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ORIGINAL RESEARCH

Association Between Modifiable Risk Factors and Pharmaceutical Expenditures Among Adults With Atherosclerotic Cardiovascular Disease in the United States: 2012–2013 Medical Expenditures Panel Survey

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***Background*—**Atherosclerotic cardiovascular disease (ASCVD) causes most deaths in the United States and accounts for the highest healthcare spending. The association between the modifiable risk factors (MRFs) of ASCVD and pharmaceutical expenditures are largely unknown.

***Methods and Results*—**We examined the association between MRFs and pharmaceutical expenditures among adults with ASCVD using the 2012 and 2013 Medical Expenditure Panel Survey. A 2-part model was used while accounting for the survey's complex design to obtain nationally representative results. All costs were adjusted to 2013 US dollars using the gross domestic product deflator. The annual total pharmaceutical expenditure among those with ASCVD was $71.6 billion, 33% of which was for medications for cardiovascular disease and 14% medications for diabetes mellitus. The adjusted relationship between MRFs and pharmaceutical expenditures showed significant marginal increase in average annual pharmaceutical expenditure associated with inadequate physical activity ($519 [95% confidence interval (CI), $12–918; P=0.011]), dyslipidemia ($631 [95% CI, $168–1094; P=0.008]), hypertension: ($1078 [95% CI, $697–1460; P<0.001)], and diabetes mellitus ($2006 [95% CI, $1470–2542]). Compared with those with optimal MRFs (0–1), those with average MRFs (2–3) spent an average of $1184 (95% CI, $805–1564; P<0.001) more on medications, and those with poor MRFs (≥4) spent $2823 (95% CI, $2338–3307; P<0.001) more.

***Conclusions*—**Worsening MRFs were proportionally associated with higher annual pharmaceutical expenditures among patients with established ASCVD regardless of non-ASCVD comorbidity. In-depth studies of the roles played by other factors in this association can help reduce medication-related expenditures among ASCVD patients. **(*J Am Heart Assoc*. 2017;6:e004996. DOI: 10.1161/JAHA.116.004996.)**

Key Words: coronary heart disease • cost • modifiable risk factors • pharmaceutical expenditure

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality globally,[1] and atherosclerotic cardiovascular disease (ASCVD) is the most common type, accounting for >370 000 deaths annually.[2] In addition to the impact on mortality, ASCVD causes significant loss of quality of life and is responsible for the highest healthcare

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Accompanying Tables S1 through S4 and Figures S1, S2 are available at http://jaha.ahajournals.org/content/6/6/e004996/DC1/embed/inline-supplementary-material-1.pdf

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expenditure for any single class of disease.[1] In 2011, the estimated annual direct cost for CVD and stroke in the United States was about $196 billion.[1] Incidence, associated morbidity, disability, mortality, and healthcare costs have been shown to depend largely on modifiable risk factors (MRFs) for CVD.[3–6]

Expenditures on prescription medication in the US general population formed 9.8% of total healthcare spending in 2014,[7] and in 2012, 26.1% of total healthcare expenditures among adults with CVD were for medications.[8] Although few studies have reported incremental healthcare costs associated with worsening cardiovascular risk factor profiles among patients with diagnosed CVD,[9,10] the association between MRFs and pharmaceutical expenditures in the United States has not been examined.

Considering the economic impact of ASCVD and the significant contribution of pharmaceutical expenditure to overall healthcare expenditure, we aimed to examine the association between MRFs and pharmaceutical expenditures (both overall and medication-specific) in a nationally representative population with established ASCVD.

Methods

Study Design and Population

We conducted a retrospective study of US adults aged ≥40 years with established ASCVD using data from the 2012 and 2013 Medical Expenditure Panel Survey (MEPS) database. MEPS, sponsored by the Agency for Healthcare Research and Quality (AHRQ), is a national survey of individuals, families, their medical providers (for medical conditions), and employers, to obtain patients' healthcare resource utilization and expenditure. Each year, the MEPS Household Components (MEPS-HC) sample is drawn from respondents of the previous year's National Health Interview Survey. It has an overlapping panel design, with each panel composed of randomly sampled noninstitutionalized US civilians. Participants are interviewed every 6 months over a period of 30 months, and their responses are reported annually to provide nationally representative estimates of sociodemographic characteristics, medical conditions, and healthcare utilization and costs.[11,12] Interviews were conducted over the telephone with participants, and their physicians, hospitals, and pharmacies were contacted to obtain additional healthcare use and cost data. The AHRQ researchers assigned person weights and variance estimation strata to participants after data collection to reflect survey nonresponse and population totals of the participants surveyed.[13]

We merged the MEPS-HC full-year consolidated, medical conditions, and prescribed medicines files for 2012 and 2013 for this study.[14,15] Pooling this 2-year data afforded us a larger and analyzable population of adults with ASCVD. Race and ethnicity were determined using the MEPS-defined categories that allow respondents to report multiple Hispanic ethnicities.

Because MEPS consists of publicly available, de-identified data files, this study was exempt from institutional review board, in accordance with US Department of Health and Human Services guidelines. Written consent was obtained from participants to contact them for interviews and to contact their healthcare providers (clinicians and pharmacies).

We classified participants as having ASCVD using the *International Statistical Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9 CM) diagnosis of the condition (Table S1)[16,17] and/or self-reported history of diagnosis of coronary heart disease, angina, myocardial infarction, and/or stroke. Our study population was limited to noninstitutionalized US adults with established ASCVD who were ≥40 years at the time of the survey (ASCVD is uncommon among younger adults), had a body mass index (calculated as weight in kilograms divided by height in meters squared) of ≥18.5 kg/m^2 (underweight individuals generally represent a sicker population),[18] and who had a final person-weight >0 to be representative of the national population at the time of the survey (Figure S1).

Pharmaceutical Expenditures

During the household interview, respondents supplied the name of any prescribed medicine that they or their family members purchased or otherwise obtained during the reference period. They were also asked for permission to obtain payment data and other information from pharmacies. With the written permission from participants, pharmacies were contacted to obtain information on the medication name, national drug code, strength, quantity, date filled, and amount paid. The multisourced, person-level medication information was then included in MEPS prescribed medicine files and linked to the Multum Lexicon databases by AHRQ researchers to assign the drugs into classes.[19] The codes we used to group CVD, diabetes, and other classes of medications are shown in Table S2. More details on the collection and management of pharmaceutical data in MEPS are provided elsewhere.[20] For each drug prescribed, the exact dollar amount paid was reported. Using these cost data, we calculated expenditures specific to the different classes of drugs. All expenditures were adjusted to constant 2013 US dollars using the gross domestic product deflator.

Modifiable Risk Factors and Comorbidity Burden

The MRFs examined in this study included inadequate physical activity, obesity, smoking, dyslipidemia,

hypertension, and diabetes mellitus. We used responses from the self-administered questionnaire to determine the MRF status of participants, and we classified each as a binary variable (favorable [0] versus unfavorable [1]). Any participant who did not engage in moderate vigorous physical activity 5 times a week; had a BMI ≥30 kg/m^2; was a smoker at the time of interview; or reported a diagnosis of a cholesterol disorder, hypertension, or diabetes mellitus was classified as having unfavorable MRFs. Based on the presence of these individual risk factors, survey participants were categorized as *poor* (≥4 cardiovascular risk factors), *average* (2–3 cardiovascular risk factors), or *optimal* (0–1 cardiovascular risk factor). We also determined the contribution of comorbidity to the association between MRFs and pharmaceutical expenditures and compared the marginal pharmaceutical expenditures associated with comorbidity and those associated with MRF profile. Participants' comorbidity burden was assessed using the grouped Charlson Comorbidity Index (GCCI), which has been described elsewhere.[21,22] For our analyses, however, we modified the GCCI by excluding acute myocardial infarction, congestive heart failure and peripheral vascular disease from our estimation of GCCI score, since these were included in our definition of ASCVD; and diabetes mellitus, since it was considered a cardiovascular risk factor. We had 3 categories for GCCI: no comorbidity (0), 1 long-term condition (1), and ≥2 long-term conditions present other than CVD and/or diabetes mellitus (2; Table S2).

Covariates

We considered age, sex, race/ethnicity, and family income as factors that were also associated with pharmaceutical expenditures; therefore, we used these as covariates in the determination of the association between MRFs and pharmaceutical expenditures. Participant age as of the last day of the survey was classified into 3 categories: 40 to 64, 65 to 74, and ≥75 years. We had 5 categories of race and ethnicity: non-Hispanic white, non-Hispanic black, Hispanic, Asian, and other (American Indian, Alaska Native, and those who reported multiple races/ethnicities). There were 4 categories of family income level expressed as a proportion of the federal poverty level: <100%, 100% to 200%, 200% to 400%, and ≥400%.

Statistical Analysis

All analyses were conducted using STATA 14 (StataCorp). We accounted for the complex sampling design of MEPS in all our analyses using the final person-weight and variance estimations (person sampling and strata). We determined the prevalence of each MRF and of the 3 MRF profiles and used χ^2 statistics to test for their variations across different sociodemographic characteristics. Because the distribution of cost data is often right-skewed secondary to the high proportion of people with no expenditure, we used a 2-part model to estimate the marginal pharmaceutical expenditure associated with each MRF (unfavorable versus favorable), the 3 MRF profiles, and the modified GCCI. The 2-part model consists of (1) a binary choice model fit for the probability of observing a positive-versus-zero annual expenditure on medications using the *probit* command and (2), contingent on having >$0 annual pharmaceutical expenditure, a generalized linear model (with γ distribution and a log link) was fitted for the >$0 expenditure to estimate the effect of MRFs on pharmaceutical expenditures.[23,24] To determine the appropriate distribution of the generalized linear model in the 2-part model, we used the modified Park test.[25] We used the *margins* postestimation command to determine the marginal and absolute pharmaceutical expenditures associated with the predictor variables in the 2-part model. The use of the 2-part model and the *margins* in STATA allowed us to estimate robust standard errors, 95% confidence intervals (CIs) and *P* values associated with each estimate of marginal expenditure (α level of significance was 0.05). This also helped avoid the difficulties associated with retransformation when ordinary least squares with the log scale was used in analyzing highly skewed expenditure data such as MEPS. In addition, because the *svy: twopm* command can be used in STATA to incorporate the complex design of MEPS in our analyses, our results can be generalizable to the US population. However, the 2-part model did not cause the data to become normal; the skewness and kurtosis tests for normality among those with positive cost value (ie, cost >0$) showed the distribution is nonnormal (joint $P<0.001$).

Results

Sample Characteristics

From 2012 to 2013, there were 75 914 respondents in MEPS, representing an average annual national estimate of 314.6 million individuals—similar to the average of the projected US civilian population of 2012 and 2013. Among this surveyed population, 4248 adults aged ≥40 years with a BMI ≥18 had ASCVD (an annual equivalent of 21.9 million US adults). The mean age was 67.7 years (SD 21.6), and 44.8% were female.

The distribution of demographic characteristics for the study population is shown in Table S3. The prevalence and the variation of the prevalence of each MRF are shown in Table 1. Hypertension was the most common MRF among ASCVD adults, with a prevalence of 81.5%. Smoking and obesity were significantly more prevalent among adults aged 40 to 65 years, whereas the prevalence of dyslipidemia was higher

Table 1. Prevalence of Individual Modifiable Risk Factors Across Sociodemographic Characteristics of Adults Aged ≥40 Years Living With ASCVD, MEPS 2012–2013

	No. of Survey Participants	Prevalence, % (95% CI)					
		Inadequate Physical Activity	Smoking	Obesity	Hyperlipidemia	Hypertension	Diabetes Mellitus
Overall	4248	65.8 (63.6–68.0)	16.6 (14.8–18.5)	39.1 (36.8–41.5)	77.1 (75.1–79.0)	81.5 (79.8–83.1)	33.0 (30.9–35.1)
Age group, y							
40–64	1647	63.7(60.4–66.9)	28.5 (25.3–32.0)	48.5 (45.1–52.0)	71.2 (68.4–73.8)	75.0 (72.0–77.8)	32.5 (29.5–35.6)
65–79	1203	59.7 (55.6–63.7)	14.3 (11.6–17.5)	41.5 (37.3–45.9)	85.9 (82.4–88.8)	85.7 (81.8–88.9)	37.0 (33.0–41.2)
≥80	1398	73.6 (69.9–77.0)	4.4 (3.2–6.0)	26.0 (22.3–30.0)	76.4 (72.3–80.2)	85.5 (82.8–87.9)	30.1 (26.9–33.6)
P value*		<0.001†	<0.001†	<0.001†	<0.001†	<0.001†	0.024†
Sex							
Men	2345	61.7 (58.8–64.5)	18.2 (15.9–20.8)	39.1 (35.8–42.4)	80.4 (77.8–82.7)	82.4 (79.9–84.6)	33.3 (30.4–36.4)
Women	1903	71.0 (68.0–73.8)	14.5 (12.3–17.0)	9.2 (36.1–42.4)	73.0 (69.8–76.0)	80.4 (77.9–82.7)	32.5 (29.5–35.7)
P value		<0.001†	0.014†	0.945	<0.001†	0.273	0.708
Race/ethnicity							
Non-Hispanic white	3191	64.7 (61.9–67.3)	17.0 (15.0–19.3)	37.7 (35.0–40.5)	78.8 (76.3–81.1)	80.5 (78.5–82.4)	29.1 (26.5–31.8)
Non-Hispanic black	485	70.5 (66.7–74.1)	20.0 (16.7–23.7)	48.6 (43.6–53.6)	69.4 (65.5–73.1)	88.9 (85.7–91.5)	40.7 (36.7–44.7)
Asian	107	58.8 (47.8–69.0	5.3 (2.4–11.4)	8.6 (4.6–15.4)	81.7 (73.0–88.0)	78.7 (68.4–86.4)	46.1 (37.0–55.5)
Hispanic	375	69.4 (64.3–74.0)	10.9 (7.7–15.3)	47.7 (42.8–52.6)	70.4 (66.0–74.5)	80.8 (76.9–84.2)	45.1 (40.6–49.8)
Other	90	76.5 (66.7–84.1)	17.8 (9.9–29.9)	38.3 (26.2–52.0)	79.3 (68.5–87.1)	82.2 (69.4–90.4)	63.2 (47.8–76.3)
P value		0.008†	0.001†	<0.001†	<0.001†	0.004†	<0.001†
Family income level‡							
<100%	646	72.2 (67.5–76.5)	28.9 (24.7–33.6)	40.5 (36.6–44.6)	77.9 (73.2–81.9)	82.6 (78.6–86.0)	34.9 (30.5–39.4)
100–200%	1027	69.1 (65.0–72.9)	17.4 (14.7–20.4)	37.8 (33.9–41.8)	76.8 (73.3–80.0)	86.3 (83.3–88.7)	35.0 (31.4–38.9)
200–400%	1185	67.6 (64.1–70.9)	13.6 (10.8–17.1)	42.2 (37.9–46.6)	76.5 (72.2–80.3)	82.0 (79.2–84.5)	33.5 (29.9–37.3)
>400%	1390	59.0 (55.0–62.9)	12.7 (10.0–15.9)	36.8 (33.0–40.8)	77.4 (74.1–80.5)	77.1 (73.1–80.6)	30.1 (26.2–34.3)
P value		<0.001†	<0.001†	0.146	0.960	<0.001†	0.212
GCCI							
0	2866	63.3 (60.7–65.9)	15.4 (13.4–17.8)	36.2 (33.6–38.8)	75.3 (72.9–77.6)	79.2 (77.1–81.2)	30.5 (28.1–32.9)
1	867	69.0 (64.8–72.9)	20.9 (17.4–24.9)	45.8 (40.9–50.7)	78.8 (74.2–82.8)	86.4 (82.6–89.5)	36.8 (32.5–41.4)
2	515	74.5 (68.6–79.6)	15.6 (11.6–20.8)	44.3 (38.5–50.3)	84.0 (79.5–87.6)	86.0 (80.0–90.4)	40.3 (33.4–47.6)
P value		<0.001†	0.026†	<0.001†	0.007†	0.003	0.004†

ASCVD indicates atherosclerotic cardiovascular disease; CI, confidence interval; GCCI, grouped Charlson Comorbidity Index; MEPS, Medical Expenditure Panel Survey.
*χ^2 Statistic used to test difference in proportions between respondents.
†Statistically significant.
‡Family income expressed as a proportion of the federal poverty level.

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among those aged 65 to 79 years; men were more likely to have hyperlipidemia than women. Most of the study participants (49.9%) reported an average MRF profile, and with the exception of sex, there was significant variation in the prevalence of MRF profiles across different sociodemographic characteristics (Table S4).

Annual Pharmaceutical Expenditures Among Those With ASCVD

Of the 4248 adults with ASCVD in 2012–2013, 95.4% used prescription medications; 86.8% used ≥1 CVD medication. The annual per capita pharmaceutical expenditures among adults with ASCVD was $3432. On average, 34% of total pharmaceutical expenditure was spent on CVD medications ($1139; 95% CI, $1063–1215), and 14% ($482; 95% CI, $407–556) was spent on antidiabetic medications. The residual 52% ($1786) was for medications other than those for CVD and diabetes (Figure 1). When projected using MEPS's complex designs, the 2012–2013 annual total pharmaceutical spending among those with ASCVD was an estimated $71.6 billion; $23.8 billion was spent on CVD medications, $10 billion was spent on diabetes medications, and approximately $37.8 billion was spent on other medications.

Effects of MRFs on Annul Pharmaceutical Expenditures Among Those With ASCVD

The unadjusted and adjusted marginal pharmaceutical expenditures associated with the presence versus absence of individual MRFs is shown in Table 2. Inadequate physical activity, dyslipidemia, hypertension, and diabetes mellitus were statistically significantly associated with total pharmaceutical expenditure after adjusting for sociodemographic characteristics and burden of comorbid conditions. The marginal pharmaceutical expenditure associated with diabetes mellitus was the highest of all MRFs at $2006 (95% CI, $1470–$2542; $P<0.001$). When different categories of medication expenditures were examined, dyslipidemia, hypertension, and diabetes mellitus were significantly associated with increased CVD medication expenditures; obesity and diabetes mellitus were associated with increased expenditures for diabetes medication; and inadequate physical activity and hypertension were significantly associated with an increase in non-CVD, nondiabetic medication expenditures.

The average annual pharmaceutical expenditure among patients with ASCVD who had an optimal MRF profile was $1400 (95% CI, $1073–1728) compared with $2672 (95% CI, $2332–3013) among those with an average MRF profile and $4516 (95% CI, $4067–4965) among those with a poor MRF

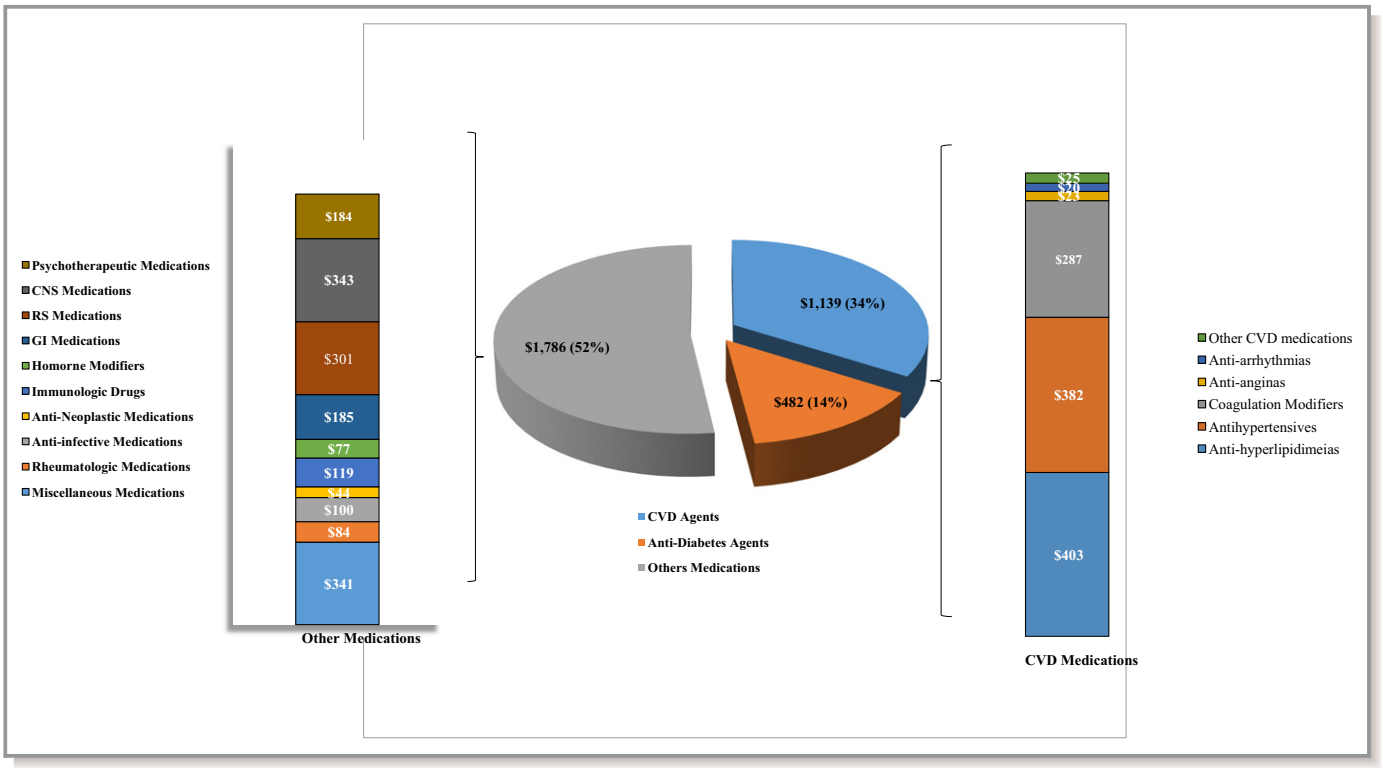

Figure 1. Annual per capita pharmaceutical expenditures for different medication classes among adults with ASCVD, MEPS 2012–2013. All costs are in 2013 US dollars. ASCVD indicates atherosclerotic cardiovascular disease; CNS, central nervous system; CVD, central nervous system; GI, gastrointestinal; MEPS, Medical Expenditure Panel Survey; RS, respiratory system.

Table 2. Marginal Pharmaceutical Expenditures Associated With Each MRF: Results From the 2-Part Econometric Model, MEPS 2012–2013

MRF	Univariate (Unadjusted)		Model 1*		Model 2†	
	Marginal Expenditures (95% CI)	*P* Value	Marginal Expenditures (95% CI)	*P* Value	Marginal Expenditures (95% CI)	*P* Value
Overall pharmaceutical expenditures						
Inadequate vs optimal physical activity	864 (336–1391)	0.001‡	893 (430–1355)	<0.001‡	520 (121–918)	0.011‡
Obesity vs normal BMI	1271 (726–1817)	<0.001‡	1146 (675–1616)	<0.001‡	349 (−106 to 8030	0.132
Currently smoking vs nonsmoker	719 (29–1409)	0.007‡	411 (−267 to 1090)	0.233	400 (−237 to 1037)	0.217
Dyslipidemia vs no dyslipidemia	1031 (396–1666)	0.002‡	1143 (627–1659)	<0.001‡	631 (168–1094)	0.008‡
Hypertension vs no hypertension	1679 (1261–2096)	<0.001‡	1679 (1302–2056)	<0.001‡	1079 (697–1460)	<0.001‡
Diabetes mellitus vs no diabetes mellitus	2557 (1997–3117)	<0.001‡	2564 (2020–3108)	<0.001‡	2006 (1470–2542)	<0.001‡
CVD medication expenditures						
Inadequate vs optimal physical activity	118 (−32 to 268)	0.123	142 (−8 to 291)	0.063	73 (−76 to 222)	0.333
Obesity vs normal BMI	223 (74–3730	0.004‡	272 (123–422)	<0.001	141 (−24 to 305)	0.093
Currently smoking vs nonsmoker	65 (−148 to 278)	0.551	145 (−73 to 363)	0.190	81 (−111 to 273)	0.408
Dyslipidemia vs no dyslipidemia	649 (502–795)	<0.001‡	631 (489–774)	<0.001‡	506 (350–663)	<0.001‡
Hypertension vs no hypertension	574 (426–723)	<0.001‡	567 (420–715)	<0.001‡	394 (230–558)	<0.001‡
Diabetes mellitus vs no diabetes mellitus	357 (202–512)	<0.001‡	406 (254–557)	<0.001‡	235 (77–393)	0.004‡
Diabetes medication expenditures						
Inadequate vs optimal physical activity	253 (120–386)	<0.001‡	255 (121–388)	<0.001‡	10 1 (−23 to 226)	0.110
Obesity vs normal BMI	502 (315–688)	<0.001‡	476 (297–656)	<0.001‡	227 (94–360)	0.001‡
Currently smoking vs nonsmoker	53 (−171 to 2765)	0.643	−15 (−213 to 183)	0.882	116 (−80 to 312)	0.245
Dyslipidemia vs no dyslipidemia	168 (10–325)	0.037‡	178 (23–333)	0.024‡	−40 (−194 to 114)	0.608
Hypertension vs no hypertension	311 (153–469)	<0.001‡	328 (198–459)	<0.001‡	77 (−75 to 228)	0.320
Diabetes mellitus vs no diabetes mellitus	1399 (1193–1606)	<0.001‡	1540 (1145–1934)	<0.001‡	1296 (1108–1484)	<0.001‡
Other medication expenditures						
Inadequate vs optimal physical activity	443 (−25 to 911)	0.063	480 (135–825)	0.007‡	319 (16–622)	0.039‡
Obesity vs normal BMI	520 (61–979)	0.027‡	340 (−25 to 704)	0.068	77 (−315 to 469)	0.698
Currently smoking vs nonsmoker	776 (187–1366)	0.01‡	324 (−181 to 828)	0.207	240 (−248 to 728)	0.333
Dyslipidemia vs no dyslipidemia	22 (−614 to 658)	0.946	160 (−296 to 616)	0.490	−144 (−568 to 280)	0.504
Hypertension vs no hypertension	626 (314–938)	<0.001‡	604 (329–878)	<0.001‡	492 (219–765)	<0.001‡
Diabetes mellitus vs no diabetes mellitus	697 (275–1120)	0.001‡	611 (242–979)	0.001‡	386 (13–759)	0.042‡

All cost are in 2013 US dollars. BMI indicates body mass index; CI, confidence interval; CVD, cardiovascular disease; MEPS, Medical Expenditure Panel Survey; MRF, modifiable risk factor.
*Model 1: Each MRF was used as a predictor and adjusted for age, sex, race/ethnicity, and income level (all variable entered as categorical variables).
†Model 2: All MRFs were entered simultaneously and adjusted for age, sex, race/ethnicity, income level, and Charlson Comorbidity Index (all variables entered as categorical variables).
‡Statistically significant.

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profile. The unadjusted and adjusted marginal pharmaceutical expenditures associated with MRF profiles are shown in Table 3. After accounting for demographics, income status, and comorbid conditions, the annual pharmaceutical expenditure was $1184 (95% CI, $805–1564) higher among those with average MRF profiles and $2823 (95% CI, $2338–3307) higher among ASCVD patients with poor MRF profiles compared with those with optimal MRF profiles ($P<0.001$).

Table 3. Per Capita Marginal Pharmaceutical Expenditures Associated With Grouped MRFs and Charlson Comorbidity Index Among Adults With ASCVD, MEPS 2012–2013

MRF Profile	Unadjusted		Adjusted*	
Overall pharmaceutical expenditures† (95% CI)				
Optimal MRF	Reference	*P* value	Reference	*P*-value
Average MRF	1272 (844–1700)	<0.001‡	1184 (804–1564)	<0.001‡
Poor MRF	3115 (2645–3586)	<0.001‡	2823 (2338–3308)	<0.001‡
CVD-medication expenditures (95% CI)				
Optimal MRF	Reference	*P* value	Reference	*P* value
Average MRF	396 (200–591)	<0.001‡	406 (231–582)	<0.001‡
Poor MRF	791 (589–993)	<0.001‡	848 (653–1043)	<0.001‡
Diabetes medication expenditures (95% CI)				
Optimal MRF	Reference	*P* value	Reference	*P* value
Average MRF	136 (84–188)	<0.001‡	131 (77–185)	<0.001‡
Poor MRF	969 (797–1141)	<0.001‡	943 (760–1126)	<0.001‡
Other medication expenditures (95% CI)				
Optimal MRF	Reference	*P* value	Reference	*P* value
Average MRF	622 (199–1045)	0.004‡	526 (134–918)	0.009‡
Poor MRF	1167 (773–1560)	<0.001‡	807 (434–1180)	<0.001‡
Modified Grouped CCI	Unadjusted		Adjusted§	
Overall pharmaceutical expenditures† (95% CI)				
0	Reference	*P* value	Reference	*P* value
1	2603 (1723–3483)	<0.001‡	2272 (1519–3025)	<0.001‡
2	2518 (1665–3371)	<0.001‡	2068 (1349–2787)	<0.001‡
CVD-medication expenditures (95% CI)				
0	Reference	*P* value	Reference	*P* value
1	53 (−130 to 236)	0.567	21 (−153 to 195)	0.811
2	132 (−70 to 334)	0.2‡	30 (−169 to 229)	0.77
Diabetes medication expenditures (95% CI)				
0	Reference	*P* value	Reference	*P* value
1	159 (21–297)	<0.024‡	29 (−101 to 160)	<0.001‡
2	375 (94–656)	0.009‡	206 (1–411)	0.048
Other medication expenditures (95% CI)				
0	Reference	*P* value	Reference	*P* value
1	2312 (1514–3111)	<0.001‡	2015 (1412–2617)	<0.001‡
2	1903 (1274–2532)	<0.001‡	1773 (1189–2357)	<0.001‡

All costs are in 2013 US dollars. ASCVD indicates atherosclerotic cardiovascular disease; CCI, Charlson Comorbidity Index; CI, confidence interval; CVD, cardiovascular disease; MRF, modifiable risk factors; MEPS, Medical Expenditure Panel Survey.

*Adjusted for age, sex, race/ethnicity, income level, CCI.

†All Costs are in 2013 USD.

‡Statistically significant.

§Adjusted for age, sex, race/ethnicity, income level, and grouped MRFs category.

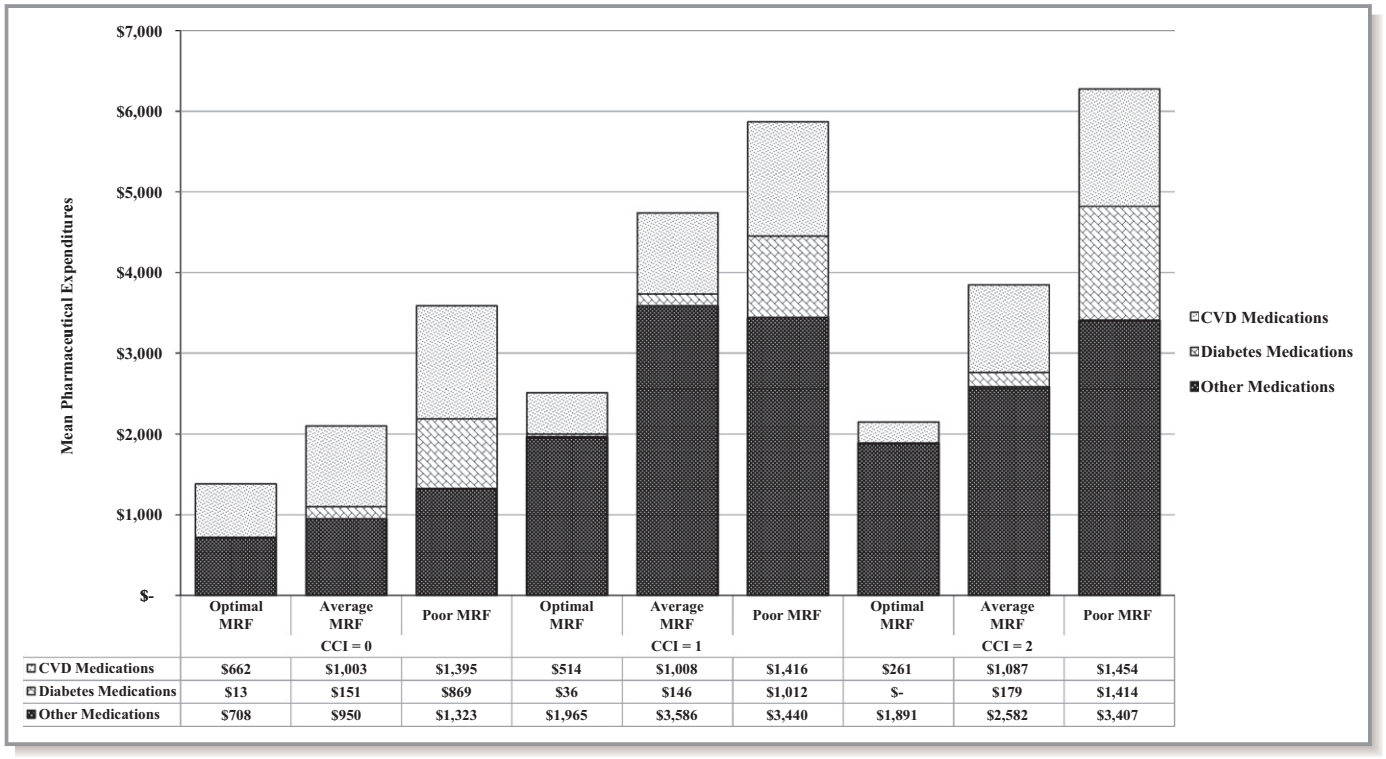
Similar trends were noted when mean expenditures for specific medication classes (CVD, diabetes, and other) were considered.

Figure 2 describes the association among both MRF profiles and increasing burden of comorbid conditions with annual pharmaceutical expenditures (overall and medication-specific). The lowest annual drug costs were observed among those with optimal MRF profiles and no major comorbid conditions ($1386). In contrast, ASCVD patients with poor MRF profiles and a GCCI of 2 had the highest annual pharmaceutical expenditures ($6948). Across worsening comorbidity, individuals with poor MRF profiles incurred the highest pharmaceutical expenditures (Figure 2). In a subanalysis of specific CVD medications, annual costs of antihyperlipidemics, antihypertensives, and coagulation modifiers significantly increased with worsening MRF profile across all categories of comorbidity burden (Figure 3).

Discussion

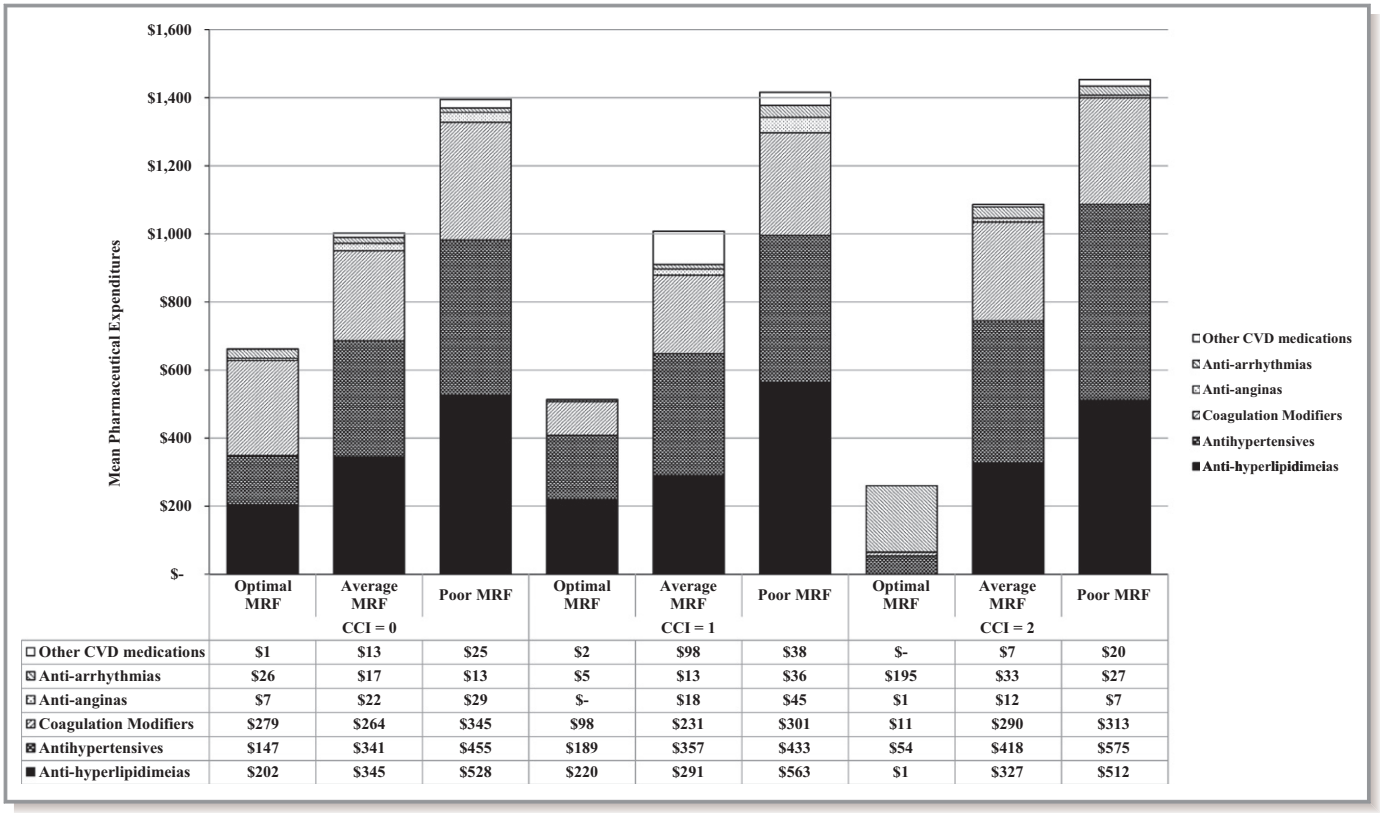
In a nationally representative population, our study demonstrated that in 2012–2013, adults with established ASCVD spent $284 billion on health care per annum. Of this, $71.6 billion was spent on medications. The contributions of medications for CVD and diabetes mellitus to the overall pharmaceutical expenditures were $23.8 billion (34%) and $10 billion (14%), respectively. More than half (52%) of the overall pharmaceutical expenditure was spent on non-CVD, nondiabetes medications. The details of the 2012–2013 per capita pharmaceutical expenditures examined in the context of the mean healthcare expenditures in our study population are shown in Figure S2. The overall pharmaceutical expenditure was significantly associated with individual MRFs; inadequate physical activity, dyslipidemia, hypertension, and diabetes mellitus as well as worsening MRF profile were all associated with higher pharmaceutical expenditure. Similar patterns were observed when expenditures for specific medication classes (CVD, diabetes, and others) were examined. These associations persisted even after accounting for underlying comorbid conditions.

Many studies have found that current MRFs are important drivers of future morbidity and mortality among individuals with established CVD in a dose-response fashion.[26–28] Although studies within and outside the United States have attempted to estimate the incremental healthcare expenditures associated with individual cardiovascular MRFs among those without established CVD,[29,30] no study has detailed the potential economic impact of CVD MRFs on pharmaceutical



	Optimal MRF	Average MRF	Poor MRF	Optimal MRF	Average MRF	Poor MRF	Optimal MRF	Average MRF	Poor MRF
	CCI = 0			CCI = 1			CCI = 2		
CVD Medications	$662	$1,003	$1,395	$514	$1,008	$1,416	$261	$1,087	$1,454
Diabetes Medications	$13	$151	$869	$36	$146	$1,012	$-	$179	$1,414
Other Medications	$708	$950	$1,323	$1,965	$3,586	$3,440	$1,891	$2,582	$3,407

Figure 2. Mean pharmaceutical expenditures associated with grouped MRFs across different levels of grouped CCI among those with ASCVD, MEPS 2012–2013. Mean expenditures were estimated using the person weight and variance estimation stratum and person sampling unit of MEPS 2012–2013. All costs are in 2013 US dollars. ASCVD indicates atherosclerotic cardiovascular disease; CCI, Charlson Comorbidity Index; CVD, cardiovascular disease; MEPS, Medical Expenditure Panel Survey; MRF, modifiable risk factor.



	Optimal MRF	Average MRF	Poor MRF	Optimal MRF	Average MRF	Poor MRF	Optimal MRF	Average MRF	Poor MRF
	CCI = 0			CCI = 1			CCI = 2		
Other CVD medications	$1	$13	$25	$2	$98	$38	$-	$7	$20
Anti-arrhythmias	$26	$17	$13	$5	$13	$36	$195	$33	$27
Anti-anginas	$7	$22	$29	$-	$18	$45	$1	$12	$7
Coagulation Modifiers	$279	$264	$345	$98	$231	$301	$11	$290	$313
Antihypertensives	$147	$341	$455	$189	$357	$433	$54	$418	$575
Anti-hyperlipidimeias	$202	$345	$528	$220	$291	$563	$1	$327	$512

Figure 3. Mean CVD medication expenditures and their association with MRF profiles across different levels of grouped CCI among those with ASCVD, MEPS 2012–2013. Mean expenditures were estimated using the person weight, variance estimation stratum, and person sampling unit of MEPS 2013. All costs are in 2013 US dollars. ASCVD indicates atherosclerotic cardiovascular diseases; CCI, Charlson Comorbidity Index; CVD, cardiovascular disease; MEPS, Medical Expenditure Panel Survey; MRF, modifiable risk factor.

costs, which remains one of the largest contributors to overall healthcare expenditures. Sullivan et al showed that among persons with cardiometabolic risk factor clusters (BMI ≥25 and any 2 of hypertension, hyperlipidemia, and diabetes mellitus), 34% of total healthcare expenditure was for prescription medications in 2006,[10] and depending on the source of payment, the proportion could be as high as 49%.[8] In Australia, Ademi et al showed that obesity, hypertension, and diabetes mellitus are predictors of higher pharmaceutical expenditures among persons with or at risk of CVD.[29]

The findings of Ademi et al are similar to ours. Our study of the US adults with ASCVD in 2012–2013 showed that individual cardiovascular MRFs such as inadequate physical activity, dyslipidemia, hypertension, and diabetes mellitus were significantly associated with higher pharmaceutical expenditures of $519, $631, $1078, and $2006, respectively, compared with adults without the respective risk factors, after accounting for sociodemographic factors and comorbidity. In addition, we found significantly higher pharmaceutical expenditures (all medications, CVD-specific medications, and non-CVD pharmaceutical expenditures) associated with poor cardiovascular MRF profiles among persons with established ASCVD in a nationally representative cohort, after accounting for underlying comorbid conditions. The adjusted average annual pharmaceutical expenditure was highest among those with a poor MRF profile ($4516) and lowest for those with an optimal MRF profile ($1400).

Another significant finding of our study is that although the study population consisted of those with established ASCVD, non-CVD medications contributed the most toward total pharmaceutical cost. This is comparable to the findings of the Cooper Center Longitudinal Study by Willis et al, in which they reported that average annual non-CVD healthcare cost was higher than CVD-related healthcare cost and that overall cost increased with worsening MRF profile.[30] These findings are not unexpected considering the complex interplay among CVD, MRFs, and associated comorbidities[31] in increasing healthcare resource utilization and cost.

Some studies have demonstrated an association between comorbidity and healthcare costs.[32–34] In our study, comorbidity was found to be associated with higher pharmaceutical expenditure among people with established ASCVD. Beyond that, our study also demonstrated that the burden of cardiovascular MRF may have a higher impact on pharmaceutical expenditure than the burden of other comorbid conditions among those with ASCVD. The marginal

pharmaceutical expenditures associated with worsening MRF profiles were larger than those associated with a higher burden of comorbid conditions (see Table 3). This underscores the importance of addressing MRF prevention in the general population, especially because the prevention of MRFs reduces the risk of ASCVD. This approach can potentially lead to pharmaceutical cost saving and, ultimately, reduced healthcare spending.

As projected, 40.5% of the US population will have a type of CVD by 2030 and will spend $818 billion in annual direct medical cost—a significant leap from the $217 billion spent in 2010.[1] It is imperative that all possible means targeted at stalling or halting this projected economic impact of CVD be explored today. An integrated approach to the management of ASCVD, its associated MRFs, and other comorbidities could be explored to reduce spending. The concept of "bundle payment" in the "one cycle of care"[35] may be adapted to prescription medications and explored among ASCVD patients, perhaps taking the approach of "one price for a year's supply" to prescriptions used in managing chronic conditions. The use of the payment-for-outcome approach in prescription medication can also encourage pharmacists and clinicians to improve on quality, rather than quantity, of services. Careful monitoring of healthcare costs and outcomes must be implemented for early identification of negative trends and prompt institution of mitigation measures.

This study has several strengths. First, MEPS's careful design and execution involved multilevel verification of information collected from participants.[36] Second, the oversampling of minority race/ethnicity such as Hispanic and black make results generalizable to all races in the United States. Third, the large sample size allowed us to adequately characterize persons with ASCVD by MRFs and yet have enough participants to estimate marginal expenditures associated with MRFs. The results of our study, however, must be interpreted in the context of the following limitations. First, we were limited to the 3-digit ICD-9-CM code used to map medical conditions, which means our observed prevalence of ASCVD may be underestimated. Second, because cardiovascular MRFs were self-reported, the true national prevalence is likely underestimated.[37] Third, the use of the Multum Lexicon drug classification system, although apt for drug classification, may overestimate expenditures for CVD medications because some CVD medications may have non-CVD uses. Fourth, MEPS does not account for over-the-counter prescription expenditures, and this may also underestimate the average pharmaceutical expenditures. Fifth, MEPS was conducted among noninstitutionalized US civilians, and thus our results are nonrepresentative of the entire US population. Finally, although we comprehensively controlled for variables chosen based on existing knowledge of factors associated with higher pharmaceutical expenditures and scientific selection of statistical models using Akaike's criteria, there may be unobserved characteristics that affect the outcomes studied, causing residual confounding; factors such as health insurance, clinicians, pharmacists, healthcare organization, drug companies, and even patient behaviors are important determinants of pharmaceutical expenditures that could not be assessed in this study.

Conclusion

Some individual MRFs and worsening MRF profiles among persons with established ASCVD are associated with a higher annual pharmaceutical expenditure. Future studies are needed to demonstrate whether patient-centered pragmatic approaches to manage and prevent MRFs will curtail the rising pharmaceutical expenditures (on all medications and CVD-specific medications) among those with ASCVD.

Disclosures

Dr Nasir is on the Advisory Board for Quest Diagnostic, and he is a consultant for Regeneron. There is no other potential conflict of interest relevant to this study.

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SUPPLEMENTAL MATERIAL

Table S1. ICD-9 CM codes of diseases classified as ASCVD, and Multum Lexicon Drug Codes for CVD, Diabetic, and other Major Medication Classes

PANEL A		PANEL B	
ICD-9-CM Code	**Disease description**	**Multum Lexicon Drug Code (s)**	**Drug description**
410	Acute myocardial infarction	**CVD Medications**	
413	Angina pectoris	41-44, 47-49, 53, 55, 56	Anti-hypertensive agents
414	Other forms of chronic ischemic heart disease:	46	Anti-arrhythmic agents
414	Coronary atherosclerosis	45	Anti-angina agents
414.1	Aneurysm and dissection of heart	19	Antihyperlipidemic agents
414.2	Chronic total occlusion of coronary artery	81	Coagulation modifiers
414.3	Coronary atherosclerosis due to lipid rich plaque	40†	Other CVD Medications
414.4	Coronary atherosclerosis due to calcified coronary lesion	**Non-CVD Medications**	**Non-CVD Medications**
414.8	Other specified forms of chronic ischemic heart disease	99	Antidiabetic drugs
414.9	Chronic ischemic heart disease, unspecified	242	Psychotherapeutic drugs
433	Pre-cerebral occlusion	57	Central Nervous System drugs
434	Cerebral artery occlusion	122	Respiratory System drugs
435	Transient cerebral ischemia	87	Gastrointestinal System drugs
436	Cerebrovascular accident	254	Immunologic drugs
437	Other cerebrovascular disease	20	Anti-Neoplastic drugs
440	Atherosclerosis	1	Anti-infective drugs
443	Other peripheral vascular diseases:	192, 194, 270	Rheumatologic drugs
447	Other arterial diseases	98, 100, 103, 217, 295	Hormones and endocrine drugs (excluding anti-diabetic drugs)
447	Other arterial diseases		

Abbreviations: ASCVD, Atherosclerotic Cardiovascular Diseases; CVD, Cardiovascular Disease; ICD-CM, International Classification of Diseases, 9th Revision, Clinical Modification; ACE, Angiotensin Converting Enzymes

†Excluding the antihypertensive, anti-arrhythmic, and anti-angina drugs.

Table S2. Charlson Comorbidity Index (CCI) Scoring System

Score	Condition
1	Myocardial Infarction **
	Congestive heart failure
	Peripheral vascular disease **
	Cerebrovascular disease **
	Chorionic pulmonary disease
	Dementia
	Connective tissue disease
	Peptic ulcer disease
	Mild liver disease (without portal hypertension)
	Diabetes (without end-organ damage) **
2	Diabetes (with end-organ damage) **
	Hemiplegia
	Renal disease (moderate or severe)
	Tumor (without metastasis)
	Leukemia (acute or chronic)
	Lymphoma
3	Liver illness (moderate or severe)
6	Tumor, with metastasis
	AIDS

** Diseases excluded from our modified CCI

Table S3. Socio Demographic Characteristics of Adults Aged 40 years and Older living with ASCVD, MEPS 2012-2013

	No. of Survey Participants	US Population Equivalent (Million)	Proportion (%)
Overall	**4,248**	**21.9**	**100.00%**
Age group (yrs)			
40-64	1,647	8.5	38.8%
65-79	1,203	6.2	28.3%
>=80	1,398	7.2	32.9%
Sex			
Men	2,345	12.1	55.2%
Women	1,903	9.8	44.8%
Race/ethnicity			
Non-Hispanic White	3,191	16.4	75.1%
Non-Hispanic Black	485	2.5	11.4%
Asian	107	0.5	2.5%
Hispanic	375	1.9	8.8%
Other	90	0.5	2.1%
Family income level*			
<100%	646	3.3	15.2%
100-200%	1,027	5.3	24.2%
200-400%	1,185	6.1	27.9%
>400%	1,390	7.2	32.7%
GCCI			
0	2,866	14.8	67.5%
1	867	4.5	20.4%
2	515	2.7	12.1%

Abbreviations: Atherosclerotic Cardiovascular Diseases; MEPS, Medical Expenditure Panel Survey; GCCI, Grouped Charlson Comorbidity Index

* Family Income expressed as a proportion of the Federal Poverty Level

Table S4. Prevalence of Modifiable Risk Factor Profile Across Socio-demographic characteristics of Adults Aged ≥40 years living with ASCVD , MEPS 2012-2013

		Prevalence % (95% CI)			
	No. of Survey Participants	**Optimal MRF [0-1 MRF]**	**Average MRF [2-3 MRFs]**	**Poor MRF [≥4 MRFs]**	***P value†***
Overall	**4,248**	**10.4 (9.0-11.8)**	**49.9 (47.7-52.2)**	**39.7 (37.5-42.0)**	
Age group (Yrs)					
40-64	1,647	11.7 (9.7-14.0)	45.0 (42.0-48.0)	43.3 (40.2-46.5)	
65-79	1,203	9.1 (6.7-12.1)	48.3 (44.5-52.1)	42.7 (38.9-46.5)	**0.0002**
>=80	1,398	9.9 (7.5-13.0)	57.2 (52.8-61.5)	32.9 (28.7-37.3)	
Sex					
Men	2,345	9.4 (7.7-11.5)	50.8 (47.8-53.7)	39.8 (36.8-42.9)	0.8542
Women	1,903	11.5 (9.4-13.9)	48.9 (45.8-52.0)	39.6 (36.6-42.7)	
Race/ethnicity					
Non-Hispanic White	3,191	11.0 (9.4-12.9)	51.3 (48.5-54.0)	37.7 (35.1-40.3)	
Non-Hispanic Black	485	6.6 (4.9-8.7)	45.6 (41.4-49.8)	47.9 (43.5-52.2)	
Asian	107	13.0 (8.1-20.3)	57.8 (47.5-67.5)	29.2 (21.0-38.9)	**<0.001**
Hispanic	375	9.4 (7.2-12.2)	45.7 (40.9-50.5)	44.9 (40.2-49.7)	
Other	90	7.4 (2.5-20.0)	33.4 (21.6-47.9)	59.2 (45.6-71.5)	
Family income level*					
<100%	646	8.2 (5.9-11.3)	44.1 (39.2-49.1)	47.7 (42.9-52.6)	
100-200%	1,027	8.0 (6.0-10.6)	50.5 (46.6-54.5)	41.4 (37.8-45.2)	**<0.001**
200-400%	1,185	9.2 (6.9-12.1)	50.4 (45.7-55.1)	40.4 (36.1-44.9)	
>400%	1,390	14.1 (11.5-17.2)	51.8 (47.8-55.8)	34.1 (30.1-38.3)	
GCCI					
0	2,866	12.1 (10.5-13.9)	52.4 (49.9-54.8)	35.6 (33.0-38.2)	
1	867	9.0 (6.0-13.4)	42.7 (38.1-47.4)	48.3 (44.152.5)	**<0.001**
2	515	3.1 (1.6-5.7)	48.6 (42.4-54.9)	48.3 (41.8-54.8)	

Abbreviations: ASCVD, Atherosclerotic cardiovascular Disease; MEPS, Medical Expenditure Panel Survey; CI, Confidence Interval; GCCI, Grouped Charlson Comorbidity Index

* Family Income expressed as a proportion of the Federal Poverty Level

† χ^2 Statistic used to test difference in proportions between respondents

Figure S1. Flow Chart Showing the Study Population Selection, MEPS 2012-2013

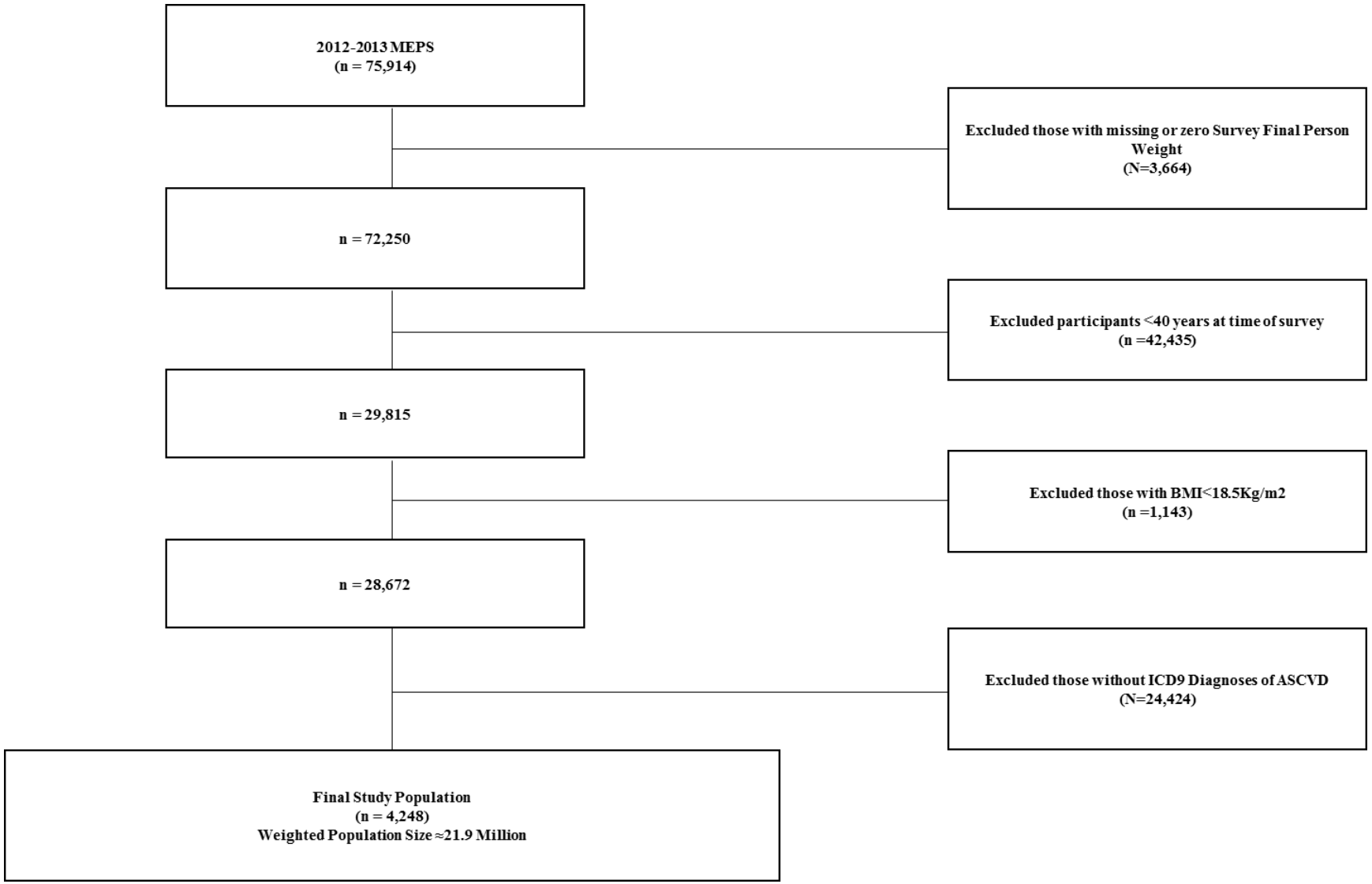
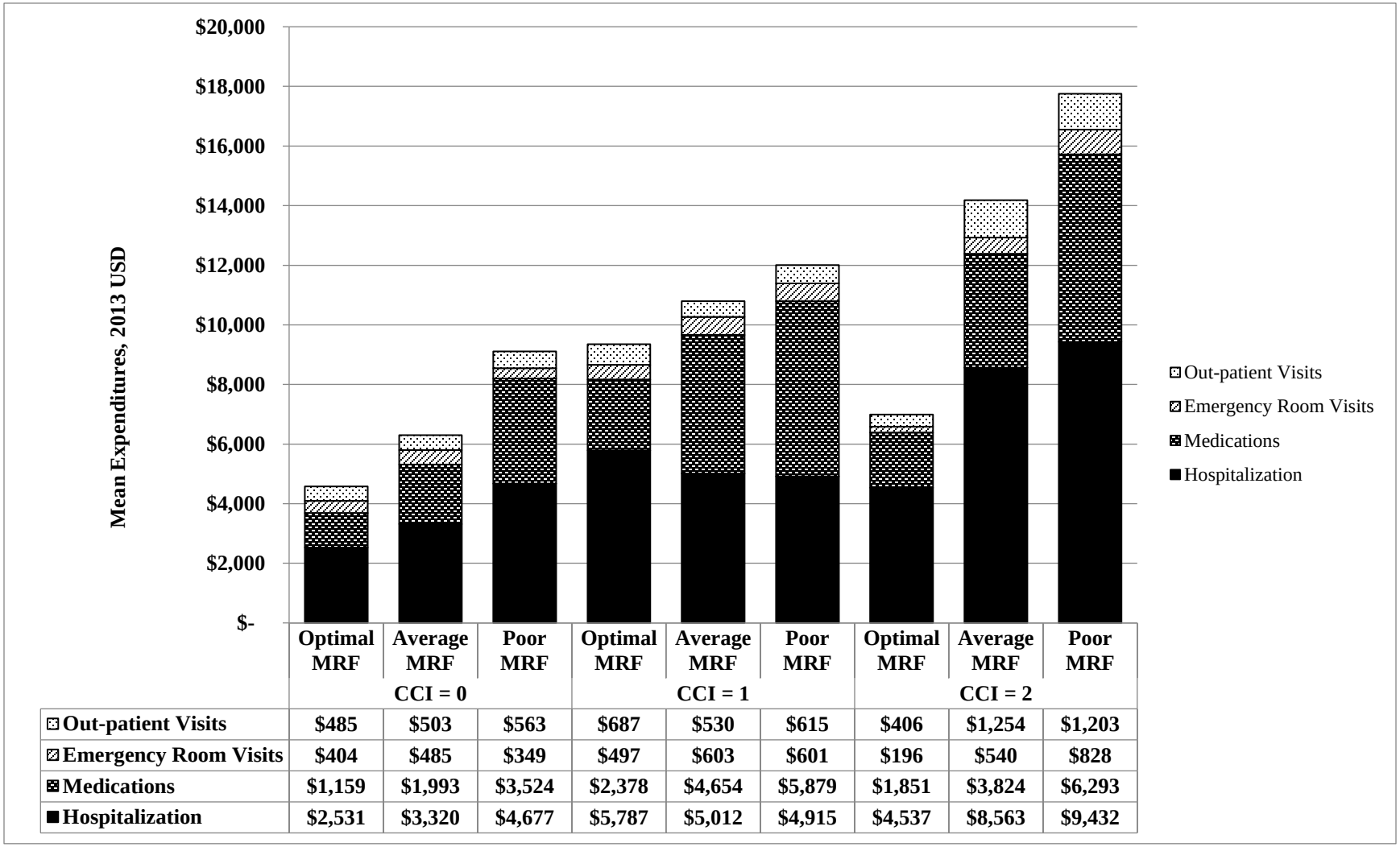


Figure S2. Mean Healthcare Expenditure Across MRF Profile and Charlson Comorbidity Index



	Optimal MRF	Average MRF	Poor MRF	Optimal MRF	Average MRF	Poor MRF	Optimal MRF	Average MRF	Poor MRF
	CCI = 0			CCI = 1			CCI = 2		
Out-patient Visits	$485	$503	$563	$687	$530	$615	$406	$1,254	$1,203
Emergency Room Visits	$404	$485	$349	$497	$603	$601	$196	$540	$828
Medications	$1,159	$1,993	$3,524	$2,378	$4,654	$5,879	$1,851	$3,824	$6,293
Hospitalization	$2,531	$3,320	$4,677	$5,787	$5,012	$4,915	$4,537	$8,563	$9,432

Association Between Modifiable Risk Factors and Pharmaceutical Expenditures Among Adults With Atherosclerotic Cardiovascular Disease in the United States: 2012–2013 Medical Expenditures Panel Survey

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