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Income and antiplatelet adherence following percutaneous coronary intervention

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ABSTRACT

Objective: To investigate the relation of annual household income to antiplatelet adherence following PCI.

Background: Treatment with 6–12 months of dual antiplatelet therapy (DAPT) following percutaneous coronary intervention (PCI) is a Class I recommendation. Adherence to these medications is essential to reduce risk of stent thrombosis and recurrent ischemic events. Social risk factors like household income modify how patients access and adhere to essential pharmacologic therapies such as antiplatelet agents.

Methods: We identified individuals presenting with PCI in an administrative claims database of commercially insured and Medicare Advantage beneficiaries from 2017 to 2019. We collected data on age, sex, race, ethnicity, educational attainment, and covariates (prevalent coronary disease, medications, healthcare visits, insurance type, copay, antiplatelet medications, and Elixhauser Comorbidity Index conditions). We related annual household income, categorized as <\$40,000; \$40–49,999; \$50–59,999; \$60–74,999; \$75–99,999; and ≥\$100 K, to proportion of days covered (PDC) in multivariable-adjusted regression models. We defined non-adherence as PDC <80%.

Results: Our dataset included 90,163 individuals (age 69.0 ± 10.9 years, 33.1% women, 25.1% non-White race) who underwent PCI. We observed graded, decreased antiplatelet adherence across income categories: rates of PDC ≥80% decreased with successively lower income. Individuals with annual income <\$40,000 had 1.5-fold higher odds of non-adherence (95% CI, 1.40–1.56) compared to those with income ≥\$100,000 after multivariable adjustment.

Conclusions: In a claims-based analysis, we determined that lower income is associated with decreased likelihood of adherence to antiplatelet agents following PCI. Our results indicate the importance of considering social risk factors in the evaluation of barriers to antiplatelet adherence following PCI.

1. Introduction

Despite medical advances in percutaneous coronary intervention (PCI) and effective medications, coronary artery disease remains a leading cause of mortality [1]. Dual antiplatelet therapy (DAPT), referring specifically to the combination of aspirin and P2Y12 receptor inhibitor, is critically important for secondary prevention of myocardial infarction (MI) as well as major adverse cardiac events following stent implantation. Professional society guidelines give a Class I recommendation for at least 12 months of antiplatelet therapy following drug-eluting stent (DES) implantation for acute coronary syndrome and at least 6 months for stable ischemic heart disease [2]. Adherence with DAPT is crucial to improving cardiovascular outcomes following

coronary intervention [3].

Social resources are relevant to treatment of cardiovascular disease given their potential to affect access to medications and adherence. The World Health Organization includes social/economic factors as one of five dimensions that influence medication non-adherence, specifically noting that non-adherence should be viewed as a multi-dimensional issue rather than determined by individual choice [4]. Non-adherence to medications has been well documented in a myriad of chronic medical conditions including cardiovascular disease [5,6]. Even after acute MI, rates of adherence to key medications have been reported as only 66–78% within the subsequent 3 months [7–9]. Low income specifically has been associated with medication non-adherence in adults with chronic diseases [10–12]. Recognizing the health and economic implication of medication nonadherence in cardiovascular disease, the

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Abbreviations list

DAPT =	Dual antiplatelet therapy
PCI =	Percutaneous coronary intervention
PDC =	Proportion of days covered
MI =	Myocardial infarction
DES =	Drug eluting stent
Optum =	Optum© Clinformatics® Data Mart
ICD-9 =	International Classification of Diseases, Ninth and Tenth Revision, Clinical Modification
CPT-4 =	Current Procedural Terminology, Version 4
ANOVA =	analysis of variance

American Heart Association released a statement that identified barriers to medication adherence, which included socio-economic factors, and called for policy and structural changes [13]. Understanding social factors associated with antiplatelet nonadherence after PCI is complex yet fundamental for optimal care of patients and necessary for effective policy and structural change.

Using a large database of de-identified health and pharmacy claims, we investigated the relation of household income to antiplatelet adherence in individuals with who underwent PCI. Our primary hypothesis was that lower income would be associated with decreased adherence to antiplatelet agents compared to individuals with higher annual household income.

2. Methods

2.1. Cohort selection

Optum© Clinformatics® Data Mart (Optum) is a de-identified U.S. administrative claims database that comprises inpatient, outpatient, emergency department, laboratory, and pharmacy health data as well as socioeconomic and geographic data longitudinally linked at the patient level. The database includes information from over 62 million commercial insurance and Medicare Advantage enrollees across the U.S. Medical claims include International Classification of Diseases, Ninth and Tenth Revision, Clinical Modification (ICD-9-CM) diagnosis codes; ICD-9 procedure codes; Current Procedural Terminology, Version 4 (CPT-4) procedure codes; Healthcare Common Procedure Coding System procedure codes; and site of service codes [14]. Given the de-identified nature of the data, the University of Pittsburgh Institutional Review Board determined this analysis did not meet the definition of protected human subjects' research.

In conducting this retrospective analysis, we selected individuals who underwent PCI during the period of January 1, 2017 to December 31, 2019. PCI was defined by CPT codes (Supplementary Table 1). Exclusion criteria included individuals with age <18 years; unknown race, sex, or income; < 30 days of enrollment after PCI; and/or lack of antiplatelet medication claim data following PCI.

2.2. Household income

Annual household income was derived from AmeriLINK Consumer Marketing Database as explicated previously [15]. Income data are collected by monthly survey from a representative cross section of the U. S. population of more than 30,000 households. Variables encompassed in the service include a highly specific geographic locator (ZIP+4), Internal Revenue Service data, address-level home value, aggregated credit, and short-term loans. To ensure validity, derived estimates of household income are compared to self-reported income collected by surveys [16]. Optum categorizes household income as <\$40,000, \$40–49,999, \$50–59,999, \$60–74,999, \$75–99,999, and ≥\$100,000.

3. Outcome ascertainment

We assessed antiplatelet adherence using proportion of days covered (PDC), a widely used validated algorithm, from index claim date following PCI until disenrollment or up to 12 months [17]. Antiplatelets were identified by the presence of a pharmacy claim corresponding to either brand or generic name ([Brilinta, Effient, Plavix] or [ticagrelor, prasugrel, clopidogrel]). Adherence was then categorized as either adherent (PDC ≥80%) or non-adherent (<80%).

3.1. Covariates

Optum includes individual-level data for age, sex, race, and ethnicity. Race and ethnicity data are determined from a combination of public records (e.g., driver's license) in approximately 30% of individuals and use of validated algorithms that incorporates first and last names and data from the U.S. Census and ZIP codes [18]. Race and ethnicity are categorized as White, Black, Asian, or Hispanic. The median years of schooling for adults ≥25 years was categorized at the ZIP+4 level from data provided by AmeriLink. Education level was then categorized as less than high school diploma, high school diploma, less than bachelor degree, bachelor degree or higher, or unknown. Additional covariates were selected based their inclusion in the Elixhauser Comorbidity Index [19]. The full list of constituent variables and their determination by administrative coding are summarized in Supplementary Table 1. Clinical covariates were defined by ICD-9-CM or ICD-10-CM codes in inpatient or outpatient claims prior to or at time of PCI. Other related covariates including ≥5 prescription medications, number of outpatient visits with cardiologist in 6 months following PCI, antiplatelet copay, insurance type, and antiplatelet type were additionally selected for their potential contributions to medication adherence.

3.2. Statistical analysis

We compared cohort characteristics across income categories using one-way analysis of variance (ANOVA) or Wilcoxon rank-sum tests for continuous variables and Pearson's chi-square tests for categorical variables. We examined associations of income with antiplatelet adherence in multivariable-adjusted logistic regression models that determined odds ratios of non-adherence (PDC <80%) by income category compared to annual household income ≥\$100,000. We further assessed effect modification of the association of income on adherence by prevalent coronary artery disease. As a sensitivity analysis, we excluded individuals with prevalent coronary artery disease defined as prior MI, PCI, or CABG to investigate for differences in risk by income level. All analyses were adjusted initially for age, sex, and race (model 1); then for age, sex, race, all relevant Elixhauser covariates, and prior MI, PCI, or CABG (model 2); and then adjusted for all covariates in model 2, plus educational attainment, insurance type, follow-up visits with cardiology, polypharmacy, copay, and antiplatelet type (model 3). All statistical analyses were performed using SAS® software for Windows, version 9.4 (Copyright © 2020 SAS Institute Inc., Cary, NC, USA).

4. Results

Following exclusions, we identified 90,163 individuals who underwent PCI eligible for our cohort as summarized in Fig. 1. Our cohort included individuals with mean age 69.0 ± 10.9 years; 33.1% women; majority white race (74.9%) with 9994 (11.1%) Black, 9786 (10.9%) Hispanic, and 2896 (3.2%) Asian individuals, as summarized in Table 1. A greater proportion of individuals of Black (54.8%) and Hispanic (36.2%) race belonged to the lowest income category compared to white (28.1%) or Asian (18.7%). Individuals in the lowest income category were more likely to be prescribed ≥5 different medications (80.6%), have higher median number of Elixhauser comorbidities (7), and have

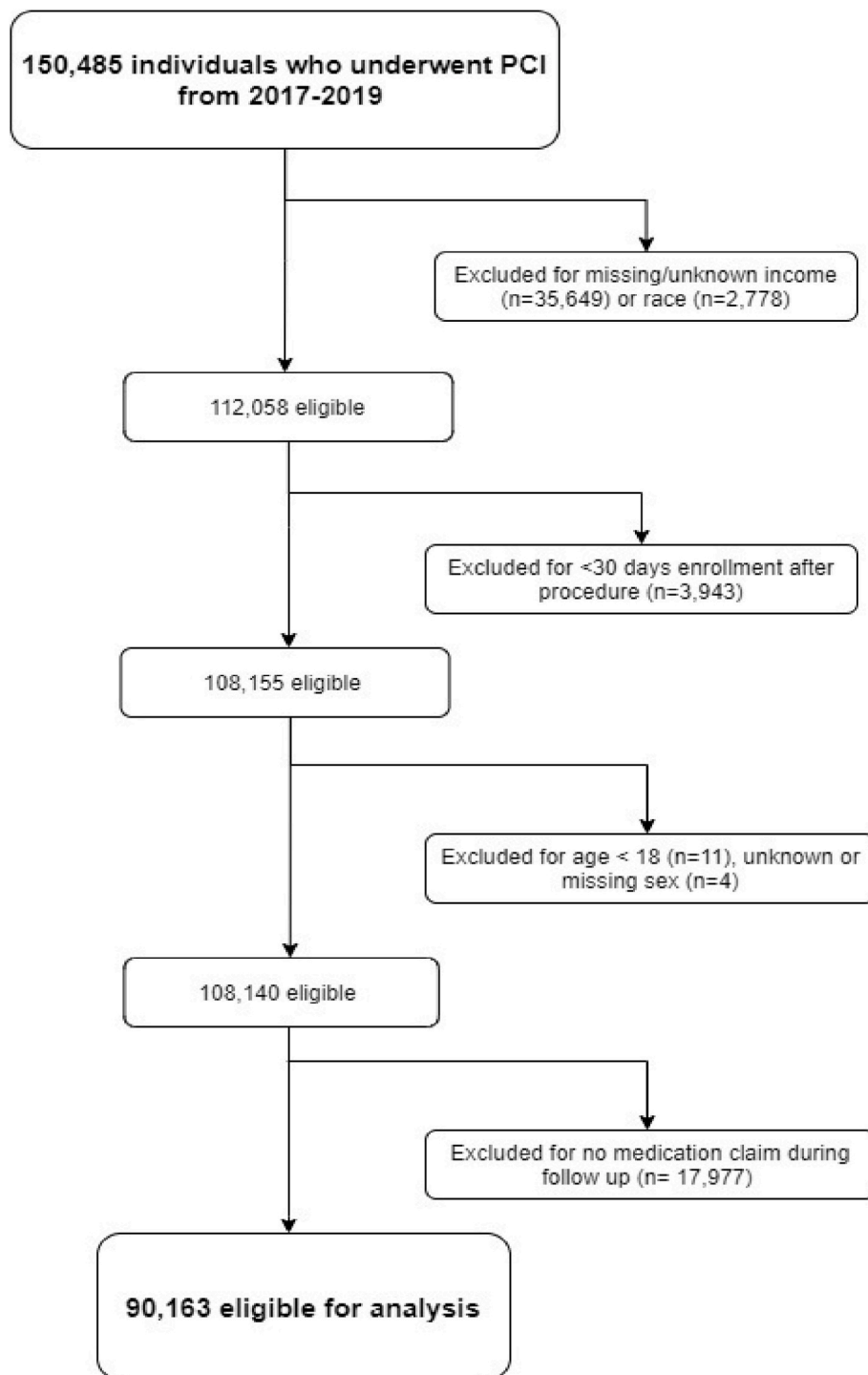


Fig. 1. Flow Chart of Cohort Selection. Fig. 1 is a flow chart of cohort selection. We identified 150,485 individuals who underwent percutaneous coronary intervention from January 1, 2017–December 31, 2019. Individuals were excluded for missing or unknown income, less than 30 days of enrollment following the procedure, age <18, missing or unknown sex, or lack of medication claim during follow-up. After exclusions, 90,163 individuals were eligible for analysis and included in our cohort.

Medicare insurance (81.7%) compared to individuals in the highest income category (66.2%, 5, 51.3%) respectively. Median copay per 30 days was lowest at \$5.80 in the lowest income category and highest at \$8.14 in the highest income category. Healthcare utilization as measured by number of cardiology visits in the six months following PCI was similar across income categories with median number of 3, and enrollment time (25th, 75th percentile) following PCI was 20 (11,31) months for the cohort and did not differ substantially across income categories.

We observed a graded decrease in proportion of days covered with decreasing income as represented by kernel density plot (Fig. 2). Table 2 provides a summary of PDC range across income categories by

antiplatelet type. In the full cohort, 97% of days were covered with P2Y12 antiplatelet agent pharmacy fills (median PDC of 97%). We noted progressive decrease in 1st quartile PDC across income categories with PDC 84% in the highest income category ($\geq \$100,000$) and PDC of 77% in the lowest income category ($< \$40,000$). Antiplatelet type did not significantly impact PDC across income categories with 97% of days covered with clopidogrel, 97% days covered with prasugrel, and 96% of days covered with ticagrelor. PDC decreased with decreasing income level for each antiplatelet medication while overall PDC of our cohort did not differ in a clinically meaningful way between the antiplatelet medications. Table 3 summarizes the odds ratio of adherence as defined by $PDC \geq 80\%$ among those who had PCI with a subsequent antiplatelet

Table 1
Characteristics of percutaneous coronary intervention cohort, 2017–2019.

Household income	<\$40,000	\$40- <\$49,999	\$50- <\$59,999	\$60- <\$74,999	\$75- <\$99,999	≥\$100,000	p-values
Age, mean (SD)	69.7 (10.9)	69.7 (10.8)	70.3 (10.5)	70 (10.6)	69 (10.8)	66.5 (11.1)	<0.0001 ^a
Gender							
Female, n (%)	13,268 (46.5%)	2820 (35.2%)	2859 (33.3%)	3151 (29.5%)	3891 (26.9%)	3879 (19.5%)	<0.0001 ^b
Male, n (%)	15,268 (53.5%)	5195 (64.8%)	5724 (66.7%)	7527 (70.5%)	10,561 (73.1%)	16,020 (80.5%)	
Race							
Asian, n (%)	541 (1.9%)	197 (2.5%)	207 (2.4%)	347 (3.3%)	548 (3.8%)	1056 (5.3%)	<0.0001 ^b
Black, n (%)	5482 (19.2%)	1026 (12.8%)	988 (11.5%)	932 (8.7%)	854 (5.9%)	712 (3.6%)	
Hispanic, n (%)	3550 (12.4%)	1124 (14%)	1128 (13.1%)	1212 (11.4%)	1357 (9.4%)	1415 (7.1%)	
White, n (%)	18,963 (66.5%)	5668 (70.7%)	6260 (72.9%)	8187 (76.7%)	11,693 (80.9%)	16,716 (84%)	
Education level							
<12th grade, n (%)	251 (0.9%)	69 (0.9%)	41 (0.5%)	33 (0.3%)	23 (0.2%)	1 (0%)	<0.0001 ^b
Highschool Diploma, n (%)	15,785 (55.3%)	3733 (46.6%)	3589 (41.8%)	3324 (31.1%)	2877 (19.9%)	1324 (6.7%)	
<Bachelor Degree, n (%)	11,672 (40.9%)	3931 (49.1%)	4585 (53.4%)	6546 (61.3%)	9959 (68.9%)	11,694 (58.8%)	
Bachelor Degree +, n (%)	794 (2.8%)	269 (3.4%)	356 (4.2%)	763 (7.2%)	1588 (11%)	6870 (34.5%)	
Medication use							
≥5 medications, n (%)	23,006 (80.6%)	6155 (76.8%)	6610 (77%)	7954 (74.5%)	10,472 (72.5%)	13,180 (66.2%)	<0.0001 ^b
Copay per 30 days, in dollars, median (Q1, Q3)	5.8 (1.6,10.8)	7.0 (2.5, 12.5)	7.6 (2.92, 15)	7.9 (3.3, 17.3)	8 (3.3, 22.5)	8.1 (3.3, 26.7)	<0.0001 ^c
Clopidogrel, n (%)	18,945 (66.4%)	5249 (65.5%)	5538 (64.5%)	6832 (64%)	8783 (60.8%)	11,068 (55.6%)	<0.0001 ^c
Prasugrel, n (%)	1724 (6%)	520 (6.5%)	520 (6.1%)	735 (6.9%)	1122 (7.8%)	1935 (9.7%)	
Ticagrelor, n (%)	7823 (27.4%)	2238 (27.9%)	2516 (29.3%)	3096 (29%)	4533 (31.4%)	6869 (34.5%)	
Health care utilization							
Number of cardiology visits, median (Q1, Q3)	3 (2, 6)	3 (2, 6)	3 (2, 6)	3 (2, 6)	3 (2, 6)	3 (2, 6)	0.03 ^c
Number of Elixhauser comorbidities, median (Q1, 3)	7 (5, 11)	7 (4, 10)	7 (4, 10)	6 (4, 9)	6 (3, 9)	5 (3, 8)	<0.0001 ^c
AMI>30 days prior to PCI, n (%)	3363 (11.79%)	917 (11.44%)	928 (10.81%)	1099 (10.29%)	1315 (9.1%)	1586 (7.97%)	<0.0001 ^b
Prior CABG, n (%)	1173 (4.11%)	319 (3.98%)	370 (4.31%)	460 (4.31%)	583 (4.03%)	737 (3.7%)	0.080 ^b
Prior PCI, n (%)	6519 (22.84%)	1789 (22.32%)	1998 (23.28%)	2447 (22.92%)	3118 (21.57%)	4269 (21.45%)	0.0003 ^b
Enrollment and insurance							
Insurance type = Medicare, n (%)	23,307 (81.7%)	6176 (77.1%)	6628 (77.2%)	7745 (72.5%)	9574 (66.3%)	10,199 (51.3%)	<0.0001 ^b
Enrollment time, in months, following procedure, median (Q1, Q3)	19 (11, 30)	20 (11, 31)	20 (12, 31)	20 (12, 31)	20 (12, 30)	20 (12, 30)	<0.0001 ^c

^a Based on ANOVA.

^b Based on chi square test.

^c Based on Wilcoxon rank-sum test.

claim. Individuals with lower incomes had significantly higher odds of non-adherence compared to the highest income group adjusted for age, sex, and race (model 1). Individuals with income <\$40,000 had 1.5-fold higher odds adjusting for covariates as described in model 3 (95% CI, 1.40–1.56); \$40–49,999, 1.4-fold higher odds (95% CI, 1.33–1.52); \$50–59,999, 1.3-fold higher odds (95% CI, 1.17–1.34); \$60–74,999, 1.2-fold higher odds (95% CI, 1.10–1.24); and \$75–99,999, 1.1-fold higher odds (95% CI, 1.08–1.21) of non-adherence compared to those with income ≥\$100,000.

Excluding individuals with prevalent coronary artery disease, individuals with lower income were still more likely to be classified as non-adherent based on sensitivity analysis (Supplementary Table 2).

5. Discussion

In a large socially and geographically diverse health claims database, we observed associations between household income and antiplatelet adherence in individuals with who underwent PCI. Specifically, we observed an inverse relation between household income and likelihood of antiplatelet adherence. The association of lower household income with decreased odds of antiplatelet adherence remained significant even after multivariable adjustment and did not vary significantly by antiplatelet medication prescribed.

Non-adherence to medical therapy is pervasive across a myriad of

chronic diseases and has been associated with increased mortality in cardiovascular disease [20]. A Canadian cohort study of patients with coronary disease following intervention found that antiplatelet medications were commonly unfilled within 120 days with 44.3% of aspirin prescriptions unfilled and 69.9% of non-aspirin antiplatelet prescriptions unfilled [8]. In a prospective trial studying the use of aspirin and mortality after acute MI, medication therapy discontinuation was common and discontinuation at one month was independently associated with lower one year survival compared to individuals who continued to take aspirin (91% vs 97%) [7]. A subsequent study of the cohort found that among patients who had DES implanted, 1 in 7 patients were no longer taking DAPT by 30 days, which was associated with increased mortality for the next 11 months (7.5% vs 0.7%, $p < 0.001$) [21]. In addition to increasing risk of mortality, medication nonadherence negatively contributes to higher utilization of health services and increased medical costs [10,22].

Socioeconomic status is relevant to health as it has been associated with diminished access to preventative care, specialty care, prescription medications and has been associated with poorer clinical outcomes [23–26]. The inverse association of income in particular with cardiovascular disease and mortality has been well established [27–29]. Prior studies have demonstrated that social risk factors are also relevant to cardiovascular medication adherence with minority race/ethnicity, lower educational attainment, low health literacy, low income, and

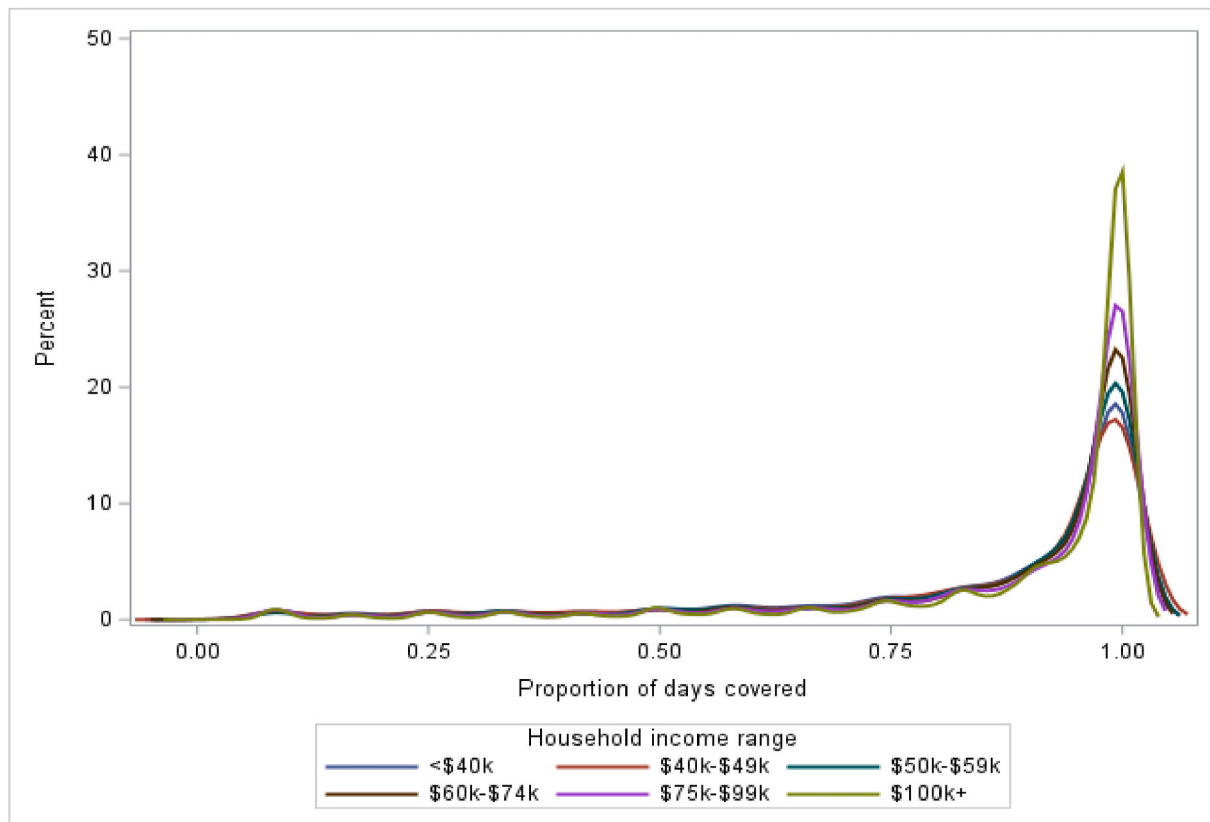


Fig. 2. Kernel Density Plot of Proportion of Days covered by Income in Cohort with Percutaneous Coronary Intervention. Fig. 2 is a kernel density plot of proportion of days covered with P2Y12 antiplatelet medication by income. Household income was categorized as <\$40,000, \$40–49,999, \$50–59,999, \$60–74,999, \$75–99,999, and ≥\$100,000. We assessed antiplatelet adherence using proportion of days covered from date of PCI until disenrollment or up to 12 months. We observed a graded decrease in proportion of days covered with decreasing income.

Table 2
Proportion of days covered across income categories by medication in cohort with percutaneous coronary intervention, 2017–2019.

Household Income	<\$40 k (n = 28,536)	\$40 k- <\$50 k (n = 8015)	\$50 k- <\$60 k (n = 8583)	\$60 k- <\$75 k (n = 10,678)	\$75 k- <\$100 k (n = 14,452)
PDC, median (Q1, Q3)/ Medication =	0.95 (0.78, 1.00)	0.96 (0.81, 1.00)	0.97 (0.82, 1.00)	0.97 (0.83, 1.00)	0.98 (0.85, 1.00)
Clpidogrel					
PDC, median (Q1, Q3)/ Medication =	0.94 (0.76, 1.00)	0.96 (0.79, 1.00)	0.96 (0.8, 1.00)	0.98 (0.87, 1.00)	0.98 (0.84, 1.00)
Prasugrel					
PDC, median (Q1, Q3)/ Medication =	0.93 (0.75, 1.00)	0.93 (0.76, 1.00)	0.95 (0.81, 1.00)	0.96 (0.83, 1.00)	0.97 (0.84, 1.00)
Ticagrelor					
Full cohort, median (Q1, Q3)	0.95 (0.77, 1.00)	0.96 (0.79, 1.00)	0.96 (0.82, 1.00)	0.97 (0.83, 1.00)	0.98 (0.84, 1.00)

unmarried status all associated with reduced adherence [7–11]. In contrast, there has been limited study with mixed results of the relation between income and medication adherence after PCI. In both Vietnamese and Israeli cohorts, low income was associated with decreased adherence to antiplatelet therapy after PCI [30,31]. In contrast a U.S. cohort study of non-white patients who underwent PCI demonstrated that income did not predict adherence to antiplatelet medications [32]. Our study now contributes further data on the relevance of income towards antiplatelet adherence in patients following PCI.

Table 3
Odds Ratios of Antiplatelet Adherence (≥80%) with Percutaneous Coronary Intervention cohort, 2017–2019.

Household income	Model 1 ^a		Model 2 ^b		Model 3 ^c	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
<\$40k	1.66 (1.59, 1.74)	<.0001	1.50 (1.43, 1.57)	<.0001	1.48 (1.40, 1.56)	<.0001
\$40k-<\$50k	1.56 (1.46, 1.66)	<.0001	1.45 (1.36, 1.54)	<.0001	1.432 (1.33, 1.52)	<.0001
\$50k-<\$60k	1.36 (1.28, 1.45)	<.0001	1.28 (1.20, 1.36)	<.0001	1.25 (1.17, 1.34)	<.0001
\$60k-<\$75k	1.25 (1.18, 1.33)	<.0001	1.19 (1.12, 1.26)	<.0001	1.17 (1.10, 1.24)	<.0001
\$75k-<\$100k	1.19 (1.13, 1.26)	<.0001	1.15 (1.09, 1.22)	<.0001	1.14 (1.08, 1.21)	<.0001
\$100k+	Referent		Referent		Referent	

^a Model 1 – adjusted for age, sex, race.

^b Model 2 – adjusted for age sex, race, Elixhauser covariates, prior MI, PCI, or CABG.

^c Model 3 – adjusted for adjusted for age sex, race, Elixhauser covariates, prior MI, PCI, or CABG, educational attainment, insurance type, follow-up visits with cardiologist, polypharmacy, co-pay, and antiplatelet type.

Antiplatelet therapy is standard of care after PCI and recognizing risk factors and barriers to antiplatelet adherence is vital to providence quality care to patients. Our analysis highlights the substantive contribution of income to antiplatelet adherence. Our findings support further investigation of practical implication of using income in the clinical setting with the goal of identifying and intervening on high-risk patient populations. The National Academy of Medicine has recommended incorporation of social and behavioral determinants into the electronic medical record due to their recognized contribution to the onset, progressive, and effective treatment of disease states [33]. With inclusion in the medical record, identification of patients at high risk for low adherence may become more feasible. Once risk for decreased adherence is recognized, the challenge is to intervene efficiently and effectively. There have been several programs associated with improved antiplatelet adherence following PCI including enrollment in Medicare Part D low-income subsidy program, phone-based motivation interviewing, providing discharge medication instructions and counseling, pharmacy led interventions, and referral to cardiac rehab [8,34–36]. Incorporation of social risk factors such as income in the electronic health record paired with by structured implementation of previously recognized successful interventions, may be a means of improving antiplatelet adherence following PCI.

Our analysis had several strengths, most significantly the availability of nationwide health claims data of over 90,000 patients who had PCI. The inclusion of both private and Medicare advantage plans and geographic diversity supports the generalizability of our analysis to the U.S. population. We would also like to summarize the important limitations in our study. First, capturing health claims data was dependent on insured status, therefore our results are not generalizable to the uninsured population or those without pharmacy coverage. Second, misclassification of pharmacy claims data may occur including users misclassified as non-users when patients pay for prescription medications out of pocket (\$4 generics, receives samples, or hospitalized) or non-users misclassified as users when prescriptions are filled but never taken [37]. Third, misclassification by diagnostic coding may occur. However, we would consider such misclassification to be non-differential with respect to antiplatelet adherence and hence would bias our results towards the null. Further, we do not expect systematic misclassification and expect our large-sized sample to the diminish the effect of any potential misclassification. Fourth, our categorization of income is limited; measurement of income is complex and may be adjusted by non-cash benefits and family size as well as broadened to include wealth and assets [38]. Fifth, income was not ascertained directly from family individual income, rather ascertained using the ZIP+4, which is a precise geographic locator but may lead to inaccuracies. Sixth, type of stent and indication for PCI was not defined, which may modify recommended duration of P2Y12 inhibitor therapy. Seventh, we are unable to determine whether patients had a clinical reason for which antiplatelet therapy with P2Y12 inhibitor was discontinued by a clinician.

6. Conclusion

In conclusion, in a retrospective analysis of a large U.S. health claims database, we observed a significant association between household income and antiplatelet adherence in individuals who underwent PCI. Our results underscore the relevance of household income as a social risk factor for antiplatelet adherence in patients with coronary artery disease. Further study must now address how to successfully incorporate social risk factors such as income into the electronic health record and implement effective interventions to increase adherence and mitigate adverse events in socially disadvantaged patient populations.

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Acknowledgments

JM and GS conceived and designed the primary aim and method of this study as well as designed and implemented data collection. JM, GS, and AL analyzed the data. JM and AL drafted the manuscript. JM supervised the project. All authors critically reviewed and developed the final manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcrp.2022.200140>.

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