Original Investigation

Associations Between Cannabis Use and Physical Health Problems in Early Midlife

A Longitudinal Comparison of Persistent Cannabis vs Tobacco Users

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IMPORTANCE After major policy changes in the United States, policymakers, health care professionals, and the general public seek information about whether recreational cannabis use is associated with physical health problems later in life.

OBJECTIVE To test associations between cannabis use over 20 years and a variety of physical health indexes at early midlife.

DESIGN, SETTING, AND PARTICIPANTS Participants belonged to a representative birth cohort of 1037 individuals born in Dunedin, New Zealand, in 1972 and 1973 and followed to age 38 years, with 95% retention (the Dunedin Multidisciplinary Health and Development Study). We tested whether cannabis use from ages 18 to 38 years was associated with physical health at age 38, even after controlling for tobacco use, childhood health, and childhood socioeconomic status. We also tested whether cannabis use from ages 26 to 38 years was associated with within-individual health decline using the same measures of health at both ages.

EXPOSURES We assessed frequency of cannabis use and cannabis dependence at ages 18, 21, 26, 32, and 38 years.

MAIN OUTCOMES AND MEASURES We obtained laboratory measures of physical health (periodontal health, lung function, systemic inflammation, and metabolic health), as well as self-reported physical health, at ages 26 and 38 years.

RESULTS The 1037 study participants were 51.6% male (n = 535). Of these, 484 had ever used tobacco daily and 675 had ever used cannabis. Cannabis use was associated with poorer periodontal health at age 38 years and within-individual decline in periodontal health from ages 26 to 38 years. For example, cannabis joint-years from ages 18 to 38 years was associated with poorer periodontal health at age 38 years, even after controlling for tobacco pack-years (β = 0.12; 95% CI, 0.05-0.18; *P* <.001). Additionally, cannabis joint-years from ages 26 to 38 years was associated with poorer periodontal health at age 38 years, even after accounting for periodontal health at age 26 years and tobacco pack-years (β = 0.10; 95% CI, 0.05-0.16; *P* <.001) However, cannabis use was unrelated to other physical health problems. Unlike cannabis use, tobacco use was associated with worse lung function, systemic inflammation, and metabolic health at age 38 years, as well as within-individual decline in health from ages 26 to 38 years.

CONCLUSIONS AND RELEVANCE Cannabis use for up to 20 years is associated with periodontal disease but is not associated with other physical health problems in early midlife.

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After major policy changes in the United States, policymakers, health care professionals, and the general public seek information about whether recreational cannabis use is associated with physical health problems later in life. Two recent reviews found that persistent cannabis use is associated with few physical health problems, with the possible exceptions being cardiovascular risks and bronchitis.[1,2] However, firm conclusions cannot be drawn due to methodological shortcomings.[3] Most studies[4-11] are cross-sectional or rely on self-reported health. These designs cannot resolve the temporal association between cannabis use and health, nor can they address the possibility that cannabis users may have biased perceptions of their health. Longitudinal studies with laboratory-based measures and physical examinations are needed.

Few longitudinal studies have characterized cannabis users' long-term health using objective, laboratory-based indexes and examinations (eTable 1 in the Supplement). Each study in eTable 1 in the Supplement focused on a single domain of physical health, providing an important but incomplete picture. In the present population-representative study of individuals followed up from birth to age 38 years, we tested associations between cannabis use over 20 years and multiple domains of physical health in early midlife. We selected the following health domains based on prior research,[1-3] demonstrated capacity to predict disease morbidity and mortality,[12-14] and biological plausibility of an effect of cannabis by early midlife: periodontal health, lung function, systemic inflammation, and metabolic risk. First, we tested whether cannabis use from ages 18 to 38 years was associated with health at age 38 years. Second, we tested whether cannabis use from ages 26 to 38 years was associated with within-individual health decline using the same measures of health at both ages. To provide a benchmark for comparison, we also tested associations between tobacco use and physical health.

Key Points

Question Is persistent cannabis use for up to 20 years associated with physical health problems (periodontal health, lung function, systemic inflammation, and metabolic health) in early midlife?

Findings In this prospective, longitudinal study of a representative birth cohort of 1037 individuals, persistent cannabis use from ages 18 to 38 years was not associated with physical health problems at age 38 years with one exception: persistent cannabis use was statistically significantly associated with poor periodontal health.

Meaning Persistent cannabis use for up to 20 years is, for the most part, not associated with physical health problems in early midlife.

Methods

Participants

Participants were members of the Dunedin Multidisciplinary Health and Development Study of New Zealand, a longitudinal investigation of health and behavior in a representative birth cohort.[15] Study members (n = 1037), representing 91.0% of eligible births and 51.6% male, were all born in 1972-1973 in Dunedin, New Zealand. Of the 1037 study participants 51.6% were male (n = 535). They were eligible for the longitudinal study based on residence in the province at age 3 years and participation in the first follow-up at age 3 years. The cohort represents the full range of socioeconomic status (SES) in the general population of New Zealand's South Island and is primarily white.[15] On adult health, the cohort matches the New Zealand National Health and Nutrition Survey (eg, body mass index, smoking status, and general practitioner visits).[15] Assessments occurred at birth and ages 3, 5, 7, 9, 11, 13, 15, 18, 21, 26, 32, and, most recently, 38 years, when 95.4% (n = 961) of the 1007 living study members took part. At each assessment phase, study members are brought to the Dunedin Multidisciplinary Health and Development Research Unit (Dunedin, New Zealand) for interviews and examinations. The Otago Ethics Committee (University of Otago, Dunedin, New Zealand) approved each phase of the study, and the study protocol was approved by the Otago Ethics Committee and the Duke University Institutional Review Board. Written informed consent was obtained from all participants.

Analyses were limited to 947 study members with laboratory health data at age 38 years because 46 study members were not seen at age 38 years, 30 were deceased, and 14 had field interviews that did not include laboratory measurements or examinations. There were no differences between those with and without health data at age 38 years on childhood health ($F = 1.42$, $P = .23$), cigarettes smoked per day at age 18 years ($F = 1.28$, $P = .26$), or frequency of cannabis use at age 18 years ($F = 2.85$, $P = .09$). **Table 1** lists characteristics of participants according to tobacco and cannabis exposure, including sex, childhood health,[16] and childhood SES,[17] which were available as covariates.

Tobacco Pack-Years

Cumulative tobacco exposure was calculated from the reported number of cigarettes smoked per day at each assessment divided by 20 and multiplied by the number of years smoked at that rate through age 38 years. One pack-year reflects the equivalent of 20 cigarettes a day for 1 year. Mean (SD) pack-years for those with age-38 health data was 6.17 (8.69). For analyses testing associations between pack-years from age 26 to 38 and change in physical health using the same measure of health at both ages, we estimated pack-years in the same way except that estimates represented cigarette use at ages 26 to 38 years (mean [SD], 3.30 [5.12] pack-years).

Cannabis Joint-Years

Pack-years, which combines information about smoking duration and intensity, is the most commonly used exposure in tobacco studies.[18] We created a parallel variable that indexes cannabis smoking. Cumulative joint-years was estimated using self-reported frequency of cannabis use over the past year (0-365 days) at ages 18 to 38 years. One joint-year reflects the equivalent of daily cannabis use for 1 year. Mean (SD) joint-years between ages 18 to 38 years for those with age-38 health

Table 1. Characteristics of Study Members According to Tobacco and Cannabis Use From Ages 18 to 38 Years[a]

	Never Used Daily	Used <5 y	Used 5 to <10 y	Used 10 to <15 y	Used ≥15 y	*r* Value[b]	*P* Value[b]
Tobacco pack-years							
No.	461	137	83	92	172	NA	NA
Male sex, No. (%)	238 (51.6)	54 (39.4)	35 (42.2)	46 (50.0)	100 (58.1)	0.07	.03
Childhood health, mean (SD)[c]	0.04 (0.97)	0.03 (0.86)	0.10 (1.00)	0.05 (0.89)	−0.15 (1.02)	−0.07	.045
Childhood SES, mean (SD)[c]	0.17 (0.98)	0.15 (0.97)	0.01 (0.87)	−0.33 (0.90)	−0.29 (1.03)	−0.20	<.001
Cannabis joint-years, mean (SD)	0.61 (2.39)	1.28 (3.17)	2.04 (3.82)	2.67 (4.35)	5.84 (6.83)	0.48	<.001
Tobacco pack-years, mean (SD)	0.00 (0.00)	2.25 (1.65)	7.44 (1.38)	12.50 (1.50)	21.82 (5.40)	NA	NA
Cannabis joint-years							
No.	265	552	42	44	37	NA	NA
Male sex, No. (%)	102 (38.5)	278 (50.4)	30 (71.4)	32 (72.7)	29 (78.4)	0.21	<.001
Childhood health, mean (SD)[c]	0.01 (0.92)	0.03 (0.97)	0.03 (0.98)	0.01 (0.90)	−0.07 (0.94)	−0.02	.61
Childhood SES, mean (SD)[c]	0.05 (1.01)	0.10 (0.99)	−0.19 (0.93)	−0.34 (0.85)	−0.42 (0.96)	−0.13	<.001
Cannabis joint-years, mean (SD)	0.00 (0.00)	0.63 (1.05)	7.38 (1.27)	12.54 (1.43)	17.83 (2.13)	NA	NA
Tobacco pack-years, mean (SD)	1.97 (5.27)	6.07 (7.84)	12.63 (9.95)	16.34 (8.86)	19.34 (11.96)	0.48	<.001
	Never Used	**Used but No Diagnosis**	**1 Diagnosis**	**2 Diagnoses**	**≥3 Diagnoses**	***r* Value[b]**	***P* Value[b]**
Persistent cannabis dependence							
No.	265	504	85	43	43	NA	NA
Male sex, No. (%)	102 (38.5)	246 (48.8)	59 (69.4)	28 (65.1)	36 (83.7)	0.22	<.001
Childhood health, mean (SD)[c]	0.01 (0.92)	0.03 (0.98)	0.02 (0.91)	−0.09 (0.96)	0.11 (0.89)	0.01	.82
Childhood SES, mean (SD)[c]	0.05 (1.01)	0.09 (0.98)	−0.12 (1.03)	−0.13 (0.99)	−0.40 (0.86)	−0.10	.004
Cannabis joint-years, mean (SD)	0.00 (0.00)	0.92 (2.37)	4.80 (5.66)	9.32 (5.36)	13.94 (4.70)	0.72	<.001
Tobacco pack-years, mean (SD)	1.97 (5.27)	5.84 (7.76)	9.64 (9.33)	15.52 (9.22)	20.58 (10.05)	0.51	<.001

Abbreviations: NA, not applicable; SES, socioeconomic status.

[a] Of the 947 with health data at age 38 years, 2 study members were missing tobacco pack-years data, and 7 study members were missing cannabis joint-years data.

[b] We report Pearson correlations between correlates and tobacco pack-years (a continuous variable), cannabis joint-years (a continuous variable), and persistent cannabis dependence (a 5-level ordinal variable).

[c] Scores were standardized to a mean (SD) of 0.00 (1.00). Overall health at ages 3, 5, 7, 9, 11, 13, and 15 years was rated by 2 Dunedin Multidisciplinary Health and Development Research Unit staff members based on review of birth records and assessment dossiers, including clinical assessments and reports of infections, diseases, injuries, hospitalizations, and other health problems obtained during standardized maternal interviews. Ratings used a 5-point scale (interrater agreement, 0.85). Socioeconomic status was defined as the mean highest occupational status level of either parent across study assessments (1 is unskilled laborer, and 6 is professional), from the study member's birth through age 15 years, on New Zealand's occupational rating of the 1970s.

data was 1.99 (4.43). For analyses of health change from age 26 to 38 years, we estimated joint-years in the same way except that estimates represented cannabis use at ages 26 to 38 (mean [SD], 1.18 [3.00]).

Persistent Cannabis Dependence

Because prior reports from the Dunedin Study have characterized cannabis users in terms of persistent dependence over time,[19,20] we also report this variable as our exposure. We assessed past-year dependence at ages 18 to 38 years with the Diagnostic Interview Schedule[21,22] according to *Diagnostic and Statistical Manual of Mental Disorders* criteria.[23,24] Persistent dependence was defined as the number of study waves out of 5 at which a study member met criteria for dependence: never used cannabis at any study wave, used at least once between ages 18 to 38 but never diagnosed, diagnosed at 1 wave, diagnosed at 2 waves, and diagnosed at 3 or more waves. For analyses of health change from ages 26 to 38 years, we again defined persistent dependence as the number of study waves at which a study member met criteria for dependence but only used cannabis data from ages 26 to 38 years.

Physical Health at Age 38 Years

Physical examinations were conducted during the assessment day at age 38 years, with blood draws between 4:15 and 4:45 PM.[25] eTable 2 in the Supplement describes each health outcome: periodontal health, lung function, systemic inflammation, metabolic syndrome, waist circumference, high-density lipoprotein cholesterol level, triglyceride level, blood pressure (systolic and diastolic), glycated hemoglobin level, body mass index, and self-reported health. We report health outcomes scored as continuously distributed outcomes be-

cause continuous measures are more sensitive to variation than categorical measures. However, for clinical relevance, the eTables in the Supplement also list results for health outcomes scored as categorical clinical outcomes. Positively skewed continuous outcomes (combined attachment loss, inflammation, triglyceride level, and glycated hemoglobin level) were log-transformed before analysis.

Physical Health at Age 26 Years

The health measures at age 38 years were also administered at age 26 years using the same procedures, with 2 exceptions.[25] First, periodontal measurements were obtained using a half-mouth design.[26] Second, serum C-reactive protein level was assayed with a sensitivity level of 1 mg/L.[27] Due to this lower sensitivity, C-reactive protein levels in the top quintile of the distribution were designated as elevated.

Statistical Analysis

To test whether cannabis use was associated with poor health in early midlife, we tested the bivariate association between cannabis use from ages 18 to 38 years and health at age 38 years (**Table 2**, model 1) and subsequently added tobacco pack-years from ages 18 to 38 years as a covariate (Table 2, model 2). To test whether cannabis use from ages 26 to 38 years was associated with health decline using the same measure of health at both ages, we tested the bivariate association between cannabis use from ages 26 to 38 years and health at age 38 years (**Table 3**, model 1) and subsequently added health at age 26 years as a covariate (Table 3, model 2), followed by tobacco pack-years from ages 26 to 38 years as an additional covariate (Table 3, model 3). All analyses controlled for sex.

Statistical analyses tested associations of tobacco pack-years (a continuous variable), cannabis joint-years (a continuous variable), and cannabis dependence (a 5-level ordinal variable) with continuous and categorical health outcomes. We analyzed continuous outcomes using ordinary least squares regression to derive β coefficients and categorical outcomes using Poisson regression models to derive relative risks (RRs). We standardized continuous variables before conducting statistical tests. Therefore, β coefficients and RRs can be interpreted as the increase in risk of the outcome given a 1-SD increase in pack-years or joint-years. To aid interpretation of β coefficients and RRs associated with continuous pack-years and joint-years, we report unstandardized, sex-adjusted means for health outcomes as a function of tobacco and cannabis use, with study members grouped according to pack-years and joint-years in 5-year increments (Table 2).

Results

Tobacco Smoking and Health

Bivariate associations showed that tobacco pack-years was associated with worse health for 8 of the 12 health outcomes, namely, periodontal health, lung function, systemic inflammation, metabolic syndrome, high-density lipoprotein cholesterol level, triglyceride level, glycated hemoglobin level, and self-reported health (Table 2, model 1). Associations remained significant for all 8 of these health outcomes after controlling for cannabis joint-years (Table 2, model 2) and after additionally controlling for childhood health and SES (eTable 3, model 3 in the Supplement). Results were similar for clinically relevant, categorically scored health outcomes (eTable 3 in the Supplement). For example, 12.3% of individuals who never used tobacco daily had periodontal disease (≥1 site with attachment loss >5 mm) compared with 52.9% of individuals with 15 or more pack-years (eTable 3 in the Supplement). Statistical tests showed that for every SD increase in pack-years (approximately 9 pack-years), the RR for periodontal disease increased by 1.63 ($P < .001$) (eTable 3 in the Supplement). Findings are consistent with prior research.[26,28-36]

Cannabis Use and Health

Bivariate associations showed that cannabis joint-years was associated with worse health for 3 of 12 health outcomes, namely, periodontal health, lung function, and self-reported health (Table 2, model 1). Adverse associations remained significant for 2 outcomes (periodontal health and lung function) after controlling for tobacco pack-years (Table 2, model 2) and after additionally controlling for childhood health and SES (eTable 3, model 3 in the Supplement). However, poorer lung function (ratio of forced expiratory volume in the first second of expiration [FEV_1] to forced vital capacity [FVC]) (hereafter FEV_1/FVC) among cannabis users was probably not indicative of airway obstruction because joint-years (unlike tobacco pack-years) was unrelated to reduced FEV_1 (eTable 4 in the Supplement). Rather, reduced FEV_1/FVC among cannabis users was attributable to higher FVC values. It is unclear whether higher FVC values reflect better health.

Unlike tobacco, cannabis joint-years was associated with slightly smaller waist circumference and lower body mass index. Furthermore, after adjusting for tobacco pack-years (Table 2, model 2), associations emerged between joint-years and better high-density lipoprotein cholesterol, triglyceride, and glycated hemoglobin levels. However, joint-years was not associated with lower risk of metabolic syndrome. Results were similar for categorically scored health outcomes (eTable 3 in the Supplement).

Results for persistent cannabis dependence (as well as results for persistent regular cannabis use [eTable 5 in the Supplement]) were almost identical to those for joint-years. Bivariate associations showed that persistent dependence was associated with worse health for 3 of 12 outcomes, namely, periodontal health, lung function, and self-reported health. Associations remained significant for 1 of those 3 (periodontal health) after controlling for tobacco pack-years (Table 2, model 2) and after additionally controlling for childhood health and SES (eTable 3, model 3 in the Supplement). Results were similar for categorically scored health outcomes (eTable 3 in the Supplement). eTable 6 in the Supplement summarizes the aforementioned findings.

Periodontal health was the only aspect of health that showed a robust adverse association in analyses of both persistent dependence and joint-years. Post hoc analyses showed that cannabis users brushed and flossed less than others and were more likely to be alcohol dependent (eTable 7 in the

Table 2. Associations Between Tobacco and Cannabis Use From Ages 18 to 38 Years and Health at Age 38 Years

	% or Mean as a Function of Use, Adjusted for Sex[a]					Statistical Tests[b]			
						Model 1, Bivariate[c]		Model 2, Plus Control for Pack-Years or Joint-Years[c]	
	Never Used Tobacco Daily/Never Used Cannabis	<5 y/No Diagnosis	5 to <10 y/1 Diagnosis	10 to <15 y/2 Diagnoses	≥15 y/≥3 Diagnoses	β (95% CI)	*P* Value	β (95% CI)	*P* Value
Periodontal health, mean attachment loss across sites, mm									
Pack-years	1.37	1.44	1.63	1.79	2.32	0.50 (0.45 to 0.56)	<.001	0.45 (0.38 to 0.51)	<.001
Joint-years	1.41	1.57	2.08	2.21	2.51	0.33 (0.26 to 0.39)	<.001	0.12 (0.05 to 0.18)	<.001
Cannabis dependence	1.41	1.57	1.75	2.06	2.58	0.33 (0.27 to 0.39)	<.001	0.09 (0.02 to 0.16)	.01
Lung function, FEV_1/FVC[d]									
Pack-years	80.98	79.74	79.78	79.67	77.58	−0.19 (−0.26 to −0.13)	<.001	−0.15 (−0.22 to −0.08)	<.001
Joint-years	80.72	80.15	77.95	78.09	76.43	−0.17 (−0.23 to −0.11)	<.001	−0.10 (−0.17 to −0.02)	.01
Cannabis dependence	80.72	80.17	78.93	78.47	76.47	−0.15 (−0.22 to −0.08)	<.001	−0.06 (−0.14 to 0.01)	.11
Systemic inflammation, C-reactive protein level, mg/L									
Pack-years	2.32	1.70	3.20	2.05	3.17	0.12 (0.05 to 0.18)	<.001	0.12 (0.04 to 0.19)	.002
Joint-years	2.48	2.33	2.09	4.01	2.28	0.06 (−0.01 to 0.13)	.07	0.00 (−0.07 to 0.08)	.95
Cannabis dependence	2.48	2.36	2.24	3.24	2.64	0.04 (−0.02 to 0.11)	.21	−0.03 (−0.11 to 0.05)	.46
Metabolic syndrome, %									
Pack-years	14.3	13.1	15.9	15.2	23.2	1.18 (1.04 to 1.35)[e]	.01	1.24 (1.06 to 1.45)[e]	.006
Joint-years	18.9	14.2	15.4	21.8	13.5	1.01 (0.88 to 1.16)[e]	.94	0.90 (0.76 to 1.07)[e]	.23
Cannabis dependence	18.9	13.3	19.5	26.5	11.0	0.99 (0.85 to 1.15)[e]	.88	0.86 (0.73 to 1.02)[e]	.09
Waist circumference, cm									
Pack-years	86.70	85.47	87.84	86.69	85.64	−0.02 (−0.08 to 0.04)	.55	0.02 (−0.05 to 0.09)	.56
Joint-years	88.15	86.00	84.57	84.97	82.93	−0.07 (−0.13 to −0.01)	.03	−0.08 (−0.15 to −0.01)	.03
Cannabis dependence	88.12	85.53	87.56	85.81	83.77	−0.07 (−0.13 to −0.01)	.04	−0.08 (−0.15 to −0.01)	.03
High-density lipoprotein level, mmol/L[d]									
Pack-years	1.46	1.48	1.43	1.45	1.38	−0.06 (−0.13 to −0.01)	.04	−0.10 (−0.17 to −0.03)	.004
Joint-years	1.40	1.45	1.58	1.56	1.35	0.03 (−0.03 to 0.09)	.39	0.08 (0.01 to 0.15)	.03
Cannabis dependence	1.40	1.47	1.43	1.39	1.48	0.03 (−0.03 to 0.09)	.36	0.09 (0.01 to 0.16)	.02
Triglyceride level, mmol/L									
Pack-years	1.99	1.99	2.08	2.27	2.22	0.07 (0.01 to 0.13)	.02	0.11 (0.04 to 0.17)	.002
Joint-years	2.12	2.07	1.88	1.98	1.84	−0.03 (−0.09 to 0.03)	.38	−0.08 (−0.15 to −0.01)	.02
Cannabis dependence	2.12	2.02	2.02	2.56	1.77	−0.02 (−0.08 to 0.04)	.51	−0.08 (−0.15 to −0.01)	.03
Systolic blood pressure, mm Hg									
Pack-years	120.92	119.26	118.04	122.01	119.51	−0.02 (−0.09 to 0.04)	.44	−0.01 (−0.08 to 0.06)	.71
Joint-years	121.33	119.68	120.69	121.93	117.20	−0.02 (−0.08 to 0.04)	.53	−0.01 (−0.08 to 0.06)	.69
Cannabis dependence	121.34	119.73	120.54	120.62	117.50	−0.05 (−0.12 to 0.01)	.10	−0.06 (−0.13 to 0.02)	.13
Diastolic blood pressure, mm Hg									
Pack-years	78.64	77.19	77.27	78.13	78.20	0.00 (−0.06 to 0.06)	.98	0.01 (−0.06 to 0.08)	.68
Joint-years	79.42	77.55	77.70	79.13	76.40	−0.01 (−0.08 to 0.05)	.69	−0.02 (−0.09 to 0.05)	.57
Cannabis dependence	79.42	77.44	79.37	77.86	75.80	−0.06 (−0.13 to 0.00)	.06	−0.09 (−0.16 to −0.01)	.02
Glycated hemoglobin level									
Pack-years	5.40	5.33	5.36	5.37	5.53	0.11 (0.05 to 0.18)	<.001	0.15 (0.08 to 0.23)	<.001
Joint-years	5.48	5.37	5.39	5.43	5.36	0.00 (−0.07 to 0.06)	.94	−0.08 (−0.15 to −0.01)	.04
Cannabis dependence	5.48	5.36	5.40	5.45	5.38	−0.03 (−0.10 to 0.03)	.34	−0.13 (−0.20 to −0.05)	.001
Body mass index									
Pack-years	27.50	26.80	27.89	27.30	26.32	−0.06 (−0.12 to 0.00)	.07	−0.02 (−0.10 to 0.05)	.51
Joint-years	28.22	26.92	26.26	26.38	25.59	−0.09 (−0.15 to −0.02)	.01	−0.07 (−0.15 to 0.00)	.05

(continued)

Table 2. Associations Between Tobacco and Cannabis Use From Ages 18 to 38 Years and Health at Age 38 Years (continued)

	% or Mean as a Function of Use, Adjusted for Sex[a]					Statistical Tests[b]			
						Model 1, Bivariate[c]		Model 2, Plus Control for Pack-Years or Joint-Years[c]	
	Never Used Tobacco Daily/Never Used Cannabis	<5 y/No Diagnosis	5 to <10 y/1 Diagnosis	10 to <15 y/2 Diagnoses	≥15 y/≥3 Diagnoses	β (95% CI)	*P* Value	β (95% CI)	*P* Value
Cannabis dependence	28.21	26.82	27.10	26.59	25.75	−0.11 (−0.17 to −0.04)	.002	−0.10 (−0.18 to −0.03)	.009
Self-reported health, mean health rating[d]									
Pack-years	3.97	3.96	3.72	3.70	3.43	−0.27 (−0.33 to −0.21)	<.001	−0.26 (−0.32 to −0.19)	<.001
Joint-years	3.86	3.88	3.53	3.46	3.47	−0.15 (−0.22 to −0.09)	<.001	−0.03 (−0.10 to 0.04)	.42
Cannabis dependence	3.86	3.91	3.55	3.55	3.27	−0.16 (−0.23 to −0.10)	<.001	−0.03 (−0.11 to 0.04)	.40

Abbreviations: FEV_1, forced expiratory volume in the first second of expiration; FVC, forced vital capacity.

[a] For presentation of percentages and means, participants were grouped according to pack-years and joint-years between ages 18-38 as follows: never used tobacco daily/never used cannabis, used <5 years, used from 5 to <10 years, used from 10 to <15 years, and used for 15+ years. Participants were grouped according to persistence of cannabis dependence as follows: never used is never used cannabis, no diagnosis is used cannabis at least once between ages 18-38 but never diagnosed, 1 diagnosis is diagnosed once between ages 18-38, 2 diagnoses is diagnosed twice, three or more diagnoses is diagnosed three or more times.

[b] Statistical analyses tested associations of cumulative tobacco pack-years (a continuous variable), cumulative cannabis joint-years (a continuous variable), and persistent cannabis dependence (a 5-level ordinal variable) with continuous outcomes (except for metabolic syndrome, which is a categorical outcome). Continuous variables were standardized for statistical tests. Therefore, β coefficients can be interpreted as the increase in risk of the outcome given a 1-SD increase in pack-years or joint-years. β Coefficients with a positive sign indicate poorer health except where noted.

[c] Model 1 controls for sex. Model 2 adds controls for joint-years in analyses of pack-years and adds controls for pack-years in analyses of joint-years and cannabis dependence. Analyses of lung function additionally control for height.

[d] β Coefficients with a negative sign indicate poorer health.

[e] Estimates are relative risks. For analyses of tobacco pack-years, numbers. range from 892 to 945 for model 1 and 886 to 938 for model 2. For analyses of cannabis joint-years and cannabis dependence, numbers. range from 888 to 940 for model 1 and 886 to 938 for model 2. The reason for different numbers. across analyses is that there was some variation in missingness for specific health measurements. Among the 947 study members included in this study, 47 refused the dental examination, 28 did not complete the lung function assessment, 35 refused phlebotomy, 9 were pregnant, 6 glycated hemoglobin samples were lost in the laboratory due to the 2011 Christchurch, New Zealand, earthquake, and there were a handful of miscellaneous assay failures.

Supplement). However, associations between cannabis use and poor periodontal health remained significant after controlling for tobacco pack-years, childhood health and SES, brushing and flossing, and alcohol dependence (eTable 8 in the Supplement).

The general lack of association between persistent cannabis use and poor physical health may be surprising. One explanation is that healthy youth select into cannabis use. Our test showed no correlation between cannabis use and childhood health (Table 1). Another explanation is that cannabis users may have healthier adult lifestyles. Tests showed that cannabis use was not associated with more physical activity, with a diet of fruits and vegetables, or with less alcohol abuse (eTable 7 in the Supplement). The absence of associations between cannabis use and poor physical midlife health could not be attributed to better initial health, more physical activity, better diet, or less alcohol abuse.

Tobacco and Cannabis Use and Change in Health

Tobacco pack-years from ages 26 to 38 years was associated with worsening periodontal health, lung function, systemic inflammation, and metabolic health (Table 3, model 2). For example, pack-years from ages 26 to 38 years was associated with increased risk of metabolic syndrome at age 38 years after accounting for metabolic syndrome at age 26 years (RR, 1.18; $P = .02$) (Table 3, model 2). Tobacco users also self-reported worse health at age 38 years, and this association persisted after accounting for self-reported health at age 26 years (Table 3, model 2).

Like tobacco use, cannabis use was associated with decline in periodontal health and lung function (Table 3, model 2) even after accounting for tobacco pack-years from ages 26 to 38 years (Table 3, model 3). Again, however, decline in the FEV_1/FVC was probably not attributable to airway obstruction because cannabis use was not robustly associated with decline in FEV_1 (eTable 9 in the Supplement). Cannabis use was not associated with deteriorating health in other domains. Results were similar for continuously scored and categorically scored health outcomes (eTable 10 in the Supplement).

Discussion

In general, our findings showed that cannabis use over 20 years was unrelated to health problems in early midlife. Across several domains of health (periodontal health, lung function, systemic inflammation, and metabolic health), clear evidence of an adverse association with cannabis use was apparent for only one domain, namely, periodontal health. Cannabis use from ages 26 to 38 years was not associated with within-individual health decline during this 12-year period with the exception of periodontal health. By comparison, tobacco use was associated with worse periodontal health, lung function, systemic inflammation, high-density lipoprotein cholesterol lev-

Table 3. Within-Individual Change in Health From Age 26 to 38 Years: Associations Between Tobacco and Cannabis Use From Ages 26 to 38 and Age-38 Health, Controlling for Age-26 Baseline Health[a]

	Model 1, Bivariate		Model 2, Plus Control for Baseline at Age 26 Years		Model 3, Plus Control for Pack-Years or Joint-Years[b]	
Health at Age 38 y	β (95% CI)	*P* Value	β (95% CI)	*P* Value	β (95% CI)	*P* Value
Periodontal health, mean attachment loss across sites, mm						
Pack-years	0.50 (0.44 to 0.56)	<.001	0.42 (0.36 to 0.47)	<.001	0.37 (0.31 to 0.43)	<.001
Joint-years	0.32 (0.25 to 0.38)	<.001	0.25 (0.19 to 0.31)	<.001	0.10 (0.05 to 0.16)	<.001
Cannabis dependence	0.37 (0.29 to 0.45)	<.001	0.30 (0.23 to 0.38)	<.001	0.11 (0.04 to 0.19)	.002
Lung function, FEV_1/FVC[c]						
Pack-years	−0.19 (−0.26 to −0.12)	<.001	−0.14 (−0.19 to −0.10)	<.001	−0.11 (−0.16 to −0.06)	<.001
Joint-years	−0.15 (−0.21 to −0.08)	<.001	−0.11 (−0.16 to −0.07)	<.001	−0.07 (−0.12 to −0.02)	.008
Cannabis dependence	−0.17 (−0.26 to −0.09)	<.001	−0.14 (−0.20 to −0.09)	<.001	−0.08 (−0.15 to −0.02)	.01
Systemic inflammation, C-reactive protein level, mg/L						
Pack-years	0.11 (0.04 to 0.18)	.003	0.11 (0.04 to 0.17)	.002	0.09 (0.01 to 0.16)	.02
Joint-years	0.08 (0.01 to 0.16)	.03	0.09 (0.02 to 0.16)	.01	0.05 (−0.03 to 0.13)	.20
Cannabis dependence	0.02 (−0.07 to 0.12)	.61	0.04 (−0.05 to 0.13)	.38	−0.02 (−0.12 to 0.07)	.62
Metabolic syndrome, %						
Pack-years	1.18 (1.03 to 1.36)[d]	.02	1.18 (1.02 to 1.35)[d]	.02	1.21 (1.04 to 1.41)[d]	.01
Joint-years	1.00 (0.86 to 1.16)[d]	.99	1.01 (0.88 to 1.17)[d]	.88	0.93 (0.79 to 1.10)[d]	.41
Cannabis dependence	1.02 (0.84 to 1.26)[d]	.80	1.07 (0.88 to 1.31)[d]	.50	0.98 (0.79 to 1.21)[d]	.84
Body mass index						
Pack-years	−0.07 (−0.14 to −0.01)	.03	0.00 (−0.04 to 0.04)	.91	0.02 (−0.03 to 0.06)	.51
Joint-years	−0.09 (−0.16 to −0.03)	.006	−0.02 (−0.06 to 0.02)	.35	−0.03 (−0.07 to 0.02)	.25
Cannabis dependence	−0.13 (−0.21 to −0.04)	.004	−0.01 (−0.07 to 0.04)	.60	−0.01 (−0.07 to 0.04)	.59
Self-reported health, mean health rating[c]						
Pack-years	−0.27 (−0.33 to −0.21)	<.001	−0.16 (−0.22 to −0.10)	<.001	−0.16 (−0.22 to −0.10)	<.001
Joint-years	−0.11 (−0.18 to −0.05)	<.001	−0.06 (−0.11 to 0.00)	.06	0.01 (−0.05 to 0.07)	.77
Cannabis dependence	−0.17 (−0.26 to −0.09)	<.001	−0.12 (−0.19 to −0.04)	.002	−0.04 (−0.12 to 0.04)	.34

Abbreviations: FEV_1, forced expiratory volume in the first second of expiration; FVC, forced vital capacity.

[a] All models control for sex. Analyses of lung function additionally control for height. Statistical analyses tested associations of cumulative tobacco pack-years (a continuous variable), cumulative cannabis joint-years (a continuous variable), and persistent cannabis dependence (a 5-level ordinal variable) with continuous outcomes (except for metabolic syndrome, which is a categorical outcome). Continuous variables were standardized for statistical tests. Therefore, β coefficients can be interpreted as the increase in risk of the outcome given a 1-SD increase in pack-years or joint-years. β Coefficients with a positive sign indicate poorer health except where noted.

[b] Model 3 adds controls for joint-years in analyses of pack-years and adds controls for pack-years in analyses of joint-years and cannabis dependence.

[c] β Coefficients with a negative sign indicate poorer health. All models control for sex. Analyses of lung function additionally control for height.

[d] Estimates are relative risks.

els, triglyceride levels, and glucose levels in early midlife, as well as health decline from ages 26 to 38 years.

Findings showed that cannabis use was associated with slightly better metabolic health (smaller waist circumference, lower body mass index, better lipid profiles, and improved glucose control). However, most of these associations emerged only after controlling for tobacco use. Effects were small but intriguing given similar reports from cross-sectional studies,[4,8,9,37-39] as well as evidence that endocannabinoids appear to be involved in the regulation of metabolism.[40] Studies[41,42] have shown that overweight patients who took rimonabant (a synthetic cannabinoid-1 receptor blocker) demonstrated reduced waist circumference and improved lipid profiles. However, it is unclear if and how recreational cannabis use (and plant-based cannabinoids) might affect metabolic health. Cannabinoid pharmacology is more complex than commonly believed,[43] and biological arguments can be made for cannabis-related worsening or improvement of metabolic health.[9,44] The only other longitudinal study[45] to characterize cannabis users' metabolic health found no association, and our finding of a small association mainly emerged after controlling for tobacco use. Moreover, cannabis use was not associated with reduced risk of metabolic syndrome. Therefore, current evidence suggests that recreational cannabis use is unlikely to improve metabolic health in the general population.

In at least 2 instances, we found no association between cannabis use and poor health when we might have expected one. In the first instance, we found no association between cannabis use and reduced FEV_1 (eTable 4 in the Supplement), which is somewhat puzzling given that tobacco use is associated with reduced FEV_1.[28,29] An association between cannabis use and reduced FEV_1 could emerge with greater exposure to cannabis.[28] Nonetheless, given no evidence of reduced FEV_1 among cannabis users, our finding of lower FEV_1/FVC among cannabis users probably did not indicate airway obstruction. Rather, reduced FEV_1/FVC appeared to reflect cannabis users' slightly larger FVC. This association with larger FVC, also re-

ported elsewhere,[28] is not understood. Overall, findings are consistent with a 2011 review concluding that there is little evidence that cannabis affects FEV_1 and airway obstruction.[46] In the second surprising instance, we found no association between cannabis use and cardiovascular risks (eg, high blood pressure and worse cholesterol levels), which may appear at odds with evidence that cannabis use increases risk for cardiovascular complications,[47-49] even among young healthy individuals.[50] Our somewhat disparate findings are reconciled by evidence that cannabis-related cardiovascular complications are likely acute cannabis effects.[38,45,47,49]

Although we found that cannabis users were generally no worse off than nonusers on almost all health indexes, they did have worse periodontal health. Cannabis use was associated with attachment loss, which can result in tooth loss.[26,36] A similar association was observed for tobacco use, consistent with previous research.[26,36,51] Tobacco's effect on periodontal disease is thought to be mediated through increased inflammation and vasoconstriction,[51] which may or may not be the case for cannabis. Cannabis use was not associated with systemic inflammation here or elsewhere,[30,39] but prior research has shown that cannabis use can induce vasoconstriction.[52,53]

This study has limitations. First, cannabis joint-years was based on self-reports obtained at ages 18 to 38 years. Validation of cannabis use through laboratory measures could have helped detect cannabis users who denied use. However, underreporting due to reluctance to admit to illegal drug use is unlikely because study members, interviewed repeatedly over the course of their lives, have learned to trust our confidentiality guarantee. Second, disentangling cannabis use and tobacco use is challenging. In New Zealand, cannabis is not typically mixed with tobacco,[10] but most participants who used cannabis also smoked cigarettes. Although we controlled for tobacco use, imperfect control might bias results toward finding spurious associations between cannabis use and poor health. However, we note that all poor health outcomes, apart from periodontal disease, were unrelated to cannabis use. Third, our findings are based on a single New Zealand cohort who began using cannabis in the 1980s to 1990s. Although our findings are generally consistent with longitudinal studies[2,54] of US samples (eTable 1 in the Supplement), tetrahydrocannabinol (the primary psychoactive ingredient in cannabis) content has increased since then.[54] If health associations are mediated by tetrahydrocannabinol, we may have underestimated the association between cannabis use and health. Fourth, our conclusions are limited to a specific set of health problems assessed in early midlife. Although this investigation is the most comprehensive study to date, cannabis use may be associated with health problems not studied here or with those that tend to emerge later in life, such as cancer. Fifth, we compared findings for cannabis against findings for tobacco. Our intent in doing so was to allay concerns that our study's methods might be unable to detect health problems. We acknowledge that participants acquired more tobacco pack-years than cannabis joint-years, with most cannabis users using daily for fewer than 5 years. Greater tobacco exposure may explain health decline associated with tobacco use but not cannabis use. If patterns of cannabis use shift and more users begin to use cannabis as they do tobacco (ie, multiple joints per day), cannabis-associated health problems might emerge. Sixth, our study cannot comment on the health effects of cannabis use in older adults or the safety of medical marijuana use in patients who are already unwell.

Conclusions

This study has a number of implications. First, cannabis use for up to 20 years is not associated with a specific set of physical health problems in early midlife. The sole exception is that cannabis use is associated with periodontal disease. Second, cannabis use for up to 20 years is not associated with net metabolic benefits (ie, lower rates of metabolic syndrome). Third, our results should be interpreted in the context of prior research showing that cannabis use is associated with accidents and injuries, bronchitis, acute cardiovascular events, and, possibly, infectious diseases and cancer, as well as poor psychosocial and mental health outcomes.[1-3,19,20,46,55-58]

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