HHS Public Access

Author manuscript

Am J Med. Author manuscript; available in PMC 2020 November 01.

Published in final edited form as:

Am J Med. 2019 November ; 132(11): 1327–1334.e1. doi:10.1016/j.amjmed.2019.04.045.

Cannabis Use and Markers of Systemic Inflammation The Coronary Artery Risk Development in Young Adults Study

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Abstract

Background: Whether cannabis use in humans plays a role in the regulation of inflammatory responses is unclear. The objective of the current research is to study cannabis-attributable immunomodulation as manifest in levels of fibrinogen, C-reactive protein (CRP), and interleukin-6 (IL-6).

Methods: The Coronary Artery Risk Development in Young Adults study is a cohort of 5115 black and white men and women enrolled in 1985-1986, and followed up for over 25 years, with repeated measures of cannabis use. Fibrinogen levels were measured at Y5, Y7, and Y20, CRP levels were measured at Y7, Y15, Y20, and Y25, and IL-6 levels were measured at Y20. We estimated the association of cannabis use and each biomarker using Generalized Estimating Equations adjusting for demographic factors, tobacco cigarette smoking, alcohol drinking, and body mass index.

Results: Compared to never use (reference), recent cannabis use was not associated with any of the biomarkers studied here after adjusting for potential confounding variables. Former cannabis use was inversely associated with fibrinogen levels ($\beta = -5.4$; 95% CI = −9.9, −0.9), whereas the associations were weaker for serum CRP ($\beta = -0.02$; 95% CI = −0.10, 0.06) and IL-6 ($\beta = -0.06$; 95% CI= −0.13, 0.02).

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Declarations of interest: none

Conclusions: A modest inverse association between former cannabis use and fibrinogen was observed. Additional studies are needed to investigate the immunomodulatory effects of cannabis while considering different cannabis preparation and mode of use.

Keywords

Cannabis; Fibrinogen; C-reactive protein; Inflammation; CARDIA; Prospective

Introduction

The discovery of endogenous cannabinoids and the cannabinoid receptors (CB1 and CB2) has provided a platform for the investigation of the health effects of cannabinoids. Whereas CB1 receptor is predominantly expressed in the central nervous system, CB2 is primarily expressed in the immune system (1). The first evidence that cannabinoids modulate immune responses and cytokine production was found in the mid-1980s (2). Both pro-inflammatory and anti-inflammatory effects of cannabis were demonstrated in pre-clinical studies (3).Yet there has been little epidemiological research on this topic (4–6), and a recent National Academy of Sciences, Engineering and Medicine report on the health effects of cannabis and cannabinoids concluded that “there is insufficient evidence to draw overarching conclusions concerning the effects of cannabis smoke or cannabinoids on immune competence (7).

We aim to add new epidemiological estimates to the cannabis-immunomodulatory body of research using the Coronary Artery Risk Development in Young Adults (CARDIA) study with 25 years of repeated measurements of cannabis use (8). Specifically, CARDIA leverages longitudinal data on cannabis use with measurement on fibrinogen, C-reactive protein (CRP), and interleukin-6 (IL-6), each integral to immune response. Fibrinogen is an important component of the coagulation cascade associated with inflammation (9, 10). CRP is an acute phase reactant synthesized primarily by the liver, with levels increasing in response to injury, infection, or inflammation (11). Interleukin-6, a precursor of CRP, is a key cytokine produced by leukocytes as well as a variety of other cells, promoting B cell differentiation, expansion and activation of T cells (12). Studying fibrinogen, CRP, and IL-6 prospectively will provide a more comprehensive understanding of the relationship of cannabis use with immune-response than previously assessed.

Methods

Study population

The CARDIA study was designed to measure risk factors for cardiovascular disease in a biracial (Black and White) cohort of 5115 women and men who underwent their initial exam in 1985-1986. The study was designed to provide approximately equal representation across groups of age, sex, race, and education.

Community-based random sampling was performed in Birmingham, Chicago, and Minneapolis. In Oakland, respondents living in Oakland and Berkeley were randomly recruited from the Kaiser Permanente health plan membership. Follow-up examinations

occurred during 1987-1988 (Year 2), 1990-1991 (Year 5), 1992-1993 (Year 7), 1995-1996 (Year 10), 2000-2001 (Year 15), 2005-2006 (Year 20), and 2010-2011 (Year 25), with retention rates at each follow-up of 91%, 86%, 81%, 79%, 74%, 72% and 72% respectively. All measurements were taken by trained and certified technicians according to the CARDIA manual of operations. Participants were asked to attend a morning examination after fasting for 12 hours and to avoid smoking and heavy physical activity for 30 minutes before the exam. Quality of the data collection was monitored by the Coordinating Center and the CARDIA Quality Control Committee. The study was approved by an institutional review board at each CARDIA study site. All participants provided written informed consent at each examination (8).

Main outcome: Markers of inflammation

Fibrinogen, mg/dL (Y5, Y7 and Y20)—At Y5, fibrinogen was assayed by the Clauss method, and at Y7 and Y20 using a nephelometry-based assay (BNII nephelometer Dade Behring, Deerfield, Illinois, USA) (13, 14).

C-reactive protein, mg/L (Y7, Y15, Y20 and Y25)—At Y7, Y15, and Y20, CRP was measured using a nephelometry-based high throughput assay (BNII nephelometer Dade Behring, Deerfield, III). At the Y25 exam, CRP was measured using a Roche latex-particle enhanced immunoturbidimetric assay kit. The two CRP measurement methods are highly associated (r = 0.99) (15).

Interleukin-6, pg/mL (Y20)—IL-6 was measured atY20 by an ultra-sensitive enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN).

Main exposure: Cannabis use

The covariate of central interest is cannabis use. A detailed self-administered questionnaire based on items from the National Household Survey on Drug Abuse was administered at each exam. All participants were asked about the frequency of lifetime use (never use, 1-2 times, 3-9 times, 10-99 times and 100+ times). Some individuals changed their response from one exam to another (32% of the participants at Y25 had a higher value for cannabis use in one or more of the earlier exams). For these participants, the longest lifetime use value was carried forward.

Recent use was determined from the following question: “During the last 30 days, on how many days did you use marijuana?”. Recent use was defined as cannabis use at least once in the 30 days prior to the interview. From this response, we additionally created a cannabis-year variable, with 1 year equivalent to 365 days of use as described elsewhere (16, 17).

Other covariates

Height and weight were measured with the participant wearing light clothing and no shoes. Height was recorded to the nearest 0.5 cm and weight to the nearest 0.2 Ib. Body mass index (Kg/m^2) was calculated as weight divided by height squared. Age at baseline was computed from the reported birth date. Sex, race, and years of education were self-reported. Tobacco use was assessed at each examination. These data, along with baseline exam data on past

years of cigarette smoking, were used to estimate lifetime exposure to cigarettes in terms of pack-years. Alcohol intake (mL/day) was computed from the self-reported frequency of beer, wine, and liquor consumed per week. Alcohol consumption was categorized as nondrinker, <1 drink (12 mL) /day, or > 1 drink per day.

Statistical Analysis

We first used descriptive statistics to compare participants at the first examination that measured a biomarker of interest (Y5) by cannabis use status. To investigate the impact of bias introduced by loss to follow-up (cohort attrition, and hence no single available measurement on fibrinogen, CRP, orY20 IL6), we used inverse probability weighting (IPW). Logistic regression modelling yielded estimates of the probability of having at least 1 fibrinogen measurement (probability of inclusion) controlling for Y0 covariates (age, sex, race, education level, examination center, cannabis use, cigarette smoking, alcohol consumption and BMI). Similar models were constructed for CRP and IL-6. There were 4623 Individuals with at least one fibrinogen measurement over the 3 exams, 4538 individuals with at least one CRP measurement over the 4 exams, and 3494 participants with IL-6 measurement at Y20. The weights applied to individuals, *j*, were the inverse of this inclusion probability.

The missing data pattern on cannabis use and other predictors was arbitrary. Using data from all 8 exams, we used multiple imputations (MI) to generate 10 complete datasets by replacing missing values of predictors using sequential regression multivariate imputations (also known as chained equations, 18). Within the imputation model, normal continuous variables were imputed by linear regression, predictive mean matching was used to impute non-normal continuous variables, and logistic regression was used to impute categorical variables.

Generalized Estimating Equations (GEE) were then used to evaluate whether cannabis use might be associated with each of the biomarkers studied here (19). The GEE approach permits inclusion of all participants for whom there is at least one response variable available rather than restricting the analysis to participants with 100% complete data, as would be required for standard multivariate analyses of variance. Slope estimates were obtained from the GEE analyses using the robust estimator method and the unstructured correlation structure. We used linear regression to model the cross-sectional association of cannabis use and log-transformed IL-6 at Y20. Analyses were performed in Stata (version 14.1; StataCorp).

Results

Table 1 displays characteristics of the participants at the first examination that measured a biomarker of interest by cannabis use status. At Y5, approximately 79% of the participants used cannabis at least once in their lifetime, and 16% used cannabis in the 30 days prior to the interview. Recent cannabis users were more likely to be males, tobacco cigarette smokers, have high school education or less, and consume more than one drink of alcoholic beverages per day.

Figure 1 displays the levels of fibrinogen and CRP at each exam by cannabis use status. Overall, cannabis users have lower levels of fibrinogen and CRP compared to never users. Levels of fibrinogen, CRP or IL6 did not differ among participants included in the current analyses or those excluded due to medical conditions associated with inflammation ($p>0.05$).

Results from the IPW model indicated that attrition was associated with recent cigarette smokers at Y0, but was not associated with recency of cannabis use at Y0 (data are not shown in figure/table).

Fibrinogen

For fibrinogen analyses, we excluded participants who were pregnant, or who reported heart disease, liver disease, cancer or HIV at the time of any of the 3 exams (n = 977). The final analytic sample size was 3646, and the mean number of fibrinogen measurements per participant was 2.5.

Using GEE with MI and IPW, we observed lower plasma fibrinogen levels summarized over the 3 exams among former cannabis users when compared to never users (Table 2 panel A). We observed an association between recent cannabis use and fibrinogen levels after adjustment for age and sex, but this association was no longer statistically significant after adjusting for BMI and other potential cofounders ($\beta = -1.6$; 95% CI= −7.3, 4.1). Our conclusions did not change when multiple imputations were not used (complete case analyses, Supplemental Table 1).

We additionally observed an association between self-reported cannabis use frequency and fibrinogen levels. The association of 11-99 uses/lifetime and 100+ uses/lifetime persisted after adjusting for BMI. When we calculated and modelled cannabis-year variable assuming no change in cannabis use status/frequency between exams, cannabis use for 1 year or less in lifetime was associated with lower fibrinogen levels (Table 3). The association of more frequent cannabis use (>1 year in lifetime) and fibrinogen levels failed to reach statistical significance after adjusting for potential confounders ($\beta = -4.4$, 95% CI = −10.7, 1.9).

CRP

For analyses on CRP levels, participants who were pregnant or ever reported heart disease, liver disease, cancer or HIV at the time of any of the 4 exams were excluded from the current analyses (n = 1229). The mean number of CRP measurements per participant was 3.1 (Final analytic n = 3309).

Recent cannabis use was not associated with CRP levels summarized over the 4 exams (Table 2 Panel B). After adjustment for age and sex, we observed attenuation in our estimates and no longer observed an association between former cannabis use and CRP. We observed an inverse association between infrequent cannabis use (11-99 times/lifetime) and CRP levels, but this association was attenuated after adjusting for BMI. Similarly, null results were observed when we used the calculated cannabis-year variable (Table 3).

IL-6

Recent cannabis use was not associated with IL-6 levels, whereas former cannabis use was associated with lower IL-6 at Y20 compared to never users (results are not shown in figure/table). This association did not persist after adjustment for potential confounders ($\beta = -0.06$, 95% Cl= −0.13, 0.02). Null findings ($p>0.05$) were observed when modelling lifetime frequency of cannabis use (self-reported or calculated cannabis-years) after adjusting for BMI (results are not shown in figure/table).

Discussion

In this biracial cohort of young adults followed to middle age, we found a modest inverse association between former history of cannabis use and fibrinogen levels. This cannabis association seems to be limited to occasional/infrequent cannabis users (1 year or less/lifetime). However, the smaller sample size of the heavy use group (1 + year/lifetime group) might not be sufficient to detect an association. The association was weaker for CRP and IL-6, and though inverse, it did not persist after adjusting for potential confounders. We did not observe evidence of an association between recent cannabis use and any of the inflammatory biomarkers studied here.

A large body of pre-clinical research exists on the immunomodulatory effects of cannabinoids. Immune cells have been shown to express cannabinoid receptors (20). Upon activation of the cannabinoid receptors, a reduction of T cell proliferation occurs that has been associated with regulation of cytokines such as IL-6 (21,22). Pre-clinical studies also indicate that cannabinoid receptors are present on circulating platelets, contributing to platelet function (23). Cannabinoid administration was found to affect platelet activation and aggregate formation through Glycoprotein IIb/IIIa, the receptor for fibrinogen on platelets (24). Fibrinogen levels might provide new insights into the risk of occlusive vascular disease among cannabis users given reports of acute cardiovascular events among cannabis users with normal coagulation profile (25).

Prior epidemiological studies of cannabis use and inflammation are scarce, and their results were inconclusive. For example, higher blood spot CRP levels have been reported among cannabis users of a community-based sample of adolescents whereas lower IL-6 levels have been detected among lifetime cannabis users in a community-based sample of middle-aged African Americans (5, 6). Analyzing data from the Third National Health and Nutrition Examination Survey (NHANES), Rajavashisth and colleagues found lower CRP values among former cannabis users, whereas using the continuous NHANES 2005-2010, we previously reported an association between recent cannabis use and lower CRP at CRP levels below the median (4, 26).

Sociodemographic variables (race, education, examination center location) and alcohol use were positive confounders and attenuated the estimates appreciably when added to the models. Tobacco cigarette smoking and cigarette pack-year acted as negative confounders, and this can be explained by the close positive association with both cannabis use and inflammatory biomarkers. Hence, tobacco cigarette smoking if not accounted for, can attenuate the inverse association of cannabis and fibrinogen levels as seen in our model.

The impact of BMI on the relationship of cannabis use and inflammation is unclear. In this study, the results were greatly attenuated with the addition of BMI as a covariate in the statistical models. An inverse association between cannabis use and BMI was reported in previous cross-sectional studies (27–29). In Waves III and IV of the National Longitudinal Survey of Adolescent Health, female participants using cannabis daily had a BMI that is approximately 3.1% lower than that of non-users, and among males, daily-users had a BMI that is approximately 2.7% ($p<0.01$) lower than that of non-users (30). Recently, we have reported attenuated BMI gain in cannabis users (31). Prior evidence from CARDIA has reported that greater lifetime cannabis use was not associated with BMI but was associated with lower waist circumference (17). We acknowledge that lower body adipose tissue might prompt lower secretion of inflammatory cytokines, and hence this might explain the inverse association observed here (32). Research aimed to elucidate the direction of this relationship suggests that the association of inflammatory biomarkers such as CRP and BMI is likely to be driven by BMI, with CRP being a corollary of elevated adiposity (33).

Overall, the study findings are of interest given the previously reported findings on the immunomodulatory effects of cannabinoids, where prior pre-clinical studies have demonstrated cannabinoid effects on immune cell proliferation, antibody formation, and cytokine production (34). The CARDIA study has numerous inherent strengths, including prospective study design with multiple measurements, detailed interviews and collection of biological specimens.

Several of the current study limitations merit attention. In addition to the inherent limitations of observational studies, cannabis use was self-reported and not assessed via biomarkers of cannabis use/exposure. Measurement errors are possible, particularly in the domain of non-reporting of actual cannabis use (35). Some participants classified as non-recent users actually might have been active users of cannabis. Although smoking is the most common mode of cannabis use, mode of cannabis use was not specified in the questionnaire. A number of combustion byproducts implicated in inflammatory processes are present in cannabis smoke (36). Hypothetically, the presence of these chemicals might affect the immunomodulatory effects of cannabis when smoked, whereas cannabis from edible food products lack their presence. The biological half-life of CRP (19 hrs) and IL-6 (2-6hrs) is less than 1 day whereas the biological half-life of fibrinogen is relatively longer (3 to 5 days) (9, 11, 12). Biomarkers of inflammation and cannabis use status might vary over shorter periods and our results might be related to the short-term effects of cannabis use and not the long-term effects. In addition, it is unclear why former but not recent cannabis use would be associated with fibrinogen and we cannot eliminate the possibility that the observed association is spurious (i.e., owing to some unobserved third variables). For example, there might be a health selection process similar to a ‘healthy smoker’ effect so that individuals might not take up/maintain the habit of cannabis use because they have an underlying health condition related to inflammation.

In conclusion, we observed that former users of cannabis had lower fibrinogen levels compared to never users. However, firm causal inferences cannot be made, as we did not observe that recent cannabis users had lower levels of fibrinogen. We also observed that

greater reported lifetime use was associated with lower fibrinogen level, but not with CRP or IL-6 level.

Given the ongoing policy debates regarding legalization of cannabis use, there is a need to study the health effects of cannabis as used (different preparations and potency, and different mode of administration), supported with the pre-clinical evidence focusing on individual cannabinoid chemicals. In clinical settings, physicians might need to monitor fibrinogen levels among cannabis users especially those who are at risk of hypofibrinogenemia. In conclusion, this investigation represents a step forward in research to promote our understanding of immunomodulatory effects of cannabis use, but it is clear that more research will be needed in order to secure more definitive evidence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the participants and staff of the CARDIA study. This work would not have been possible without them. The CARDIA study is conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with the University of Alabama at Birmingham (HHSN268201300025C and HHSN268201300026C), Northwestern University (HHSN268201300027C), the University of Minnesota (HHSN268201300028C), the Kaiser Foundation Research Institute (HHSN268201300029C) and Johns Hopkins University School of Medicine (HHSN268200900041C). The CARDIA study is also partially supported by the Intramural Research Program of the National Institute on Aging (NIA) and an intra-agency agreement between the NIA and NHLBI (AG0005). This manuscript has been reviewed by CARDIA for scientific content. The views expressed in this manuscript are those of the authors and do not necessarily represent the views of the National Institutes of Health or the U.S. Department of Health and Human Services.

Funding source: Michigan State University, National Center for Complementary and Integrative Health (AT009156 to OA) and National Institute of Drug Abuse (K05DA01579 to JCA). Dr. Sidney is the Oakland, California CARDIA Field Center PI (National Heart, Lung, and Blood Institute HHSN268201800004I).

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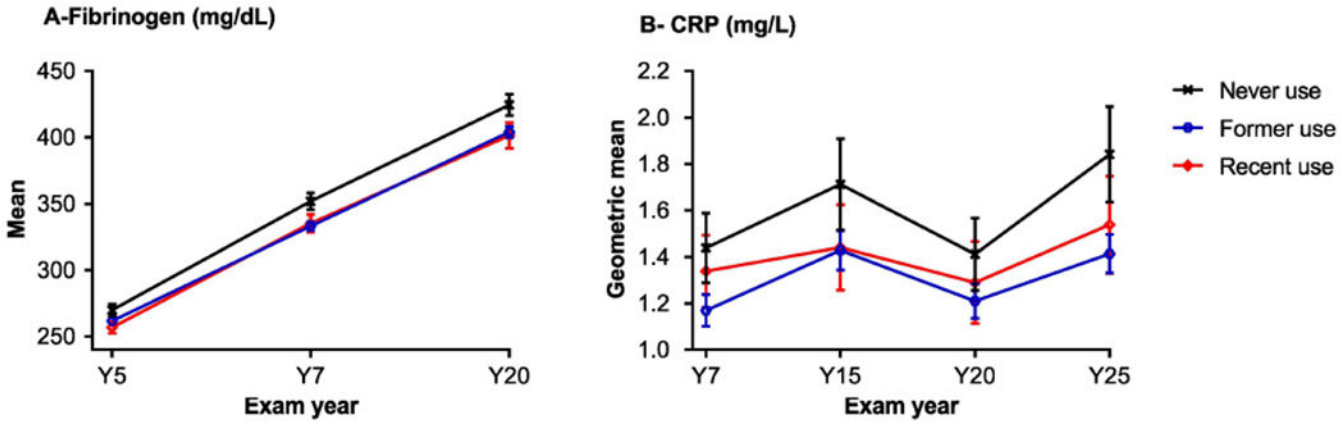

Figure 1:

Fibrinogen and CRP levels by cannabis use at each exam. CARDIA Study; Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA

Plotted bars represent 95% confidence intervals.

Table 1:

Characteristics of the study participants at the first exam a biomarker was measured (Y5, n=4307V CARDIA Study: Birminaham. AL: Chicaao. IL: Minneaoolis. MN: and Oakland. CA

Characteristics	**Cannabis use status at Y5**			
	Never (n = 907)	**Former (n = 2699)**	**Recent (n = 701)**	***P*-value[a]**
	Mean (SD) or n (column %)[b]			
Mean age (years)	29.3 (3.9)	30.2 (3.5)	29.8 (3.6)	<0.0001
Women	555 (61.2%)	1545 (57.2%)	271 (38.7%)	<0.0001
African American	541 (59.6%)	1192 (44.2%)	364 (51.9%)	<0.0001
Examinadon center				<0.0001
Birmingham	324 (35.7%)	526 (19.5%)	87 (12.4%)	
Chicago	195 (21.5%)	601 (22.3%)	126 (18.0%)	
Minneapolis	179 (19.7%)	792 (29.3%)	234 (33.4%)	
Oakland	209 (23.0%)	780 (28.9%)	254 (36.2%)	
≤12 years of education	261 (28.8%)	803 (29.8%)	304 (43.4%)	<0.0001
Recent tobacco cigarette smokers	87 (9.6%)	785 (29.1%)	359 (51.4%)	<0.0001
Lifetime tobacco cigarette pack-year (years)	0.9 (3.2)	3.6 (6.4)	4.8 (6.2)	<0.0001
Alcohol drinking				<0.0001
0 drink/day	639 (70.6%)	1187 (44.0%)	128 (18.3%)	<0.0001
≤1 drink/day	180 (19.9%)	808 (30.0%)	171 (24.5%)	
>1 drink/day	86 (9.5%)	702 (26.0%)	399 (57.2%)	
BMI (Kg/m^2)	27.0 (6.5)	26.0 (5.8)	25.8 (5.2)	<0.0001

[a] *P*-value for global test: ANOVA for continuous variables and Pearson $\chi 2$ tests for categorical variables.

Percentages may not add up to 100% due to rounding.

Table 2:

Estimated relationship[a] of cannabis use status (at Y5, Y7, Y20) and fibrinogen levels (mg/dl at Y5, Y7, Y20, n = 3646), and cannabis use status (at Y7, Y15, Y20, Y25) and CRP levels (mg/L at Y7, Y15, Y20, Y25, n = 3309). CARDIA Study; Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA

Cannabis use	Never use	Recency of use		Lifetime frequency of use		
		Any former use	Recent use	1-10 times	11-99 times	100+times
Panel A: Fibrinogen β (95% CI)						
Crude	0 (reference)	−11.5 (−16.9, −6.1)	−11.4 (−17.9, −5.0)	−3.9 (−10.4, 2.7)	−12.2 (−18.6, −5.8)	−16.8 (−22.9, −10.8)
Model 1[b]	0 (reference)	−9.8 (−15.0, −4.6)	−6.8 (−13.0, −0.6)	−4.8 (−11.1, 1.5)	−12.4 (−18.5, −6.3)	−10.2 (−16.1, 4.4)
Model 2[c]	0 (reference)	−6.2 (−11.5, −0.9)	−2.4 (−8.9, 4.1)	−2.1 (−8.3, 4.0)	−8.0 (−14.2, −1.9)	−7.8 (−13.9, −1.6)
Model 3[d]	0 (reference)	−5.4 (−9.9, −0.9)	−1.6 (−7.3, 4.1)	−2.5 (−7.7, 2.8)	−5.4 (−10.7, −0.2)	−7.1 (−12.5, −1.7)
Panel B: natural log (CRP) β (95% Cl)						
Crude	0 (reference)	−0.12 (−0.22, −0.03)	−0.13 (−0.24, −0.02)	−0.06 (−0.18, 0.05)	−0.16 (−0.28, −0.05)	−0.14 (−0.25, −0.03)
Model 1[b]	0 (reference)	−0.09 (−0.19, 0.00)	−0.07 (−0.19, 0.04)	−0.07 (−0.18, 0.05)	−0.15 (−0.27, −0.04)	−0.05 (−0.16, 0.06)
Model 2[c]	0 (reference)	−0.06 (−0.15, 0.04)	−0.04 (−0.15, 0.08)	−0.03 (−0.14, 0.08)	−0.10 (−0.22, 0.01)	−0.04 (−0.15, 0.07)
Model 3[d]	0 (reference)	−0.02 (−0.10, 0.06)	0.00 (−0.10, 0.10)	−0.02 (−0.12, 0.07)	−0.02 (−0.12, 0.07)	−0.01 (−0.10, 0.08)

[a]Slope estimates were obtained from the generalized estimating equation modelling using the robust estimator method and the unstructured correlation matrix. Terms for year of examination were added to all models to capture variability in the assay or ambient time trends not subsumed by age

[b]Estimates were adjusted for age (years) and sex.

[c]Estimates were additionally adjusted for Y0 demographics (race, examination center location), and time-dependent education level, recent tobacco use, tobacco cigarette pack year, and alcohol drinking status

[d]Estimates were additionally adjusted for time-dependent BMI (Kg/m^2)

Missing data on cannabis use and other covariates were handled by multiple imputations (10 dataset)

Inverse probability weighting was applied to all analyses. The mean ± SD of the IPW used in the fibrinogen analyses was 1.1 ± 0.06 (range: 1.0, 1.4), and the mean ± SD of the IPW used in the CRP analyses was 1.1 ± 0.07 (range: 1.0, 1.5).

Table 3:

Estimated relationship[a] of cannabis-years (at Y5, Y7, Y20) and plasma fibrinogen (mg/dl at Y5, Y7, Y20, n = 3646) levels, and cannabis-years (at Y7, Y15, Y20, Y25) and CRP (mg/L at Y7, Y15, Y20, Y25, n = 3309) levels. CARDIA Study; Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA

Cannabis use	**Never use**	**Cannabis-years**		
		<6 months of use/lifetime	**6 months-1 year of use/lifetime**	**>1 year of use/lifetime**
		Panel A: Fibrinogen		
			β (95% CI)	
Crude	0 (referent)	−8.7 (−14.3, −3.0)	−16.0 (−22.1, −9.8)	−14.0 (−21.0, −6.9)
Age-sex adjusted	0 (referent)	−9.3 (−14.6, −3.9)	−10.3 (−16.2, −4.4)	−6.4 (−13.2, 0.5)
Multivariable adjusted[b]	0 (referent)	−5.5 (−10.8, −0.1)	−7.4 (−13.5, −1.2)	−4.5 (−11.6, 2.6)
Additionally adjusted for BMI[c]	0 (referent)	−4.1 (−8.7, 0.5)	−6.9 (−12.4, −1.5)	−4.4 (−10.7, 1.9)
		Panel B: ln (CRP, β (95% CI)		
Crude	0 (referent)	−0.13 (−0.23, −0.03)	−0.15 (−0.26, −0.04)	−0.09 (−0.20, 0.02)
Age-sex adjusted	0 (referent)	−0.13 (−0.22, −0.03)	−0.07 (−0.18, 0.04)	0.01 (−0.10, 0.12)
Multivariable adjusted[b]	0 (referent)	−0.07 (−0.17, 0.02)	−0.04 (−0.16, 0.07)	0.00 (−0.11, 0.12)
Additionally adjusted for BMI[c]	0 (referent)	−0.03 (−0.11, 0.05)	−0.02 (−0.12, 0.08)	0.02 (−0.08, 0.12)

[a]Slope estimates were obtained from the generalized estimating equation modelling using the robust estimator method and the unstructured correlation matrix. Terms for year of examination were added to all models to capture variability in the assay or ambient time trends not subsumed by age

[b]Estimates were adjusted for Y0 demographics (age, sex, race, examination center location), and time-dependent education level, recent tobacco use, tobacco cigarette pack year, and alcohol drinking status

[c]Estimates were additionally adjusted for time-dependent BMI (Kg/m^2).

Missing data on cannabis use and other covariates were handled by multiple imputations (10 dataset)

Inverse probability weighting was applied to all analyses. The mean ± SD of the IPW used in the fibrinogen analyses was 1.1 ± 0.06 (range: 1.0, 1.4), and the mean ± SD of the IPW used in the CRP analyses was 1.1 ± 0.07 (range: 1.0, 1.5).