Socioeconomic Status and Nonadherence to Antihypertensive Drugs: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Although conventional wisdom suggests that low socioeconomic status (SES) is a robust predictor of medication nonadherence, the strength of this association remains unclear. Objectives: 1) To estimate the proportion of studies that identified SES as a potential risk indicator of nonadherence, 2) to describe the type of SES measurements, and 3) to quantify the association between SES and nonadherence to antihypertensive pharmacotherapy. Methods: A systematic review and meta-analysis research design was used. We searched multiple electronic databases for studies in English or French examining nonadherence to antihypertensive medications measured by electronic prescription databases where explanatory factors were considered. Two authors independently assessed quality, described the SES measure(s), and recorded its association with nonadherence to antihypertensives. A random-effects model meta-analysis was performed, and heterogeneity was examined by using the I² statistic. Results: Fifty-six studies with 4,780,293 subjects met the inclusion criteria. Twenty-four of these studies (43%) did not report any SES measures. When it was reported (n = 32), only seven (13%) examined more than one component but none performed a multidimensional assessment. Most of the studies relied on income or income-related measures (such as prescription-drug benefits or co-payments) (27 of 32 [84%]). Meta-analysis could be quantified in 40 cohorts reported in 30 studies. Overall, the pooled adjusted risk estimate (95% confidence interval 0.87–0.92; I² = 95%; P < 0.001). Similar patterns were observed in all subgroups examined. Conclusions: Published studies have not found a strong association between low SES and nonadherence to antihypertensive medications. However, important limitations in the assessment of SES can be identified in virtually all studies. Future studies are required to ascertain whether a stronger association is observed when SES is determined by comprehensive measures. Keywords: antihypertensive medications, drug adherence, pharmacy, population-level, socioeconomic status.

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Introduction

Socioeconomic status (SES) is a multidimensional construct that represents an individual’s position relative to other people in the community. It is commonly considered a product of the interaction between material and social factors. Material factors include income, education, and employment, whereas social factors are usually represented by living arrangements and family structure [1]. In health care research, low SES has proven to be a strong predictor of health care utilization, morbidity, and premature death [2–5]. Nonadherence to chronic medications, such as antihypertensives (AHTs), can also be determined by low SES [6,7].

SES is an intriguing factor in the search for determinants of population-level nonadherence to AHTs because of its associations with economic, social, and education-related factors. Indeed, all these factors may affect regular medication use [8]. Although the relationship between SES and nonadherence has been inconsistent [9], we hypothesized that methodological approaches may have attenuated an important relationship. Electronic prescription databases are the methods most frequently used for the assessment of nonadherence [10,11]; however, they often lack important patient-level information required to describe SES in detail. As a result, indirect measures of income such as receipt of prescription-drug benefits through government co-payments are often used as sole indicators of SES in many studies [12–15], while direct measures of income from taxation records are rarely used [6]. In addition, studies generally do not account for SES factors not related to income and even fewer incorporate multiple SES measurements representing different dimensions [16,17]. Finally, several population-based studies can be identified in which SES factors are absent altogether [18–20].
To understand the extent to which SES may affect nonadherence to AHT medications, as well as the approaches used to account for it, we conducted a systematic review and meta-analysis of the literature pertaining to SES and nonadherence to AHT medications by using population-based electronic prescription data. Our study had three objectives: 1) to estimate the proportion of studies that identified SES as a potential risk indicator of nonadherence, 2) to describe the type of SES measurements that were used in each study, and 3) to quantify the association between SES and nonadherence to AHT medications.

### Methods

#### Search Strategy


#### Study Selection

Studies were included if they satisfied the following criteria: 1) examined nonadherence to AHT medications; 2) used electronic prescription databases as the source of nonadherence information; 3) conducted multivariable modeling to determine the independent effect of explanatory covariates on the outcome of nonadherence; and 4) were published in English or French. Eligible AHT medications included angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, beta-blockers, calcium channel blockers, or thiazide diuretics for any indication. Studies were not restricted by design or publication date. In some cases, we contacted authors of studies to clarify or obtain data.

#### Review Procedure and Assessment of Methodological Quality

The identification of studies was carried out in two steps. First, after removal of duplicates, two of the authors (M.W.A. and M.L.) examined the titles and abstracts identified in the initial search. Second, the same two reviewers (M.W.A. and M.L.) examined full-text articles for each study identified in the first step for both eligibility and methodological quality. Disagreement between the two reviewers was resolved by additional review and discussion and then, if required, with tie-breaking by a third reviewer (D.F. B.). Quality of included studies was assessed by the reviewers (M. W.A. and M.L.) with a checklist developed by the International Society for Pharmacoeconomics and Outcome Research (ISPOR) for retrospective database studies [21,22]. This checklist has been used in systematic reviews previously [23], and it consists of 27 quality review questions related to data source, research design, study population, variable definitions, statistics, and discussion. From each study, we determined whether a SES measure was corresponding to the measure of SES. In addition, we abstracted information on region of origin, publication year target medication(s), adherence measurement (medication possession ratio [MPR]-related vs. discontinuation-related [11]), number of subjects (total/low SES/higher SES), follow-up (observation) days, and the number of SES domains captured in each study. We categorized SES covariates as income-related and non-income-related and subcategorized income-related SES covariates as follows: income level, health-plan coverage or medication co-payment amount, and receipt of social assistance or income security benefits. Income-level factors were identified as direct (e.g., by linking taxation data to dispensation records) or indirect (e.g., from census neighborhood or coverage type).

#### Statistical Analysis

We assessed the agreement in study inclusion/exclusion between reviewers in each step by using Cohen’s kappa statistic (κ) [24]. We adopted the following interpretations for κ: 0.60 < κ ≤ 0.79 was considered good agreement, and κ ≥ 0.80 was considered very good agreement [25]. We assessed heterogeneity by using the I² statistic and the corresponding Tau-squared (τ²) test. This statistic represents the proportion of variability that can be attributed to between-studies variability [26]. We adopted the following interpretations for the I² statistic: 0% to 40%, low heterogeneity; 41% to 74%, moderate heterogeneity; and 75% to 100%, considerable heterogeneity. All estimates were pooled where possible irrespective of the level of heterogeneity observed and subgroup analyses completed to explore potential sources of study heterogeneity [27]. We then conducted a random-effects model meta-analysis by using the inverse-variance method to estimate the effect of SES on medication nonadherence from the pooled data [26-28]. A random-effects model accounts for potential heterogeneity between the populations and unmeasured confounding [28]. For studies reporting more than one nonadherence measure, we prioritized MPR-related outcomes over other measures. The MPR is calculated usually by summing all days’ supply during a certain period of observation of the medication and dividing it by the total days of that period [10]. For studies reporting more than one SES variable, we used the measure with the largest effect size regardless of the direction of the association. When categorical SES measures had more than two levels, we reported the risk estimate of the highest SES level relative to the lowest. Subgroup analyses were conducted for type of nonadherence measurement, type of medication, type of SES measurement, and region of origin of the data. We used the Z test for overall effects and the chi-square statistic to test for differences in between-groups effects [29]. Finally, because ethnicity may be considered an indirect SES measurement [30,31], we performed sensitivity analyses by including ethnicity as a measure of SES to assess the proportion of studies that identified SES as a potential risk indicator of nonadherence. In addition, we performed a sensitivity analysis by using the estimate with the lowest effect size instead of the highest for studies reporting more than one SES variable. We evaluated publication bias visually by using the funnel plot [32]. We adopted the protocol developed by The Cochrane Collaboration and used Review Manager (Version 5.1.7, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011) to perform the meta-analysis [27].

### Results

#### Included Studies

Our search identified 11,351 titles/abstracts, with 56 studies meeting our inclusion criteria (Fig.1; eTable 1). Overall agreement for inclusion/exclusion of studies between the reviewers was
found to be good (κ = 0.79, and κ = 0.69 for first and second steps, respectively) (Fig. 1). Of these 56 included studies, 8 studies [33–39] scored less than 50% on the methodological quality review. The median methodological quality score was 68%, and the interquartile range was 19%.

Table 1 summarizes the characteristics of included studies. The total number of subjects included in our review was 4,708,293 (range 236–1,075,285 per study). Most of the studies were conducted in Europe (11 of 56 [20%]) and North America (34 of 56 [61%]). Studies ranged from assessing one AHT medication (6 of 56 [11%]) to assessing combinations of two medications or more. Nonadherence was measured by discontinuation/nonpersistence (25 of 56 [45%]), MPR-related measurements (26 of 56 [47%]), or both (5 of 56 [8%]). The follow-up duration was 180 days or less in 13 studies, 181 days to 365 days in 31 studies, and more than 365 days in 8 studies.

SES Measures
Overall, 24 of 56 studies (43%) did not assess SES with any material or social measure. When ethnicity was considered as an eligible SES measure, however, the proportion of studies with no SES measure decreased to 19 of 56 studies (34%). An SES measure was lacking in all studies published before 2004 (9 studies), compared with 15 of 47 studies (32%) published between 2004 and 2012. Of the 32 studies that assessed SES, 2 studies did not report estimates of the effect of SES on nonadherence and could not be obtained from authors [40,41].

No study organized SES variables into multidimensional scales or indices such as a deprivation index [42,43]. From all studies that assessed SES, 25 studies (78% [25 of 32]) identified only one SES measure among their study subjects. Of these, prescription-drug coverage or medication co-payment amount based on income was most commonly used (17 of 25 studies) [9,15,38,44–57]. Four studies captured the income level [41,58–60], three studies used social assistance benefits or income security benefits [61–63], and only one study used the education level [64].

Seven studies (22% [7 of 32]) identified more than one SES measure in their study population. All the studies contained at least one income-related variable, and three identified income-related measures only [36,39,65]. Nonincome variables in the

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Fig. 1 – Flow chart for titles/abstracts and articles included in the review. CI, confidence interval.
remaining studies included education and employment [66], education [67], living alone [40], or household composition [6].

In total, seven studies captured the income level either alone or in addition to other SES measures. Of these, classification into income groups was obtained directly by linking taxation data to dispensation records in three studies [6,59,67], indirectly from census neighborhood income in two studies [40,58], and indirectly from low-income drug coverage in two studies [60–65].

Table 1 – Characteristics of included studies.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number of subjects</th>
<th>% of total sample (n = 4,708,293)</th>
<th>Number of studies (%) (N = 56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Region of data origin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>North American</td>
<td>2,666,720</td>
<td>56.6</td>
<td>35 (62.5)</td>
</tr>
<tr>
<td>Europe</td>
<td>880,224</td>
<td>18.7</td>
<td>10 (17.9)</td>
</tr>
<tr>
<td>Other countries</td>
<td>1,161,349</td>
<td>24.7</td>
<td>11 (19.6)</td>
</tr>
<tr>
<td>Date of publication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before 2004</td>
<td>206,025</td>
<td>4.4</td>
<td>9 (16.1)</td>
</tr>
<tr>
<td>2004 and after</td>
<td>4,502,268</td>
<td>95.6</td>
<td>47 (83.9)</td>
</tr>
<tr>
<td>AHT medication(s) studied</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEIs</td>
<td>27,114</td>
<td>0.6</td>
<td>6 (10.7)</td>
</tr>
<tr>
<td>ARBs</td>
<td>18,396</td>
<td>0.4</td>
<td>2 (3.6)</td>
</tr>
<tr>
<td>BBs</td>
<td>102,690</td>
<td>2.2</td>
<td>6 (10.7)</td>
</tr>
<tr>
<td>CCBs</td>
<td>29,324</td>
<td>0.6</td>
<td>2 (3.6)</td>
</tr>
<tr>
<td>HCTZ</td>
<td>17,949</td>
<td>0.4</td>
<td>2 (3.6)</td>
</tr>
<tr>
<td>Other (if more than one medication was studied)</td>
<td>4,512,820</td>
<td>95.8</td>
<td>38 (67.8)</td>
</tr>
<tr>
<td>Adherence measure type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPR related</td>
<td>3,058,762</td>
<td>65</td>
<td>26 (46.4)</td>
</tr>
<tr>
<td>Discontinuation</td>
<td>1,351,749</td>
<td>28</td>
<td>25 (44.6)</td>
</tr>
<tr>
<td>Both</td>
<td>297,782</td>
<td>6.3</td>
<td>5 (9.0)</td>
</tr>
<tr>
<td>Number of SES measurements</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>2,961,112</td>
<td>62.9</td>
<td>24 (42.9)</td>
</tr>
<tr>
<td>1</td>
<td>1,546,235</td>
<td>32.8</td>
<td>25 (44.6)</td>
</tr>
<tr>
<td>&gt; 1</td>
<td>200,946</td>
<td>4.3</td>
<td>7 (12.5)</td>
</tr>
<tr>
<td>If SES was not assessed (N = 24), did study assess ethnicity?</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>1,761,764</td>
<td>37.4</td>
<td>5 (8.9)</td>
</tr>
<tr>
<td>No</td>
<td>1,199,348</td>
<td>25.5</td>
<td>19 (33.9)</td>
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<tr>
<td>SES measure</td>
<td></td>
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<tr>
<td>One SES measure not related to income</td>
<td>28,395</td>
<td>0.6</td>
<td>1 (1.8)</td>
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<tr>
<td>One SES measure related to income</td>
<td>1,711,195</td>
<td>24.9</td>
<td>17 (30.4)</td>
</tr>
<tr>
<td>Prescription drug coverage or medication co-payment amount</td>
<td>267,379</td>
<td>5.7</td>
<td>4 (7.1)</td>
</tr>
<tr>
<td>Income level</td>
<td>79,266</td>
<td>1.7</td>
<td>3 (5.4)</td>
</tr>
<tr>
<td>Social assistance benefits or income security benefits</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>More than one SES measure</td>
<td>4,525</td>
<td>0.1</td>
<td>2 (3.6)</td>
</tr>
<tr>
<td>Two income-related measures</td>
<td>24,443</td>
<td>0.5</td>
<td>1 (1.8)</td>
</tr>
<tr>
<td>Three income-related measures</td>
<td>104,200</td>
<td>2.2</td>
<td>3 (5.4)</td>
</tr>
<tr>
<td>Income-related measure + one measure not related to income</td>
<td>14,219</td>
<td>0.3</td>
<td>1 (1.8)</td>
</tr>
<tr>
<td>Income-related measure + two measures not related to income</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Method to measure income</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct</td>
<td>150,609</td>
<td>3.2</td>
<td>3 (5.4)</td>
</tr>
<tr>
<td>Indirect</td>
<td>53,603</td>
<td>1.1</td>
<td>2 (3.6)</td>
</tr>
<tr>
<td>Follow-up days category</td>
<td>200,370</td>
<td>4.3</td>
<td>2 (3.6)</td>
</tr>
<tr>
<td>Up to 180</td>
<td>1,426,148</td>
<td>30.3</td>
<td>13 (23.2)</td>
</tr>
<tr>
<td>181–365</td>
<td>2,753,990</td>
<td>58.5</td>
<td>31 (55.4)</td>
</tr>
<tr>
<td>&gt; 365</td>
<td>502,138</td>
<td>10.7</td>
<td>8 (14.3)</td>
</tr>
</tbody>
</table>
| ACEIs, angiotensin-converting enzyme inhibitors; AHT, antihypertensive; ARBs, angiotensin receptor blockers; BBs, beta-blockers; CCBs, calcium channel blockers; HCTZ, hydrochlorothiazide; MPR, medication possession ratio.

Nonadherence with Higher SES

Excluding the two studies in which an estimate could not be obtained [40,41], we extracted data for 40 cohorts in 30 studies reporting an SES variable. Higher SES was associated with a lower risk of nonadherence in 31 of 40 cohorts (77.5%), with no difference in 1 cohort, and with a higher risk of nonadherence in 8 cohorts (Fig. 2). Overall, the pooled adjusted risk estimate indicated a lower risk of nonadherence among individuals with a higher SES: 0.89 (95% CI 0.87–0.92; P < 0.001); however, high
heterogeneity was observed ($r = 0.01$; $I^2 = 95$%). Inspection of the funnel plot did not suggest potential publication bias (Fig. 3).

To explore heterogeneity in the results, we performed several subgroup analyses. Similar results, however, were observed in studies scoring above 50% on the quality checklist (pooled adjusted risk estimate 0.90; 95% CI 0.87–0.92; $I^2 = 95$%) and scoring below 50% (pooled adjusted risk estimate 0.86; 95% CI 0.66–1.12; $I^2 = 84$%). A subgroup analysis was not performed on measures not related to income because they were identified only in one study. Studies that used discontinuation as the end point (pooled adjusted risk estimate 0.91; 95% CI 0.87–0.96; $I^2 = 92$%) showed results consistent with those that used MPR-related measures (0.88; 95% CI 0.85–0.92; $I^2 = 93$%), and studies from North America and Europe (0.90; 95% CI 0.87–0.94; $I^2 = 95$%) produced results similar to those from other countries (0.86; 95% CI 0.81–0.92; $I^2 = 87$%).

In the sensitivity analysis, the use of the measure with the lowest effect size (for studies reporting more than one SES variable) did not change the pooled adjusted risk estimate (0.90; 95% CI 0.88–0.92; $I^2 = 95$%). Smaller heterogeneity was observed in certain cohorts restricted by the specific type of medication used. Pooled adjusted risk estimates representing the effect of higher SES were different for cohorts receiving angiotensin-converting enzyme inhibitors (0.83; 95% CI 0.79–0.88; $I^2 = 0$%), beta-blockers (0.77; 95% CI 0.66–0.9; $I^2 = 95$%), calcium channel blockers (0.98; 95% CI 0.85–1.14; $I^2 = 70$%), hydrochlorothiazide (0.81; 95% CI 0.74–0.90; $I^2 = 98$%).

![Fig. 2 – Pool risk estimates of nonadherence with high socioeconomic status. CI, confidence interval; SE, standard error; SES, socioeconomic status.](image)
that current knowledge about SES and nonadherence is with respect to AHT medications. In reality, it must be recognized that evidence supporting this view remains theoretical at best, at least in studies focused on AHT medications. This estimate, however, is based on studies that used electronic prescription databases as the source of nonadherence information. Electronic prescription databases, however, are the most frequently used source of nonadherence information among large populations [10]. Third, it is highly likely that the pooled risk estimates were affected by the lack of detailed SES information and the inconsistent approaches to SES measurement in the published literature. Indeed, the vast majority of SES measures were restricted to income-related measures. Fourth, we used the checklist developed by ISPOR for retrospective database studies to assess publications’ quality. However, a new questionnaire developed by the Academy of Managed Pharmacy/National Pharmaceutical Council/ISPOR Comparative Effectiveness Research Collaborative Initiative could have improved our quality assessment [79]. Last, although we did not observe any publication bias, it is possible that negative studies assessing SES and nonadherence could not be published.

SES is frequently overlooked in studies of nonadherence to AHT medications using electronic prescription databases, and it has never been examined in a comprehensive way. Based on the available literature, higher SES appears to be associated with a small reduction in the occurrence of nonadherence to AHT medications. This estimate, however, is based on studies that contained many limitations. Thus, more research is clearly needed, and as a result, SES cannot be considered a strong predictor of medication nonadherence because the evidence supporting this view remains theoretical at best, at least with respect to AHT medications. In reality, it must be recognized that current knowledge about SES and nonadherence is extremely poor.

To our knowledge, this is the first systematic review specifically evaluating the effects of SES on nonadherence to AHT medications and the results suggest that more research is needed to ensure a consistent and comprehensive approach to the assessment of SES as a possible risk indicator. We chose hypertension as a disease state because of its prevalence, chronicity, lack of symptoms, and treatability [68]. It has been clearly shown that the prevalence of nonadherence to AHT medications is high and adverse health outcomes are commonly observed compared with those demonstrating optimal adherence [69–71]. As a result, even small improvements in nonadherence are likely considered clinically meaningful [72–75].

The most probable explanation for these findings is that administrative databases including electronic prescription databases do not have ready access to SES information. The importance of the SES factors as potential risk indicators of nonadherence, however, may also be underrecognized. Accordingly, our understanding of the complex relationship between SES and medication nonadherence is likely incomplete because it is based on studies using a very limited set of SES measures, at least in studies focused on AHT medications.

SES could be an important determinant of nonadherence through its effect on not only affordability and access to medications but also health literacy and medication knowledge [76]. Indeed, higher SES reduced the risk estimate of nonadherence in 31 of 40 cohorts examined; however, the opposite effect of SES was observed in 8 of 40 cohorts examined. Thus, our systematic review confirms and characterizes the inconsistent findings relating to SES and nonadherence reported in previous narrative reviews [11,77,78].

Our review had several limitations. First, our study examined AHT studies only, and so the results may not generalize to other chronic disease medications. Second, we included only those studies that used electronic prescription databases as the source of nonadherence information.Electronic prescription databases, however, are the most frequently used source of nonadherence information among large populations [10]. Third, it is highly likely that the pooled risk estimates were affected by the lack of detailed SES information and the inconsistent approaches to SES measurement in the published literature. Indeed, the vast majority of SES measures were restricted to income-related measures. Fourth, we used the checklist developed by ISPOR for retrospective database studies to assess publications’ quality. However, a new questionnaire developed by the Academy of Managed Pharmacy/National Pharmaceutical Council/ISPOR Comparative Effectiveness Research Collaborative Initiative could have improved our quality assessment [79]. Last, although we did not observe any publication bias, it is possible that negative studies assessing SES and nonadherence could not be published.

Among published studies of nonadherence to AHT medications using electronic prescription databases, 43% did not account for any SES measure despite their theorized importance as a determinant of nonadherence [8]. When SES was assessed, the vast majority of studies identified single factors relating to income and none examined SES by using a comprehensive measure. Pooled analyses indicated that higher SES is associated with an 11% decrease in the adjusted risk of nonadherence; however, inconsistencies in previous attempts to understand this complex issue. As a result, SES cannot be considered a strong predictor of medication nonadherence because the evidence supporting this view remains theoretical at best, at least with respect to AHT medications. This estimate, however, is based on studies using a very limited set of SES measures, at least in studies focused on AHT medications.
Fig. 4 – Pool risk estimates of nonadherence with high socioeconomic status, stratified by medication studied. CI, confidence interval.
needed to help clarify this relationship. Considering the public health importance of this outcome and the relative lack of knowledge about its determinants, failure in taking SES into account could prevent targeting of interventions for those who need them.

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