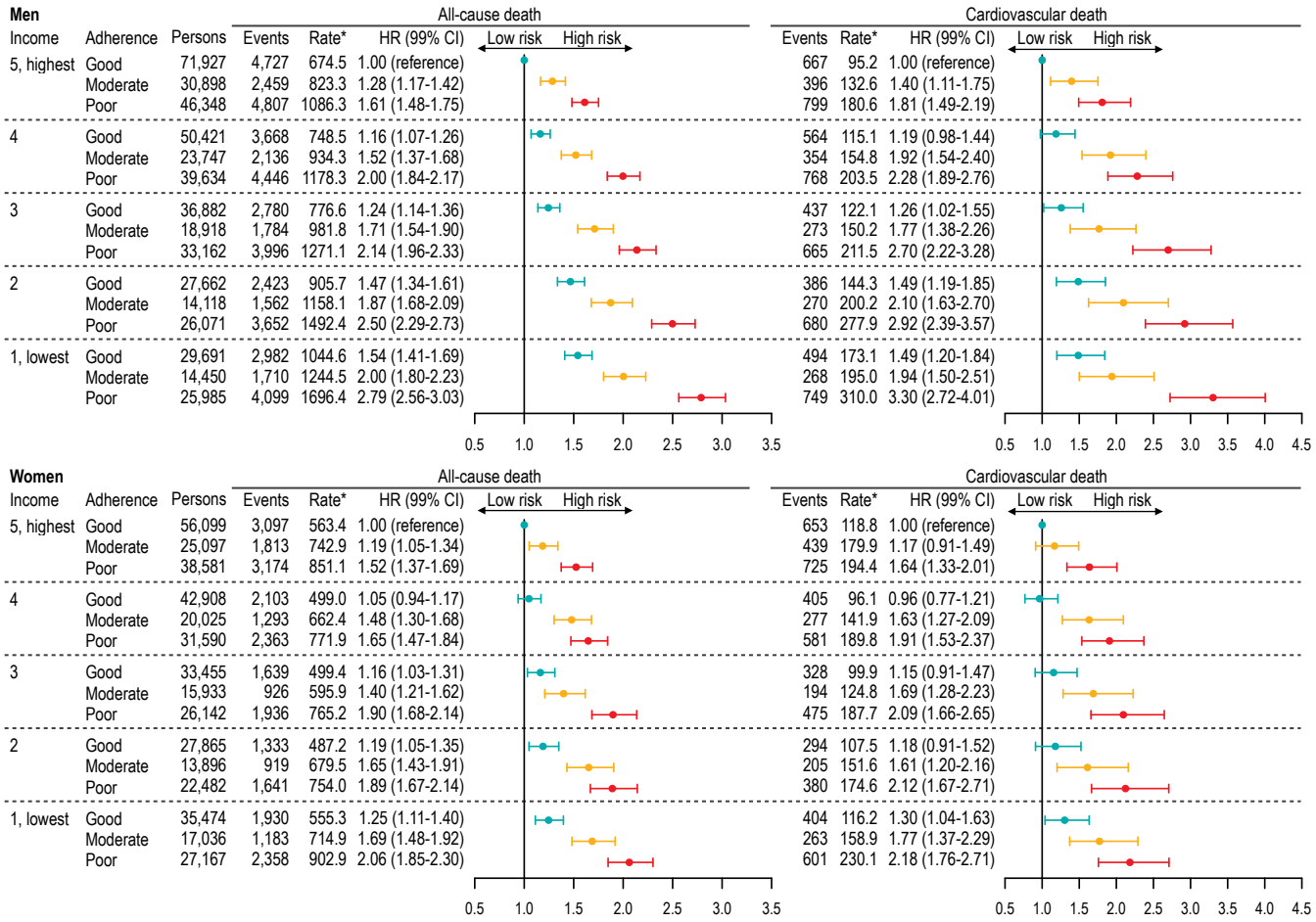
P for interaction between income and adherence in men and women were 0.305 and 0.002 for ASCVD and 0.100 and 0.520 for heart failure. *Rate per 100,000 person-years. ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; HR, hazard ratio.

Figure S3. Combined effect of household income and medication adherence on hospitalizations for myocardial infarction and stroke in men and women.



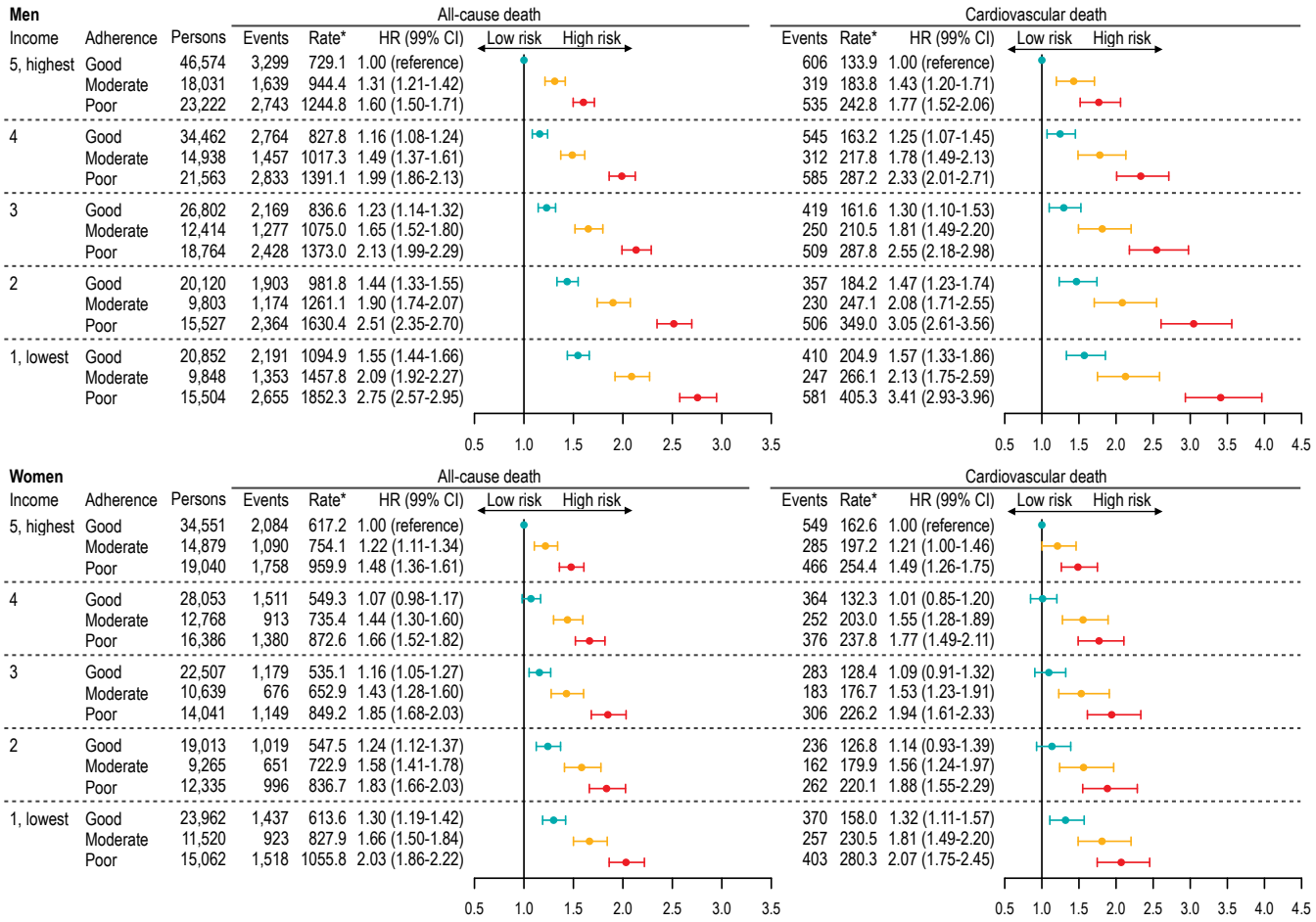
P for interaction between income and adherence in men and women were 0.093 and 0.459 for myocardial infarction and 0.116 and 0.001 for stroke. *Rate per 100,000 person-years. CI, confidence interval; HR, hazard ratio.

Figure S4. Combined effect of household income and medication adherence on all-cause and cardiovascular death in men and women who initiated monotherapy.



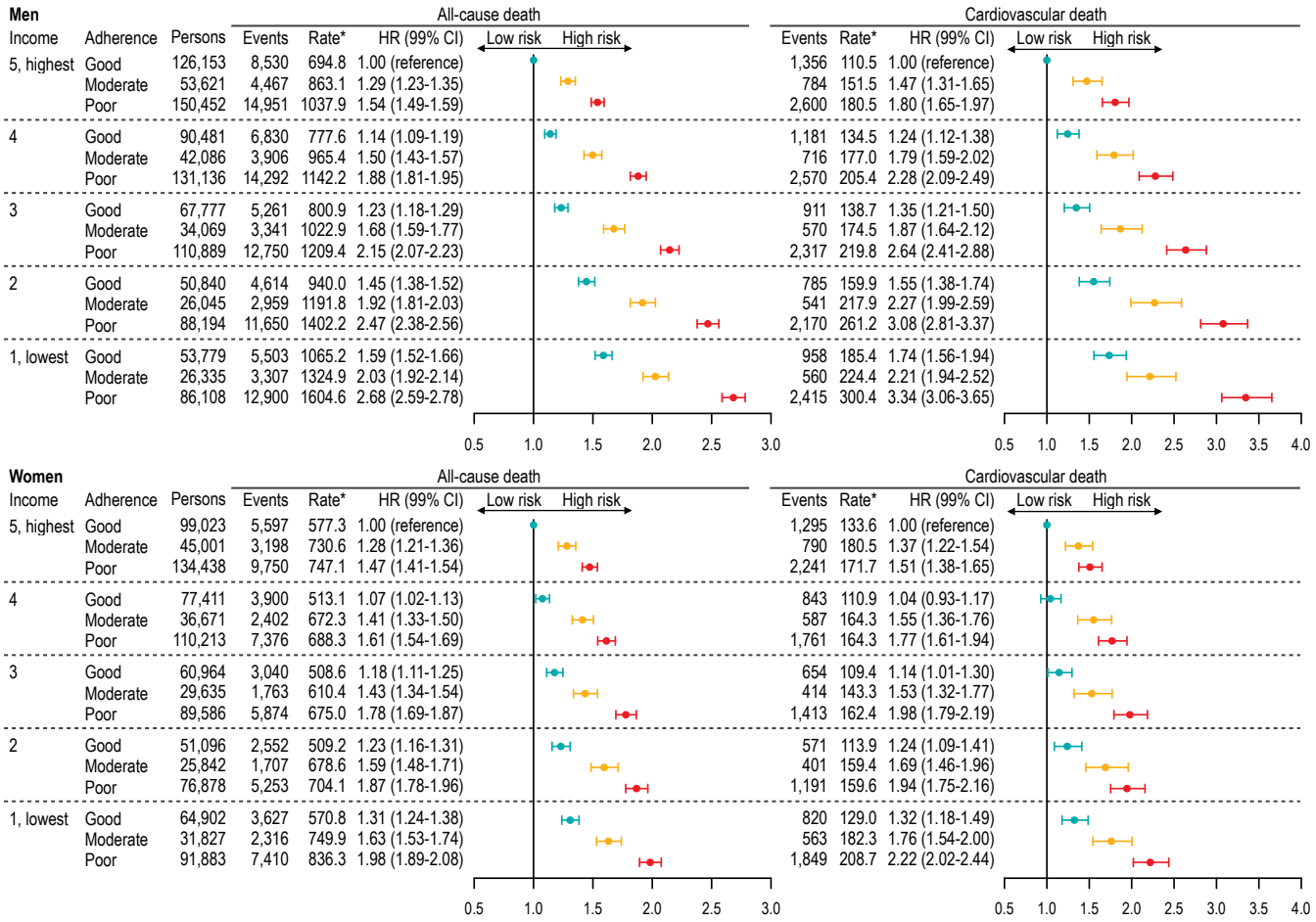
P for interaction between income and adherence in men and women were 0.045 and 0.207 for all-cause death and 0.086 and 0.972 for cardiovascular death. *Rate per 100,000 person-years. CI, confidence interval; HR, hazard ratio.

Figure S5. Combined effect of household income and medication adherence on all-cause and cardiovascular death in men and women who initiated combination therapy.



P for interaction between income and adherence in men and women were 0.009 and 0.463 for all-cause death and 0.012 and 0.694 for cardiovascular death. *Rate per 100,000 person-years. CI, confidence interval; HR, hazard ratio.

Figure S6. Combined effect of household income and medication adherence on all-cause and cardiovascular death in men and women who had ≥1 claim for antihypertensive medication.



P for interaction between income and adherence in men and women were <0.001 and 0.194 for all-cause death and 0.030 and 0.110 for cardiovascular death. *Rate per 100,000 person-years. CI, confidence interval; HR, hazard ratio.

Figure S7. Blood pressure change from baseline on follow-up according to medication adherence. Error bars represent 99% confidence intervals.