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Racial/Ethnic Disparities in ART Adherence in the United States: Findings From the MACH14 Study

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Abstract

Background—Minority race/ethnicity is generally associated with antiretroviral therapy nonadherence in US-based studies. Limitations of the existing literature include small samples, subjective adherence measures, and inadequate control for potential confounders such as mental health and substance use, which have been consistently associated with poorer adherence.

Methods—Individual-level data were pooled from 13 US-based studies employing electronic drug monitoring to assess adherence. Adherence was operationalized as percent of prescribed doses taken from the first 12 (monthly) waves of data in each study. Depression symptoms were aggregated from several widely used assessments, and substance use was operationalized as any use of cocaine/stimulants, heroin/opiates, ecstasy, hallucinogens, or sedatives in the 30–365 days preceding baseline.

Results—The final analytic sample of 1809 participants ranged in age from 18 to 72 years and was 67% male. Participants were 53% African American, 14% Latino, and 34% White. In a logistic regression adjusting for age, gender, income, education, and site, race/ethnicity was

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significantly associated with adherence ($P < 0.001$) and persisted in a model that also controlled for depression and substance use ($P < 0.001$), with African Americans having significantly lower adherence than Latinos [odds ratio (OR) = 0.72, $P = 0.04$] and whites (OR = 0.60, $P < 0.001$). Adherence did not differ between whites and Latinos (OR = 0.84, $P = 0.27$).

Conclusions—Racial/ethnic differences in demographics, depression, and substance abuse do not explain the lower level of antiretroviral therapy adherence in African Americans observed in our sample. Further research is needed to explain the persistent disparity and might examine factors such as mistrust of providers, health literacy, and inequities in the health care system.

Keywords

HIV/AIDS; race/ethnicity; antiretroviral treatment; medication adherence

INTRODUCTION

Antiretroviral therapy (ART) has led to marked reductions in mortality and morbidity among HIV-positive individuals, yet from the outset optimal adherence to prescribed regimens has remained essential to its success.[1,2] Identifying subgroups at risk for nonadherence and tailoring treatment to address their needs or to otherwise address factors causing the disparities may help optimize treatment success.

Racial/ethnic minority group status has been linked repeatedly to lower levels of ART adherence and viral suppression among HIV-positive cohorts in the United States.[3–10] For example, in a large sample of patients enrolled in an integrated health care system (thus equalizing access to care), Silverberg et al[11] reported that adjusted mean refill adherence, operationalized as the percentage of days with antiretroviral (ARV) medication coverage between refills, was lower among patients who were African American (64%) or Hispanic (65%) compared with white (70%). Based on data from the Multicenter AIDS Cohort Study, Lee et al[12] reported that after controlling for site, age, financial difficulties, popper use, crack use, and viral load, Hispanics were 2.2 (95% CI: 1.5 to 3.2) and African Americans were 1.4 (95% CI: 1.1 to 1.8) times more likely than whites to report having taken less than 100% of all their prescribed HIV medication doses over the previous 4 days.

Most prior studies have important methodological limitations. Some have small samples, which limits statistical power, and others use only self-reports of adherence, which can overestimate actual adherence. In addition, few prior studies adequately controlled for potential confounders known to be important in racially and ethnically diverse populations including depression[13] and substance use.[14–16] Psychiatric disorder and drug dependence are highly prevalent among individuals with HIV, with positive screening for each as high at 50% in the HIV Cost and Services Utilization Study.[17] Although data on racial/ethnic differences in these potential barriers to adherence are mixed,[11,17,18] racial/ethnic minority groups in the United States seem to have less access to high quality treatment for these conditions, which may exacerbate their effects on nonadherence.[19,20]

Most of the studies examining racial/ethnic difference in adherence included African Americans, with smaller numbers of and fewer comparisons with Latinos. Those including Latinos generally showed them to be at greater risk for nonadherence than Whites.[21] Waldrop-Valverde et al[22] concluded that there is no consensus on whether African Americans adhere worse than individuals from other racial/ethnic groups, with demonstrated differences possibly due to adherence measurement error or comorbidities such as depression and substance abuse.

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In the present study, we analyzed data from the Multi-site Adherence Collaboration on HIV (MACH14) to examine the association of race/ethnicity to adherence. Advantages of MACH14 were that adherence was measured electronically, the population was large relative to most prior studies, African Americans and Latinos were well represented, and we were able to control for key potential confounders including depressive symptomatology and substance use.

METHODS

Data Source

Data came from a National Institute of Mental Health–funded project combining data from 16 studies of electronically monitored ART adherence conducted at 14 sites in the United States.[23] Demographic, psychosocial, and biological data assessed across the studies were combined in the pooled data via the creation of new variables incorporating data across studies. The present study focused on 13 studies conducted at 11 research sites, excluding the 3 studies that collected no data on income or education level. Only individuals self-identifying as African American, Latino, or white were included. Prospective predictors were taken from the baseline assessment (ie, the first assessment point at which they were collected). As indicated below, we used a missing indicator approach to deal with missing data.[24]

Measures

Demographic Characteristics—These included site, gender, age in years, income (percent reporting an annual household income of more than $10,000), and education level (percent graduating high school). Race/ethnicity was determined by self-identification as white, African American, or Latino.

ART Adherence—Adherence was measured with the Medication Event Monitoring System (MEMS; http://www.aardex.ch), a pill bottle and cap that electronically records the date and time of each opening as a presumptive dose. The adherence outcome was operationalized as percent adherence across the entire period the participant was observed, up to 12 months. Specifically, adherence was calculated separately for each of the first 12 months after a participant's baseline assessment. Each month was defined as a 4-week period with the percent adherence calculated across monitored ARV medications. Percent ART adherence was calculated as the number of doses taken divided by the total number of doses prescribed during each 4-week period. An overall index of ART adherence was derived by averaging adherence for each of the monthly intervals during which a participant was monitored. For studies that followed participants for less than 12 months, the adherence outcome reflected the average for the monitored months.

Depression

Different measures of depression were administered across studies as follows: 4 used the Beck Depression Inventory version II[25]; 1 used the original version of the Beck Depression Inventory[26]; 3 used the Center for Epidemiological Studies Depression Scale[27]; 2 used the depression subscale of the Brief Symptom Inventory[28]; and 1 used the Primary Care Screener for Affective Disorders.[29] To aggregate data from these different scales, we first calculated standardized Z scores (ie, subtracting the normative—not the study—mean of the scale from the sum of the scale items in the particular study and then dividing by the normative standard deviation).[30] This approach, which we used successfully in a prior study (Wagner et al[31]) circumvents the potential bias of participants in each study receiving Z scores based on their level of depression relative to the other participants in that particular study rather than the wider population.

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The participant's *Z* score was denoted as missing if more than half of the depression scale items were missing for that individual. Based on this continuous measure, we determined a 3-category diagnosis of "minimal, mild/moderate, or severe" depression, reflecting established diagnostic cutoffs for each depression measure. A fourth category of "missing" was included for participants who were administered a depression scale without diagnostic cut-offs or for whom a depression score was not available.

Substance Use—Because multiple drug use is common and combining a range of substances used may create a more reliable predictor than individual drug use indicators,[32] we computed a categorical indicator encompassing any use of the following substances: cocaine/stimulants, heroin/opiates, ecstasy, hallucinogens, or sedatives. Alcohol use was not included in the indicator as drinking to intoxication was assessed only at a single site, so it was not possible to differentiate problem drinking. The time frame of substance use varied by study and ranged from the last 30 to 365 days. An additional category of "missing" was included for participants without substance use data.

Statistical Analysis

Descriptive analyses were performed to identify means, standard deviations, and bivariate correlations of the demographic, depression, substance use, and adherence variables. We used logistic regression in combination with robust standard error correction to evaluate medication adherence as a continuous variable between 0 and 1. This approach has been previously recommended for the analysis of continuous percentage data.[33,34] (The magnitude and statistical significance of the results were comparable under a linear regression model.) The unadjusted association between adherence and the demographic, depression, and substance use variables was examined with logistic regression. Additional logistic regression models were used to examine subgroup associations between race/ethnicity and adherence at each level of the other demographic, depression, and substance use variables.

Because the data originated from multiple studies, we first conducted preliminary analyses to identify any site-specific associations between the medication adherence outcome and each of the demographic, depression, and substance variables. For each predictor variable, the adherence outcome was regressed on site, the predictor, and the predictor × site interaction in separate models. An omnibus Wald χ^2 test of the predictor × site interactions evaluated whether the relation between the predictor and medication adherence varied by site. The interaction effect with site was significant for race/ethnicity, age, depression, and substance use. Consequently, we controlled for the main effect of site and its interactions with those 4 variables in the final model. Site effects were modeled using a fixed effect approach because of the small number of clusters and because the sites were not sampled randomly from all possible locations in the United States. Based on the final model, adjusted mean adherence was calculated for African American, Latino, and white participants with all other variables held at their mean levels. In the case of categorical covariates such as gender, the mean level represented the average proportion of individuals in the respective categories. Consequently, the adjusted mean reflected a weighted average of adherence across the different subgroups.

Next, a sequential logistic regression was used to determine if the association of race/ethnicity with ART adherence would persist after controlling for relevant (1) demographic and (2) substance use and depression confounders. Omnibus Wald χ^2 tests evaluated whether the variables in each step of the model were collectively associated with medication adherence. In step 1, race/ethnicity (predictor 1), age in years (2), gender (3), annual household income (4), and education (5) were entered into the model to account for

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demographic associations with medication adherence. In step 2, substance use (6) and depression (7) were entered to assess the additional effect of mental health symptoms on adherence after controlling for demographic factors, site, and the interaction of site with all predictors that varied by site. As site was not of substantive interest in the final results, we report the average effect across sites all predictions, weighted by the relative sample size among the cities included in the analysis.

RESULTS

Participant Characteristics

The final analytic sample of 1809 participants ranged in age from 18 to 72 years and was mostly (67%) male. Participants were 53% African American (n = 951), 14% Latino (n = 250), and 34% white (n = 608). Although most were well educated (66% had a high school or general education degree and 11% had a college degree), more than half (59%) reported an annual household income of less than $10,000. Forty-one percent were heterosexual, 33% were gay or lesbian, and 14% were bisexual. With respect to baseline medication, 31% of participants were on a once-daily regimen, 61% were on a twice-daily regimen, and 8% were on a thrice-daily regimen (Table 1). Regimens were based on a protease inhibitor (51%), a nucleoside reverse transcriptase inhibitor (29%), a nonnucleoside reverse transcriptase inhibitor (16%), a nucleotide reverse transcriptase inhibitor (3%), a fusion inhibitor (<1%), or another medication (<1%).

To assess for differences between participants with complete data (60%), those who were missing substance use only (2%), depression only (15%), or both substance use and depression data (23%), χ^2 tests and 1-way analyses of variance were conducted on categorical and continuous demographic characteristics, respectively. There was no racial/ethnic difference between individuals with complete data and those without. Individuals with complete data were more likely to have at least a high school diploma [χ^2 (2) = 20.39, P < 0.001], possess a higher annual household income [χ^2 (4) = 21.11, P < 0.001], be female [χ^2(1) = 11.22, P = 0.001], and be of older age [F(1,1807) = 18.21, P < 0.001].

Descriptive and Bivariate Analyses

Means, standard deviations, and bivariate correlations of the adherence, demographic, substance use, and depression variables are presented in Table 1. The mean standardized depression score was 0.77 (SD = 1.65). Among the subgroup of participants from studies that used a depression scale with established diagnostic cutoffs (n = 1115), 60% (n = 673) had none or minimal signs of depression, 25% (n = 282) had mild to moderate depression, and 14% (n = 160) had severe depressive symptomatology. Among the participants with substance use data (n = 1364), 65% reported using no substances in the 30–365 days preceding their baseline assessment, 26% reported using one substance, and 10% reported using 2 or more substances. African American [35%; χ^2 (1) = 6.38, P = 0.01] and Latino [48%; χ^2 (1) = 21.93, P < 0.0001] participants were more likely to report use of at least 1 substance compared with white participants (28%).

Mean adherence levels by race/ethnicity and other prospective predictors are reported in Table 2. African American (65%), Latino (64%), and white (72%) evidenced an omnibus difference in mean adherence, χ^2 (2) = 22.96, P < 0.001. With respect to bivariate analyses, all the predictor variables had statistically significant associations with adherence (P < 0.05).

Sequential Logistic Regression

The sequential logistic regression model results are presented in Table 3. The demographic variables in step 1 were collectively associated with medication adherence [omnibus χ^2 (36)

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= 172.32, $P < 0.0001$]. When controlling for only demographic variables, race/ethnicity was a significant predictor of ARV medication adherence [omnibus test: χ^2 (21) = 119.09, $P < 0.0001$]. The substance use and depression variables introduced in step 2 improved upon the prediction of medication adherence [χ^2 (24) = 61.94, $P < 0.0001$]. When controlling for demographics, substance use, and depression, race/ethnicity remained a significant predictor of medication adherence [omnibus test: χ^2 (21) = 122.10, $P < 0.0001$].

The relationship between race/ethnicity and adherence was comparable in the model controlling for only demographic variables (step 1) and the model controlling for demographics in addition to substance use and depression (step 2). In the full model controlling for all variables, the odds of 100% medication adherence were 40% lower [odds ratio (OR) = 0.60, 95% CI: = 0.52 to 0.70, $P < 0.001$] among African Americans compared with white participants and 28% lower (OR = 0.72, 95% CI: = 0.53 to 0.98, $P = 0.04$) compared with Latino participants. The odds of 100% medication adherence were comparable among Latinos compared with white participants (OR = 0.84, 95% CI: = 0.61 to 1.15, $P = 0.27$). Adjusted mean adherence in the full model was 61% among African Americans (95% CI: = 59% to 64%), 69% among Latinos (95% CI = 63% to 75%), and 72% among white participants (95% CI: = 69% to 75%). Mean adherence among African Americans was significantly lower than adherence among Latinos (Estimate = −8%, $P = 0.04$) and whites (Estimate = −11%, $P < 0.001$). The difference in mean adherence between Latinos and whites was not statistically significantly (Estimate = 3%, $P = 0.27$).

DISCUSSION

In this analysis of pooled data from 13 studies in the United States, racial/ethnic disparities in adherence persisted even after controlling for key demographic variables (ie, sex, age, income, education, and site), depression, and substance use. The underlying mechanisms leading to these racial/ethnic disparities remain unclear, although we can speculate based on the experience of individuals of minority race/ethnicity in the United States.

The marginalization experienced by racial/ethnic minorities is the United States can be understood as involving overt discrimination as well as “microaggressions”, which are “brief and commonplace daily verbal, behavioral, or environmental indignities, whether intentional or unintentional, that communicate hostile, derogatory, or negative racial slights and insults toward people of color”.[35] As discrimination is related to worse health outcomes and maladaptive health behaviors,[36] it may be implicated in worse ART adherence.[37] For example, among 152 HIV-positive African American men who have sex with men, Bogart et al[38] found that 40% reported racial discrimination in the last 6 months, which was significantly associated in longitudinal analyses with lower adherence. Racial/ethnic minorities who experience discrimination may find it more difficult to trust their providers, a distrust which may also negatively impact adherence. For example, Saha et al[39] found that compared with white patients (n = 201), African Americans (n = 1104) expressed lower levels of trust in their provider, which was associated with worse adherence.

Levels of trust in providers may have a basis in experience. A study of 1886 participants (54% white, 28% black, 14% Hispanic) from the HIV Cost and Services Utilization Study[21] found that 40% reported having a discriminatory health care experience since their HIV diagnosis and that 24% failed to “completely” or “almost completely” trust their health care providers. In a structural equation model in the same study, discrimination predicted distrust, weaker treatment benefit beliefs, and, in turn, poorer adherence. Distrust seemed to operate on medication adherence by increasing treatment-related psychological distress and weakening treatment benefit beliefs.

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Related recent work from Bogart et al[38] has pointed to conspiracy beliefs as possible explanations. Among 177 blacks, they identified 2 distinct belief categories: genocidal beliefs (eg, HIV was created by humans) and treatment-related beliefs (eg, people on ART are the government's guinea pigs). Although both genocidal and treatment-related conspiracy beliefs were related to electronically monitored adherence in univariate analyses, in multivariate tests only the latter were linked to a lower likelihood of optimal adherence at 1 month. Most of this work has been done with African Americans; more work with Latinos is needed.

Health literacy is another possible explanation for racial/ethnic disparities in ART adherence. People with low literacy may not be able to read or identify their medications, which makes it difficult for them to adhere to their prescribed regimens.[40] HIV-positive African Americans with low levels of educational literacy have been found to be more nonadherent to ART.[41] In addition, Osborn et al[42] found that when health literacy was included as a mediator in their analyses, the association of African American race and worse 4-day self-reported ART adherence was reduced to nonsignificance. More specifically, Waldrop-Valverde et al[22] investigated numeracy or the ability to understand and use numbers in daily life. They found that poor management of a simulated ARV regimen among African American men and women with HIV was mediated by lower numeracy.

The current research points to many possible directions for future intervention. As Bogart et al[43] have pointed out, adherence interventions designed to address culturally specific roots of nonadherence may help to overcome medical mistrust. These might involve culturally tailored components delivered ideally by peer advocates or community-level interventions with recognized popular opinion leaders. Also, future work will need to disaggregate the racial/ethnic categories summarized for convenience here into the broad groupings of "African Americans" and "Latinos." Earlier work based on the Multi-site AIDS Cohort Study, for example, indicated that blacks of Caribbean descent had worse adherence than those from other regions.[12] There may be important Latino subgroup differences as well. We know of no work that has begun to investigate these differences.

Limitations of the present study include the reliance on self-report measures of depression and substance use and their lack of uniformity in measurement across studies. For example, a consistent duration for substance-use assessment across all studies (instead of the actual range of 30–365 days) would have been preferable but would have necessitated our limiting the analyses to the few studies that used the same duration for measurement. Our current analysis represents a conservative estimate of controlling for any substance use at all but may mask the adherence-reducing effects of more intensive substance use. This could potentially affect our main findings if this higher severity of substance use was more common in one racial/ethnic group than another. Our approach to combining the different depression measures, though recommended per Anastasi,[30] is limited by the quality of the normative estimates available (Wagner et al[31]) and the degree to which the different scales' items tapped different aspects of depression. The threat to validity is thought to be minimal; however, as the norms are based on very large population samples and there is good overlap of items on these scales. Furthermore, in the prior study we demonstrated that the findings observed using this approach approximated findings obtained from using a more conservative approach of converting raw scores using standard cut-offs for mild/moderate/severe depression across all measures. As such, we are confident in this recoded variable's ability to control for the effects of depression in the analyses presented here.

Another limitation is that data on all variables were not available from each study, although participants with missing data on depression and substance use were retained in the analyses by creating a category for missing data (ie, a missing indicator approach). A broader

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assessment of mental health would have been helpful, perhaps validated by clinician rating. Importantly, the MACH14 data set had a limited array of variables available for investigation. Factors we could not include here—such as self-efficacy, social support, housing status, food insecurity, or insurance status—may have accounted for the race/ethnicity and adherence association.

In conclusion, this study of pooled data from 13 different US studies confirmed prior reports of racial/ethnic disparities in ART adherence, even when adherence was more objectively measured and analyses adjusted for key demographic variables, substance use, and depression. The findings may help to explain the worse health outcomes for racial/ethnic minorities with HIV in the United States and suggest a need for interventions targeting their adherence to achieve the US National HIV/AIDS Strategy goal to reduce HIV-related health disparities. There is a need for more research on the mechanisms of these racial/ethnic disparities to inform intervention development and better address these inequities.

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TABLE 1

Descriptive Data and Intercorrelations for Main Variables (n = 1809)

	2	3	4	5	6	7	Mean	SD	Range
1. Adherence	0.09*	0.06*	0.08*	0.08*	−0.14*	−0.16*	0.67	0.29	0–1
2. Age in yrs	—	0.05*	0.04	0.12*	−0.03*	0.00	41.69	8.18	18–72
3. Male gender	—	—	0.12*	0.15*	0.00	0.00	0.67	0.47	0–1
4. Income >$10,000	—	—	—	0.22*	−0.10*	−0.11*	0.41	0.49	0–1
5. Education	—	—	—	—	−0.05	−0.12*	1.88	0.57	1–3
6. Depression diagnosis	—	—	—	—	—	0.17*	1.54	0.73	1–3
7. Substance use	—	—	—	—	—	—	0.35	0.48	0–1

*$P < 0.05$.

Education (<high school diploma, high school graduate, >high school); depression (1 = minimal/Normal, 2 = mild to moderate, 3 = Severe).

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TABLE 2

Race/Ethnicity Differences in Mean HIV Medication Adherence by Demographics, Depression, and Substance Use

Variable	All	African American	Latino	White	χ^2	*df*	*P*
All Participants	0.67	0.65	0.64	0.72	22.96	2	<0.001
Gender	—	—	—	—	6.37	1	0.01
Male	0.69	0.67	0.64	0.72	12.67	2	0.002
Female	0.65	0.62	0.64	0.71	9.92	2	0.01
Annual household income	—	—	—	—	13.12	1	<0.001
≤$10,000	0.65	0.64	0.62	0.69	5.85	2	0.05
>$10,000	0.70	0.67	0.67	0.75	16.86	2	<0.001
Education	—	—	—	—	12.58	2	0.002
<H.S. diploma	0.63	0.65	0.57	0.63	4.94	2	0.08
H.S. diploma/some college	0.68	0.66	0.66	0.73	18.23	2	<0.001
College degree	0.70	0.62	0.70	0.74	7.01	2	0.03
Age	—	—	—	—	14.92	1	<0.001
≤41 years	0.65	0.64	0.60	0.69	10.04	2	0.01
>41 years	0.69	0.66	0.71	0.75	18.02	2	<0.001
Substance use	—	—	—	—	34.83	2	<0.001
No	0.71	0.67	0.69	0.77	26.67	2	<0.001
Yes	0.62	0.61	0.62	0.63	0.08	2	0.96
Missing	0.67	0.67	0.62	0.70	3.88	2	0.14
Depression diagnosis	—	—	—	—	24.96	3	<0.001
Normal	0.70	0.67	0.69	0.78	26.14	2	<0.001
Mild to moderate	0.67	0.65	0.57	0.73	9.74	2	0.01
Severe	0.58	0.54	0.67	0.60	2.73	2	0.26
Missing	0.66	0.66	0.62	0.69	5.02	2	0.08

The χ^2 test for all participants tests the bivariate association between race and medication adherence. The χ^2 test on the first line for each variable evaluates the bivariate association between the variable and medication adherence.

df = degrees of freedom.

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TABLE 3

Summary of Sequential Logistic Regression Model Predicting Adherence (n = 1809)

	Step 1				Step 2			
Variable	**OR**	**SE**	**95% CI**	***P***	**OR**	**SE**	**95% CI**	***P***
Step 1: demographics								
Race/ethnicity	Omnibus: χ^2 (21) = 119.09			<0.001	Omnibus: χ^2 (21) = 122.10			<0.001
African American vs. White	0.62	0.05	0.53 to 0.71	<0.001	0.60	0.05	0.52 to 0.70	<0.001
Latino vs. White	0.85	0.13	0.62 to 1.16	0.30	0.84	0.14	0.61 to 1.15	0.27
Age in yrs	1.01	0.004	1.00 to 1.02	0.01	1.01	0.004	1.00 to 1.02	0.01
Male gender	1.05	0.08	0.91 to 1.21	0.53	1.04	0.08	0.90 to 1.20	0.62
Annual household income >$10k	1.09	0.07	0.96 to 1.24	0.19	1.06	0.07	0.93 to 1.20	0.33
Education	Omnibus: χ^2 (2) = 6.97			0.03	Omnibus: χ^2 (2) = 8.08			0.02
HS diploma vs. <HS diploma	1.22	0.09	1.05 to 1.42	0.01	1.24	0.10	1.06 to 1.44	0.01
College degree vs. <HS diploma	1.23	0.15	0.97 to 1.56	0.09	1.29	0.16	1.01 to 1.64	0.04
Step 2: substance use and depression								
Substance use	—	—	—	—	Omnibus: χ^2 (11) = 39.43			<0.001
Yes vs. no	—	—	—	—	0.74	0.08	0.60 to 0.92	0.01
Missing vs. no	—	—	—	—	0.57	0.17	0.32 to 1.02	0.06
Depression	—	—	—	—	Omnibus: χ^2(13) = 15.92			0.25
Mild to moderate vs. normal	—	—	—	—	0.87	0.08	0.72 to 1.05	0.15
Severe vs. normal	—	—	—	—	0.76	0.12	0.56 to 1.03	0.07
Missing vs. normal	—	—	—	—	0.79	0.09	0.62 to 0.99	0.04

The model controlled for the main effect of site and the interaction of site with all variables, except for education. All parameter estimates are weighted by site. χ^2 (36) = 172.32, $P < 0.0001$, for step 1; χ^2 (24) = 61.94, $P < 0.0001$, for step 2.