C-Reactive Protein and substance use disorders in adolescence and early adulthood: A Prospective Analysis

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Abstract

Background—Dysregulated immune function and elevated inflammation markers are seen in adults with chronic diseases, including some psychiatric disorders, but evidence on inflammation in the case of drug abuse is conflicting.

Objective—To test the concurrent and predictive relations between C-reactive protein (CRP) and use and abuse of alcohol, nicotine and cannabis in a longitudinal, population sample of adolescents and young adults, at the period of highest increase in drug use.

Methods—Data from the prospective population-based Great Smoky Mountains Study (N = 1,420) were used, covering children in the community assessed at ages 9–16, 19, and 21. Structured interviews were used to assess substance abuse symptoms and DSM-IV substance use disorders. Bloodspots were collected at each assessment and assayed for CRP.

Results—CRP levels were higher in the presence of nicotine, alcohol, and cannabis use and nicotine dependence. In prospective analyses, higher CRP levels predicted cannabis use and nicotine dependence, and nicotine use predicted higher CRP levels, once covariates were included in the models. Significant covariates were age, race (American Indian), and obesity.

Conclusions—The inter-relationship of CRP and substance abuse has implications for the later health risks associated with early drug and alcohol use and abuse.

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1. INTRODUCTION

The acute phase protein C-reactive protein (CRP) is a marker of systemic inflammation (Volanakis, 2001; Black et al., 2004) that is associated with chronic and costly diseases, including cardiovascular and metabolic disease (Raison et al., 2006; Shah et al., 2009; Miller et al., 2011) and with shortened life expectancy (Crimmins and Finch, 2006). Research on correlates of heightened inflammation typically focuses on middle and older adulthood, when disease endpoints are clearly diagnosable. Heightened inflammation is, however, detectable by adolescence (Copeland et al., 2012a, 2012b), and already associated with precursors to chronic disease, including vascular changes (Lim et al., 2009; Reinehr et al., 2006) and obesity. Once established, elevated CRP appears to be fairly stable across time (Macy et al., 1997).

There is no question that beyond certain levels alcohol, cannabis, nicotine, and a range of illicit drugs are harmful to health and, like inflammation, predictors of early mortality. So far, however, there is little research on whether inflammation is one of the pathways that link substance use disorders (SUD) with health outcomes. Evidence for links between substance use and abuse and inflammation is equivocal and varies by substance of abuse. There is evidence that "chronic alcohol consumption augments pro-inflammatory cytokine production in the brain. In contrast, moderate amounts of alcohol consumption have been shown to reduce risk of type 2 diabetes and coronary heart disease, perhaps by exerting anti-inflamatory properties" (Hendricks and van Tol, 2005, in Kelley and Dantzer, 2011). A U-shaped cross-sectional relationship between CRP and alcohol consumption is widely documented (e.g., Albert et al., 2003; Imhof et al., 2001; Pai et al., 2006), but most in studies, including these, alcohol users showing abuse or dependence have elevated CRP.

In inflammatory conditions, cannabinoids have long been used to reduce pain in rheumatoid arthritis and Crohn's disease, and may protect against diabetes (Rajavashisth et al., 2012). Again, high levels of use may nevertheless be harmful. On the other hand, cigarette smoking has been shown to increase production of numerous pro-inflammatory cytokines (Arnson et al., 2010; O'Loughlin et al., 2008), although it is not clear whether any amount is harmful (Arnson et al., 2010) or only heavy smoking (O'Loughlin et al., 2008). It is also important to distinguish between nicotine ingestion and cigarette smoking, which may have different relationships with inflammation ((Heeschen et al., 2003; Benowitz, 2003; Catanzaro et al., 2007; Furie et al., 2000). Thus, it is important to distinguish among drugs of addiction, and among levels of use, in examining the effects of drug use on inflammatory processes. At the same time, it is possible that known correlates of inflammation, such as exposure to stressors, increase risk of SUDs, and that inflammation may serve as a mediator of their effect on drug use.

With data from a longitudinal study with repeated assessments over adolescence and early adulthood, we tested two sets of hypotheses: that use of drugs of addiction precedes higher

levels of CRP, and that higher levels of CRP precede substance use disorders. In these analyses we controlled for factors known from the literature to be associated with higher CRP levels (Davey Smith et al., 2005; Benson et al., 2009; Skinner et al., 2010; Elovainio et al., 2006a): age, low socioeconomic status, obesity, psychotropic medications, other medications and some psychiatric disorders.

2. METHODS AND MATERIALS

2.1 Participants

The Great Smoky Mountains Study is a longitudinal study of the development of psychiatric disorders in rural and urban youth (Costello et al., 1996, 2003). A representative sample of three cohorts of children, age 9, 11, and 13 at intake, was recruited from 11 counties in western North Carolina using a household equal probability, accelerated cohort design. All children scoring above a predetermined cut point (the top 25% of the total scores) on the CBCL externalizing scale (Achenbach, 1991), plus a 1 - in - 10 random sample of the remaining 75% of the total scores, were recruited for detailed interviews. In data analyses, each subject is assigned a weight inversely proportional to their probability of selection, and all results presented here are representative of the population from which the sample was drawn; they are not biased by the oversampling procedure. About 8% of the area residents and the sample are African American, less than 1% are Hispanic, and 3% are American Indian. Of all subjects recruited, 80% (N=1420) agreed to participate. Across all waves, participation rates averaged 84% (range: 74–94%).

2.2 Procedure

A parent (biological mother for 83% of interviews) and the participant were interviewed by trained interviewers separately until the subject was 16; thereafter subjects only were interviewed, at ages 19 and 21. Consent forms approved by the Duke University Medical Center Institutional Review Board were signed before each interview. Participants could give consent for the interview but not the blood sampling if they chose. Each parent and child received an honorarium for their participation.

Blood samples were obtained at the beginning of each in-person assessment (Worthman and Stallings, 1997). Two finger-prick samples (yielding 10 blood spots total per visit) were collected at 20-minute intervals, applied to standardized collection paper, immediately refrigerated upon drying, and express shipped (without refrigeration) to the laboratory within two weeks of collection. Samples were then stored at −28°C until they were assayed. This protocol is consistent with the rigorous quality control program developed for newborn screening programs (Mei et al., 2001) and has been used in other epidemiologic studies (McDade et al., 2004; Williams and McDade, 2009).

2.3 Assessment of substance use and addiction

Substance use was defined as use of any potentially addictive substance, including tobacco, in the past 3 months. Addiction was defined as abuse and/or dependence (O'Brien et al., 2006) as defined by the Diagnostic and Statistical Manual of the American Psychiatric Association, 4th edition (American Psychiatric Association, 1994). Interviewers used the

Child and Adolescent Psychiatric Assessment (CAPA) until age 16, and after that using its upward extension, the Young Adult Psychiatric Assessment (YAPA; Angold and Costello, 2000, Angold et al., 1999). These structured interviews were administered, coded, and checked by trained interviewers. A detailed glossary provides the operational rules for each item assessed (devepi.mc.duke.edu/eMeasures/CAPA/glossary.pdf). The time frame for determining the presence of most behaviors was the past three months (unless otherwise indicated) to minimize recall biases, although onset dates were also collected for all symptoms. Scoring programs written in SAS combined information about the date of onset, duration, and intensity of each symptom to create diagnoses according to DSM-IV (American Psychiatric Association, 1994). A symptom was counted as present if reported by either parent or child or both, as is standard in clinical practice. Two-week test-retest reliability of diagnoses from the CAPA and YAPA is comparable to that of other highly-structured child psychiatric interviews (Angold and Costello, 1995). Construct validity as judged by 10 different criteria including comparison to other interviews and ability to predict mental health service use is good to excellent (Angold and Costello, 2000).

Substance use data were collected for 18 substances, of which the 3 considered here are nicotine, alcohol, and cannabis (other drugs were too rarely reported, especially at earlier ages, for reliable analysis). Data on nicotine were analyzed including and excluding snuff (2.8% prevalence) and chewing tobacco (0.8% prevalence). The results were not significantly different so results for the whole data set are reported.

In these analyses, we use the term "substance use disorder" (SUD) to indicate abuse of or dependence on alcohol or cannabis, or dependence on nicotine. We do not make a distinction between abuse and dependence following the recommendation of Directors of NIDA and NIAAA (O'Brien et al., 2006), and evidence that a distinction between symptoms of abuse and dependence cannot be made on the grounds of severity (Hartman et al., 2008; Saha et al., 2006; Langenbucher et al., 2004).

2.4 Assessment of C-Reactive Protein

Our assay for CRP in whole-blood spots was a biotin-streptavidin based immunofluorometric system (Copeland et al., 2012a). One assay was completed for each subject at each observation. Microtiter plates coated with Streptavidin A (Invitrogen, Carlsbad, CA) bind CRP with a biotinylated capture antibody, clone C2 (Advanced ImmunoChemical, Long Beach, CA). A second Europium-labeled antibody (clone C6; Advanced ImmunoChemical Inc., Long Beach, CA) then binds to the Streptavidin A Biotin–C2–CRP complex; fluorescence of the resultant complex is directly proportional to the CRP concentration in each well. Minimum detectable dose for the assay is .010 mg/L. For low, medium, high, and very high controls (.022, .259, 1.208, and 3.271 mg/L, respectively), within-assay coefficient of variation (CV)(precision) is 2.0%, 1.2%, 1.6%, and 1.4%, respectively, while between-assay CV (reliability) runs 14.4%, 13.9%, 12.3% and 10.9%, respectively. CRP remains stable in dried blood spots for at least 5 days at room temperature or 14 days at 4 °C, and stable for years at −26 °C (McDade et al., 2007).

A validation study was performed with matched serum and blood spot samples assayed for CRP (n=38). As has been reported for many other analytes (Worthman and Stallings, 1997;

McDade et al., 1997), a close linear correlation was identified between serum and blood spot CRP values (n=29; R^2 = .98, p<.0001). Serum equivalents therefore were calculated using the following algorithm based on the serum-blood spot regression: serum (hsCRP) = 1.38*(Blood Spot CRP Value) –0.97. Blood spot CRP assays have been used in a number of epidemiologic studies (Williams and McDade, 2009; McDade et al., 2006, 2005). Observations with values above 10 mg/L indicate frank infection and were removed from statistical analysis (N=109 from a total of 6000 observations), whereas values below that index the extent of chronic low grade systemic inflammation associated with cardiovascular and metabolic risk (Pearson et al., 2003) Because other studies have used different cutpoints to indicate current infection,(27–30) analyses were repeated using cutpoints of 7 mg/L and 3 mg/L. Results were essentially the same, so we present results excluding values greater than 10 mg/L.

2.5 Assessment of covariates and stressors

Variables included as covariates or stressors were those associated with variation in CRP levels (Woodward et al., 2003; Elovainio et al., 2006b; O'Connor et al., 2009) or used as covariates in other longitudinal studies involving CRP (Gimeno et al., 2009; Stewart et al., 2009; Janicki Deverts et al., 2010; Matthews et al., 2010). These included age, sex, race, BMI, low SES, physical illness, medication use, and other psychiatric disorders, collected using the CAPA until age 16, and the YAPA thereafter (Angold and Costello, 2000; Angold et al., 1999). BMI was calculated from weight and height measurements completed at each assessment. A physical health problems survey adapted from the Centers for Disease Control and Prevention's National Health Interview Survey Child Health Supplement (1988) was administered at all interviews to assess 39 common ailments (e.g., diabetes, anemia, and infectious mononucleosis). A binary variable indicating any health ailment within the last 12 months was used for all analyses. Medication use within the prior year was also assessed from the Child and Adolescent Services Assessment (Ascher et al., 1996). Two covariates were included in these analyses: any psychotropic medication, and any other prescribed medication. Low SES was coded if the subject's family displayed any two of the following three indicators: income below the federal poverty line, low parental education attainment, low parental occupation status. Other physiological covariates studied with CRP in older samples at risk for cardiovascular problems (e.g., blood pressure, lipids, or insulin) were not assessed.

2.6 Analytic framework

CRP values were positively skewed and so were $\log_{10}$-transformed, adjusting the values by adding 1 to avoid negative numbers upon transformation. Models predicting drug symptoms employed Poisson regression, those predicting diagnostic status employed logistic regression and those predicting CRP employed linear regression. Predictive models used lagged values from the prior assessment to predict current levels of the outcome variable. As such, only subjects with multiple assessments were included, while subjects with more than two assessments contributed multiple observations. The covariance matrix for the predictive analyses was specified as autoregressive. All associations were tested using weighted regression models in a generalized estimating equations framework implemented by SAS PROC GENMOD. The robust variance (sandwich type) estimates derived from generalized

estimating equations adjust the standard errors of the parameter estimates for the stratified design and for subjects contributing multiple observations.

Missing data—By age 21, 8,806 assessments had been completed. Of these, bloodspots were obtained for 6,087 (69.1%). Bloodspots were not available either because the subject refused or because the participant had moved out of the study area and subsequent interviews were completed by phone. For in-person interviews, 79.4% of subjects agreed to provide bloodspots. Comparisons of observations in which blood spots were collected to those in which the subjects refused indicated no significant differences on any of the SUD outcomes. Of the 6,087 blood samples, 6000 (98.6%) were successfully assayed for CRP. For this set of analyses, 109 were removed because CRP levels were above 10 mg/L, indicating current infection. Thus, both CRP and phenotypic data were obtained for 5,891 observations on 1,334 of the 1,420 study participants (93.9%). The median number of CRP samples provided was 5 (mean =4.8 (SD=2.2), range =1–9).

3. RESULTS

Table 1, Column 1, shows the prevalences for the drug use diagnoses and covariates included in the analyses. In this fairly young sample (mean age 14.1, SD 7.9) the mean $\log_{10}$CRP level was rather low (0.19 mg/L, SD 0.20 mg/L). Any drug (use (excluding abuse or dependence) was reported in one in four interviews, and abuse/dependence in one in ten. As shown in Column 2, $\log_{10}$CRP levels were significantly higher in youth with any use (alcohol, nicotine and cannabis), and any abuse or dependence, specifically nicotine dependence.

As the second part of Column 2 shows, higher levels of CRP were associated with being 13 or over, being female, American Indian, poor, obese (BMI 30), in sub-optimal health, on psychotropic or other prescribed medications, and having any psychiatric disorder, but with no specific diagnosis. All of these factors continued in the multivariate model. Further analyses indicated that the reason for the higher CRP levels in American Indians was that they were at much higher risk of obesity (1 in 3, versus 1 in 9 white youth) and also more likely to be poor.

Tables 2 and 3 show results of a series of lagged regression models testing the bi-directional predictions to and from CRP and substance-related outcomes. Bolded numbers indicate statistically significant findings at p<.05. The first column shows the association between predictor and outcome controlling only for demographic variables (age, sex, race (American Indian vs. other) and previous history of the outcome; e.g., in Table 2, prediction from CRP level to any drug use, controlling for drug use at the previous assessment. The second column includes these variables and also the ones that were significantly associated with CRP in bivariate analyses (Table 1): fair or poor health, psychotropic or other prescribed medications, obesity (BMI>=30), and any psychiatric disorder excluding SUD. Because race and obesity were strongly associated with CRP levels in multivariate analyses, the interaction terms were also included in column 2 analyses.

Table 2 displays the results for lagged models predicting from prior CRP levels to the current substance-related outcomes. In the simple models without covariates, higher CRP levels at the previous wave predicted a higher likelihood of any cannabis use, but not alcohol use or nicotine use. It predicted abuse or dependence of any drug, and specifically cannabis abuse/dependence and nicotine dependence. When the covariates were added, any abuse/dependence and nicotine dependence remained significant, and there was a trend for cannabis use and abuse/dependence to be predicted by CRP ($p<.1$). In every case the significant covariates were age (older), race (American Indian), and obesity.

Table 3 displays the results of predicting from each substance variable to later CRP levels. Only one form of SUD – nicotine use – predicted higher levels of CRP. Significant covariates were age and having a diagnosis of depression.

4. DISCUSSION

The first notable finding of this study of inflammatory processes and SUD is that the bivariate cross-sectional associations were much stronger between CRP level and most forms of SUD than they were between CRP and other psychiatric disorders (Table 1). Apart from the "illicit drug" groups, which were very small in this fairly young sample, CRP levels were higher in youth with tobacco, alcohol, or cannabis use, and with nicotine dependence. Thus the data presented here are consistent with earlier work showing that cross-sectionally, higher levels of CRP are associated with both drug use and addiction (Arnson et al., 2010; O'Loughlin et al., 2008). In other examples of a link with tobacco, it is known that inflammatory cells produce a variety of mediators in response to smoking (Gonçalves et al., 2011). For example, Wannamethee et al.'s study of smoking and inflammatory markers in 2,920 British men showed that current smokers had higher levels of CRP than never-smokers, and a cross-sectional study of 2,999 Chinese men found that CRP increased across never, former and current smokers (Lao, 2009). Some work (Furie et al., 2000) also has linked elevated CRP levels to smokeless tobacco, and this needs further investigation. In the case of cannabis, a recent analysis of the NHANES data (Rajavashisth et al., 2012) found that the prevalence of elevated C reactive protein (>0.5 mg/dl) was significantly less among past or current users than among non-marijuana users, suggesting support for the idea that cannabis is anti-inflammatory. The GSMS had too few opiate users for the increase in CRP associated with opiate addiction (Reece, 2012b) to be seen here. Lastly, there is considerable evidence that adult non-drinkers and heavy drinkers have higher CRP concentrations than moderate drinkers (Imhof et al., 2001; Albert et al., 2003). However, this u-shaped relationship may not yet be visible in adolescence.

It is notable that in these data the associations between drugs and CRP were positive; that is, there was no sign of an anti-inflammatory effect, as some reports have suggested (Kelley and Dantzer, 2011; Roy et al., 2011). For example, the cross-sectional analyses of CRP levels (Table 1, Column 2) do *not* support the idea that cannabis protects against elevated CRP (16), at least in this young sample. Cross-sectional bivariate analyses again agreed with the literature (Raison et al., 2006; Miller et al., 2009; Copeland et al., 2012a, 2012b) in showing higher levels of CRP in older participants and in those with high BMI. As expected, higher CRP levels were associated with several intercorrelated indicators of lower socio-

economic status (poverty, less parental education, lower parental occupational status) as well as of poor health. The many significant associations with CRP levels seen in the cross-sectional data underline the difficulty of distinguishing between causal pathways and correlations among risk factors. As others have shown, (Davey Smith et al., 2005) there may be a strong association between inflammation and a disease endpoint that is nevertheless not causal.

Turning from correlation to prediction, CRP levels predicted a higher likelihood of cannabis use or abuse/dependence, of any abuse/dependence, and of nicotine dependence at the next assessment, controlling for previous history of SUD. Once other factors were entered into the models, the predictive relationships from CRP to cannabis use and addiction became non-significant, but those between CRP and any abuse/dependence and nicotine dependence remained. In every case, the same 3 covariates remained in the model: age, race (American Indian) and obesity. Significant findings may be the result of a pre-existing but unmeasured association between CRP and other risk factors for nicotine use, such as exposure to smoking in the household.

The associations in this study between CRP and some risk factors (high BMI, low SES, medication use, less than optimum health) are consistent with the literature linking higher CRP with lower socioeconomic status and its attendant risks (Miller et al., 2009). On the other hand we found no association with most psychiatric disorders, unlike earlier studies. This may be because earlier studies often used clinical samples, or because they did not include relevant covariates. A previous paper (Copeland et al., 2012a) from this study linked higher CRP with repeated episodes of depression, rather than with any particular episode, but we lacked power to test whether repeated depression mediated the effect of drug use or addiction on CRP.

Predicting from diagnosis to CRP only one finding was significant: that from nicotine use to higher levels of CRP at the next assessment, controlling for past CRP level. In predictions from diagnosis to CRP, age was a significant covariate but race and BMI were not. A history of psychiatric comorbidity was significant, but this was not specific to any particular disorders.

Further work is needed to explore the reasons why nicotine was the only substance among those tested to show cross-sectional, predictive, and consequent relationships to high CRP. A limitation of the analyses is that the data for nicotine use and dependence is presented without distinguishing between effects of smoking cigarettes and ingesting nicotine (Hastie et al., 2008). Space in this paper is insufficient to explore the different associations of CRP with smoking and non-smoking tobacco use (snuff and chewing tobacco), which we will pursue in more detail elsewhere. Despite a growing literature linking smoking and CRP (Villegas et al., 2012; Yanbaeva et al., 2007) work on the biological mechanism is ongoing (Lee et al., 2012; Mao et al., 2012; Rose et al., 2010).The closer association of CRP to nicotine than to alcohol and cannabis may have something to do with the youth of the sample: we will be able to test this in later study waves.

These analyses suggest that the rather confused literature concerning a causal relationship between inflammatory processes and drug use may be responding to the fact that drug use is closely associated with a range of inflammation-related health risks, including obesity; indeed, some (Volkow et al., 2008) have argued that food and drug addiction result from similar mechanisms; i.e., by increasing dopamine in limbic regions.

The Great Smoky Mountains Study sample has several limitations. It is not representative of the U.S. population (African Americans and Latinos are underrepresented). Nor does it include sufficient numbers of individuals addicted to opiates (Reece, 2012a), methamphetamine, or other illicit drugs to test for association with CRP in this age group.

The time between any two assessments was never less than a year, yet both CRP levels and substance symptoms vary over shorter periods. For example, levels of CRP begin to rise within hours following acute infection and peak within 48 hours. In looking at the bi-directional associations it is important to keep in mind that the pathways evident over longer periods of time (> 1 year) may differ from those over shorter periods (1 month or 1 hour).

Population studies have consistently shown that there is no clear cut-point between "normal" and elevated levels of CRP (Kushner et al., 2010). In these analyses we excluded values above 10 mg/L (1.5% of all observations) as likely to signal current physical illness. Using the standard definition of "elevated" CRP as >3mg/L, 89.2% of GSMS observations were lower than this, compared with, for example, 62% of about 9,000 subjects (mainly adults) from the 1999–2002 National Health and Nutrition Examination Survey (Woloshin and Schwartz, 2005). Thus, this young and fairly healthy sample may not show effects seen in older or clinical samples.

This study shows that there are both concurrent and predictive associations between several types of drug use and addiction and inflammatory cytokines. CRP showed a strong relationship to obesity, which is well known to be associated with many correlates of drug use and addiction, such as poverty, forming a complex nexus of biological and environmental exposures predictive of later disease and mortality. The association between CRP and substance use disorders even quite early in life, and the increased levels of inflammation with age, together point toward a potential for a stronger relationship between substance use and inflammation later in life

Acknowledgments

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Table 1

3-month prevalence of substance use disorders and covariates, and bivariate associations with CRP

	Column 1: Total sample (n=5,891 observations)	Column 2: Bivariate association with CRP:
CRP: Mean mg/L (SD)	0.88 (1.05)	
CRP: Mean log CRP, mg/L (SD)	0.19 (0.20)	
Substance use in past 3 months:	**Percent (95% CI)**	**Beta (Standard Error) p**
	25.6 (23.0, 28.4)	**0.94 (0.01) p<.0001**
Any use[&]	17.3 (15.6, 19.2)	**0.92 (0.02) p<.0001**
Alcohol use [&]	12.2 (10.4, 14.4)	**0.91 (0.01) p<.0001**
Nicotine use[&]	7.5 (6.2, 8.9)	**0.92 (0.02) p=.0006**
Cannabis use[&]	1.4 (1.0, 2.0)	0.97 (0.03) p=.437
Other illicit drug use[&]	10.9 (9.4, 12.7)	**0.92 (0.02) p<.0001**
Any abuse or dependence	4.0 (3.2, 5.1)	0.96 (0.02) p=.121
Alcohol abuse or dependence	5.3 (4.3, 6.4)	**0.89 (0.02) p<.0001**
Nicotine dependence	3.8 (3.1, 4.7)	0.98 (0.02) p=.283
Cannabis abuse/dependence	0.06 (0.04, 1.0)	0.99 (0.01) p=.651
Other illicit abuse or dependence		
Covariates:	**Percent (95% CI)**	
Age (number of observations):		
9–12	30.4 (28.5, 32.3)	1.00 (0.01) p=.8222
13–16	45.0 (43.2, 47.2)	**0.98 (0.01) p<.0001**
19–21	24.4 (22.4, 26.3)	**0.99 (0.01) p=.003**
Sex (% male)	51.0 (46.6, 55.5)	**1.03 (0.02) p=.047**
Race (% American Indian)	89.6 (87.4, 91.9)	**3.2 (0.07) p<.0001**
Low SES	20.0 (17.6, 22.4)	**0.95 (0.01) p=.0002**
Fair/poor health	33.7 (30.9, 36.5)	**0.97 (0.01) p<.006**
Psychotropic medication	5.5 (4.1, 8.3)	**0.92 (0.03) p=.002**
Other prescribed medication	16.1 (13.0, 19.9)	**0.92 (0.01) p<.0001**
Body mass index >=30	10.6 (8.7, 13.0)	**0.78 (0.02) p<.0001**
Any psychiatric diagnosis[$]	14.1 (12.4, 16.0)	1.01 (0.13) p=.387

[&]Excluding abuse or dependence

[$]Excluding Substance Use Disorders

Associations significant at p<.05 are shown in bold

Table 2

Predictions from CRP to drug use and addiction

Predictor At Preceding assessment	Outcome	Effects of prior predictor					
		Simple		Adjusted for covariates		Significant covariates $
		β (SE)	P	β (SE)	P	
CRP	Any use	1.00 (0.01)	.768			
CRP	Alcohol use	1.00 (0.01)	.781			
CRP	Nicotine use	1.01 (0.01)	.301			
CRP	Cannabis use	**1.03 (0.01)**	**.006**	1.02 (0.01)	.057	1, 3, 4
CRP	Any abuse/dependence	**1.05 (0.02)**	**.004**	**1.04 (0.02)**	**.034**	**1, 3, 4**
CRP	Alcohol abuse/dependence	1.01 (0.03)	.662			
CRP	Nicotine dependence	**1.06 (0.02)**	**.004**	**0.06 (0.02)**	**.001**	**1, 3, 4**
CRP	Cannabis abuse/dependence	**1.03 (0.02)**	**.003**	1.03 (0.02)	.079	1, 3, 4

Predictions significant at p<.05 are shown in bold

$ Significant covariates: 1=age (older), 2=male sex, 3=White, 4=BMI, 5=low SES, 6=poor or fair health, 7=psychotropic medication, 8=other medication, 9=any psychiatric disorder excluding SUD

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Table 3

Prediction from drug use and addiction to CRP levels

Predictor at preceding assessment	Out-come	Effects of prior predictor					
		Simple		Adjusted for covariates		Significant covariates
		β (SE)	P	β (SE)	P	
Any use	CRP	1.09 (0.36)	.768			
Alcohol use	CRP	0.78 (0.42)	.643			
Nicotine use	CRP	**1.10 (0.81)**	**.027**	**2.67 (1.25)**	**.033**	**1, 9**
Cannabis use	CRP	1.57 (1.10)	.514			
Any abuse/dependence	CRP	0.86 (0.55)	.824			
Alcohol abuse/dependence	CRP	0.24 (0.23)	.146			
Nicotine dependence	CRP	0.73 (0.51)	.658			
Cannabis abuse/dependence	CRP	3.31 (3.10)	.19538			

$^{\$}$Significant covariates: 1=age (older), 2=male sex, 3=White, 4=BMI, 5=low SES, 6=poor or fair health, 7=psychotropic medication, 8=other medication, 9=any psychiatric diagnosis