Data supplement for Hasin et al., U.S. Adults With Pain, An Increasingly Vulnerable Group for Nonmedical Cannabis Use and Cannabis Use Disorder: 2001–2002 and 2012–2013. Am J Psychiatry (doi: 10.1176/appi.ajp.2019.19030284)

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TABLE S1. DSM-IV Cannabis Use Disorder in U.S. adults with and without pain, 2001-2002 and 2012-2013, after modifying DSM-IV dependence to include cannabis withdrawal and to require 3 of 7 criteria

	2001-2002 (NESARC) N=43,093	**2012-2013 (NESARC-III) N=36,309**
Modified DSM-IV Cannabis Use Disorder		
With pain (predicted prevalence, % (SE) [a]	1.78 (.21)	4.32 (.39)
Without pain (predicted prevalence, % (SE) [a]	1.37 (.08)	2.76 (.14)
Difference between those with & without pain (95% CI)	**0.42 (0.01, 0.83) [b]**	**1.55 (0.77, 2.33) [b]**
Difference in differences (95% CI), 2012-2013 vs. 2001-2002	Reference	**1.14 (0.32, 1.96) [c]**

[a] Adjusted for sociodemographic covariates (age, gender, race/ethnicity, education level, marital status, and family income), and pain x covariate interactions.

[b] Differences in prevalence whose 95% CI do not include 0.0 are statistically significant at p<.05 and are bolded

[c] Difference in prevalence differences (DiD) between 2012-2013 and 2001-2002 tested for significance via interaction contrast (additive interaction). Differences in difference estimates whose 95% CI do not include 0.0 are statistically significant at p<.05 and are bolded

TABLE S2. Any non-medical cannabis use, frequent non-medical use and DSM-IV cannabis use disorder among U.S. adults with and without pain, 2001-2002 and 2012-2013, in models that omitted covariate x pain interaction terms

	2001-2002 (NESARC) N=43,093	**2012-2013 (NESARC-III) N=36,309**
Past-year cannabis use outcomes		
Any non-medical cannabis use		
With pain (predicted prevalence, % (SE) [a]	5.37 (.38)	12.85 (.59)
Without pain (predicted prevalence, % (SE) [a]	3.74 (.14)	9.05 (.26)
Difference between those with & without pain (95% CI)	**1.63 (0.90, 2.36) [b]**	**3.80 (2.68, 4.92) [b]**
Difference in difference (95% CI), 2012-2013 vs. 2001-2002	Reference	**2.17 (0.88, 3.46) [c]**
Frequent non-medical cannabis use		
With pain (predicted prevalence, % (SE) [a]	1.42 (.20)	5.23 (.39)
Without pain (predicted prevalence, % (SE) [a]	1.11 (.08)	3.46 (.14)
Difference between those with & without pain (95% CI)	0.31 (-0.06, 0.68) [b]	**1.77 (1.03, 2.51) [b]**
Difference in difference (95% CI), 2012-2013 vs. 2001-2002	Reference	**1.46 (0.64, 2.28) [c]**
DSM-IV Cannabis Use Disorder (CUD)		
With pain (predicted prevalence, % (SE) [a]	1.81 (.21)	4.22 (.35)
Without pain (predicted prevalence, % (SE) [a]	1.35 (.07)	2.75 (.14)
Difference between those with & without pain (95% CI)	**0.46 (0.05, 0.87) [b]**	**1.47 (0.76, 2.18) [b]**
Difference in difference (95% CI), 2012-2013 vs. 2001-2002	Reference	**1.00 (0.22, 1.78) [c]**

[a] Adjusted for sociodemographic covariates (age, gender, race/ethnicity, education level, marital status, and family income).

[b] Differences in prevalence whose 95% CI do not include 0.0 are statistically significant at p<.05 and are bolded

[c] Difference in prevalence differences (DiD) between 2012-2013 and 2001-2002 tested for significance via interaction contrast (additive interaction). Differences in difference estimates whose 95% CI do not include 0.0 are statistically significant at p<.05 and are bolded

TABLE S3A. Any non-medical cannabis use, frequent non-medical use and DSM-IV cannabis use disorder in U.S. adults with and without pain, 2001-2002 and 2012-2013, in models that included 3-way interactions of pain, survey, and age, to determine if results varied between age groups

	Any non-medical cannabis use	**Frequent non-medical cannabis use**	**DSM-IV cannabis use disorder**
Age groups	Group contrasts between age groups[a] in the DiD tests (95% CI)		
Ages 18-29 vs. ≥65	-0.51 (-4.96, 3.94)	2.45 (-0.57, 5.47)	**3.82 (0.57, 7.07)**
Ages 30-44 vs. ≥65	1.67 (-1.35, 4.69)	0.48 (-1.19, 2.15)	0.22 (-1.43, 1.87)
Ages 45-64 vs. ≥65	1.41 (-0.31, 3.13)	0.81 (-0.07,1.69)	0.40 (-0.40,1.20)

[a] Differences in the prevalence of cannabis outcomes between those with and without pain (representing the association between pain and cannabis use outcome) were estimated separately for each survey and age-group combination. Then, the absolute difference in cannabis outcomes by pain status in 2012-2013 (NESARC-III) and 2001-2002 (NESARC) was estimated separately for each age group. The estimates above represent the age group contrasts of these differences (e.g. the between-survey change in the prevalence difference was 3.82 percentage points greater among those aged 18-29 than in those aged ≥65); contrasts whose 95% CI do not include 0.0 are statistically significant at p<.05 and are bolded. Models were adjusted for sociodemographic characteristics (age, gender, race/ethnicity, education level, marital status, and family income), pain x sociodemographic interactions, and survey x age interaction.

In Table 3B, stratified results are shown for DSM-IV cannabis use disorder because of the significant difference in those 18-29 vs. ≥65.

TABLE S3B. DSM-IV cannabis use disorder in U.S. adults with and without pain, 2001-2002 and 2012-2013, stratified by age group, from the regression modeling of three-way interaction between pain, survey, and age.

	2001-2002 (NESARC) N=43,093	**2012-2013 (NESARC-III) N=36,309**
Cannabis use disorder		
Ages 18-29		
With pain (predicted prevalence, % (SE) [a]	4.38 (.84)	10.29 (1.50)
Without pain (predicted prevalence, % (SE) [a]	3.23 (.25)	5.39 (.45)
Difference between those with & without pain (95% CI)	1.15 (-0.50, 2.80)	**4.90 (1.88, 7.92)** [b]
Difference in difference (95% CI), 2012-2013 vs. 2001-2002	Reference	**3.75 (0.50, 7.00)** [c]
Ages 30-44		
With pain (predicted prevalence, % (SE) [a]	1.98 (.42)	4.14 (.63)
Without pain (predicted prevalence, % (SE) [a]	1.19 (.14)	3.21 (.27)
Difference between those with & without pain (95% CI)	0.79 (-0.07, 1.65)	0.93 (-0.40, 2.26)
Difference in difference (95% CI), 2012-2013 vs. 2001-2002	Reference	0.14 (-1.43, 1.71)
Ages 45-64		
With pain (predicted prevalence, % (SE) [a]	0.74 (.21)	1.97 (.31)
Without pain (predicted prevalence, % (SE) [a]	0.35 (.09)	1.26 (.16)
Difference between those with & without pain (95% CI)	0.39 (-0.04, 0.82)	**0.71 (0.08, 1.34)** [b]
Difference in difference (95% CI), 2012-2013 vs. 2001-2002	Reference	0.32 (-0.44, 1.08)
Ages ≥65		
With pain (predicted prevalence, % (SE) [a]	0.02 (.02)	0.27 (.13)
Without pain (predicted prevalence, % (SE) [a]	0.01 (.01)	0.34 (.14)
Difference between those with & without pain (95% CI)	0.01 (-0.03, 0.05)	-0.07 (-0.44, 0.30)
Difference in difference (95% CI), 2012-2013 vs. 2001-2002	Reference	-0.08 (-0.45, 0.29)

[a] Adjusted for sociodemographic covariates (age, gender, race/ethnicity, education level, marital status, and family income), pain x covariate interactions, and survey x age interaction.

[b] Differences in prevalence whose 95% CI do not include 0.0 are statistically significant at p<.05 and are bolded

[c] Difference in prevalence differences (those with and without pain; DiD) between 2012-2013 and 2001-2002, tested for significance via interaction contrast between NESARC-III and NESARC. DiD estimates whose 95% CI do not include 0.0 are statistically significant at p<.05 and are bolded.

TABLE S4. Any non-medical cannabis use, frequent non-medical use and DSM-IV cannabis use disorder in U.S. adults with and without pain, 2001-2002 and 2012-2013, in models that additionally adjusted for state MML and included NESARC participants only from states that were also included in NESARC-III

	2001-2002 (NESARC) N=41,706	**2012-2013 (NESARC-III) N=36,309**
Past-year cannabis use outcomes		
Non-medical cannabis use		
With pain (predicted prevalence, % (SE) [a]	5.36 (.39)	11.85 (.60)
Without pain (predicted prevalence, % (SE) [a]	3.90 (.15)	8.76 (.27)
Difference between those with and without pain (95% CI)	**1.46 (0.68, 2.24)** [b]	**3.09 (1.97, 4.21)** [b]
Difference in difference (95% CI), 2012-2013 vs. 2001-2002	Reference	**1.63 (0.40, 2.86)** [c]
Frequent non-medical cannabis use		
With pain (predicted prevalence, % (SE) [a]	1.39 (.19)	4.74 (.42)
Without pain (predicted prevalence, % (SE) [a]	1.18 (.08)	3.30 (.14)
Difference between those with and without pain (95% CI)	0.21 (-0.16, 0.58) [b]	**1.43 (0.63, 2.23)** [b]
Difference in difference (95% CI), 2012-2013 vs. 2001-2002	Reference	**1.22 (0.38, 2.06)** [c]
DSM-IV Cannabis use disorder (CUD)		
With pain (predicted prevalence, % (SE) [a]	1.80 (.22)	4.01 (.40)
Without pain (predicted prevalence, % (SE) [a]	1.42 (.08)	2.67 (.14)
Difference between those with and without pain (95% CI)	0.38 (-0.05, 0.81) [b]	**1.34 (0.56, 2.12)** [b]
Difference in difference (95% CI), 2012-2013 vs. 2001-2002	Reference	**0.96 (0.14, 1.78)** [c]

[a] Adjusted for sociodemographic covariates (age, gender, race/ethnicity, education level, marital status, and family income), and pain x covariate interactions.

[b] Differences in prevalence whose 95% CI do not include 0.0 are statistically significant at p<.05 and are bolded

[c] Difference in prevalence differences (DiD) between 2012-2013 and 2001-2002 tested for significance via interaction contrast (additive interaction). Differences in difference estimates whose 95% CI do not include 0.0 are statistically significant at p<.05 and are bolded

TABLE S5. Any non-medical cannabis use, frequent non-medical use and DSM-IV cannabis use disorder in U.S. adults with and without pain, 2001-2002 and 2012-2013, in models that included 3-way interactions of pain, survey, and medical marijuana law (MML) status at the time of the survey, to determine if results varied between participants in MML and non-MML states.

	Any non-medical cannabis use	**Frequent non-medical cannabis use**	**Cannabis use disorder**
State MML status [a]	Between-State MML status contrasts [b] (95% CI)		
Early MML states vs. Never MML states	-1.61 (-5.53, 2.31)	1.03 (-1.07, 3.13)	-1.99 (-4.17, 0.19)
Late MML states vs. Never MML states	0.37 (-3.57, 4.31)	-0.25 (-2.33, 1.83)	-0.95 (-3.54, 1.64)
Late MML states vs. Early MML states	1.98 (-3.10, 7.06)	-1.28 (-4.00, 1.44)	1.04 (-1.90, 3.98)

[a] Early MML states passed an MML by 2001 (CA, CO, HI, ME, NV, OR, WA); Late MML states passed an MML between 2002-2012 (AZ, CT, MD, MA, MI, MT, NJ, NM, VT); Never MML states did not pass an MML by 2012. NESARC participants in states not included in NESARC-III (AK, DE, ID, NH, RI, SD, WV, WY) were excluded.

[b] Differences in the prevalence of cannabis use outcomes between those with and without pain (representing the association between pain and cannabis use outcome) were estimated separately for each survey and state MML combination. Then the absolute difference between the association of the outcome with pain in 2012-2013 (NESARC-III) and 2001-2002 (NESARC) was estimated separately for each state MML group. The estimates above represent the state MML status contrasts of these changes in association; contrasts whose 95% CI do not include 0.0 are statistically significant at $p<.05$ (none in this table were). Models were adjusted for individual-level sociodemographic characteristics (age, gender, race/ethnicity, education level, marital status, and family income), pain x sociodemographic interactions, and state-level sociodemographics (percent of state that was: male, without high school diploma, under thirty, and white), state MML status, state MML status x survey interaction, and pain x state MML status interaction.

Supplementary Material: Additive vs. Multiplicative Interaction

In the paper, "US adults with pain, an emerging risk group for non-medical cannabis use and cannabis use disorder: 2001-2002 and 2012-2013", we present evidence of additive interaction effects of pain and time period on cannabis outcomes. In our main analysis, absolute risk differences between those with and without pain were determined in each of the two surveys (2001-2002 and 2012-2013), and whether these risk differences *differed* between the 2001-2002 and 2012-2013 surveys (i.e., differences in differences) was tested. We found that the absolute differences in risk for the cannabis outcomes between those with and without pain did differ between the surveys, with significantly greater differences found in 2012-2013 than in 2001-2002.

Relative risk and between-survey differences in the relative risk ratios of the cannabis outcomes between those with and without pain were also tested via multiplicative interaction. These did not differ significantly between the surveys (time periods). When results for additive and multiplicative interaction do not agree, the nature and purpose of the research question becomes important in deciding which type of interaction is appropriate (1, 2). The purpose of our research question was to determine whether, in the context of a changing marijuana landscape (more permissive laws, more favorable attitudes, increasing use), adults with pain constituted a group with growing vulnerability to adverse cannabis outcomes (e.g., frequent non-medical use; cannabis use disorder), in which case clinical and public health treatment and prevention efforts are now more important than they once were. A large methodological literature (1-19) suggests that for such a purpose, additive interaction results provides the most accurate information.

To illustrate the rationale for using additive interaction to indicate the presence of synergy for the effects of pain and period, consider the following scenario and abbreviated proof of concept (see Rothman, Greenland, and Lash for an extended proof in general form (6). We partition the population into 6 groups, defined by their potential outcomes under each of four possible combinations of exposure to pain and period (survey) (i.e., their response types), as illustrated in Table S6. (Note that in defining these 6 groups, we make the standard assumption of monotonicity of effects (6), i.e., there is no one in the population for whom pain causes them *not* to use cannabis, nor that being in the period 2012-13 *prevents* the cannabis use outcome.) The groups include the two types for whom exposure makes no difference, i.e., the cannabis outcome is present (Type 1) or absent (Type 6) regardless of exposure to pain or period. Type 3 individuals have the cannabis outcome if they were exposed to pain, regardless of period. Type 5 individuals only have the cannabis outcome if they were in the 2012-13 survey *AND*

exposed to pain. Type 5 is the “synergistic” type because among these individuals, only confluence of the two exposures is sufficient for outcome occurrence. Let p_1 indicate the proportion of the population that is Type 1, p_2 the proportion that is Type 2, and so on (see Table S6).

With the further standard assumption of no unmeasured confounding, then the covariate-adjusted predicted risk of any non-medical cannabis use among individuals *with pain in 2001-2002* in the observed data (i.e., 5.15%, Table 1) estimates the proportion that would have this cannabis outcome if exposed to pain in 2001-2002 – i.e., it estimates ($p_1 + p_2 + p_3$). Similarly, the predicted risk of any non-medical cannabis use among individuals *without pain in 2001-2002* in the observed data (i.e. 3.74%) estimates the proportion that would have this cannabis outcome if they were not exposed to pain in 2001-2002 – i.e., it estimates (p_1). Thus, the risk difference for pain in 2001-2002 (1.41%) estimates ($p_1 + p_2 + p_3$) - (p_1) = ($p_2 + p_3$). By the same logic, the risk difference for pain in 2012-2013 (3.40%) estimates ($p_1 + p_2 + p_3 + p_4 + p_5$) - ($p_1 + p_2 + p_4$) = ($p_3 + p_5$). The difference in these risk differences (1.99%) estimates ($p_3 + p_5$) - ($p_2 + p_3$) = ($p_5 - p_2$). p_2 is a proportion and is thus ≥ 0. If the difference in risk differences is some number greater than 0, then p_5 (the proportion of individuals in the population who would only get the outcome *when exposed to pain in 2012-2013*) must be at least as big as ($p_5 - p_2$) (Table 1, 1.99%). The absolute difference in risk differences (i.e, the additive interaction effect) thus serves as a direct estimate of the lower bound of the proportion of individuals in the population of the synergistic type. In contrast, the ratio of risk ratios (i.e., multiplicative interaction effect) does not have an interpretation in terms of the response types, and is therefore not directly relevant to inference about synergistic types, i.e., Type 5. Thus, the multiplicative scale is not appropriate for our research question, while interaction on the additive scale is directly informative about the proportion of the population (and hence the number of people) impacted by the interaction.

The explanation provided above underlies the well-established fact that statistical interaction is scale dependent: statistical interaction can occur on the additive scale, multiplicative scale, neither, or both (7, 8). As demonstrated in methodological texts (9-11), simulation studies (9, 12-14), and decades of empirical work (15-19), additive interaction is most informative when the goal is to detect a particular group (or a newly vulnerable group) at risk so that limited public health resources can be targeted to those most in need, or newly in need. Our results based on additive interaction indicate that in the context of the changing marijuana landscape (more permissive laws, more accepting attitudes, and increasing prevalence of use), those in pain are

a group whose vulnerability to the risks of frequent non-medical cannabis use and cannabis use disorder is growing, thus now warranting greater clinical and public health attention than they did in 2001-2002. We hope that our findings can be used to guide such attention.

TABLE S6. Types of individuals defined by potential cannabis outcomes (1=yes, 0=no) with and without pain in the two time periods (surveys)

Type	2001-2002, without pain	2001-2002, with pain	2012-2013, without pain	2012-2013, with pain	Proportion of the population of this type
1	1	1	1	1	*(p_1)*
2	0	1	1	1	*(p_2)*
3	0	1	0	1	*(p_3)*
4	0	0	1	1	*(p_4)*
5	***0***	***0***	***0***	***1***	***(p_5)***
6	0	0	0	0	*(p_6)*
Proportion of the population in each exposure group	p_1	$p_1+p_2+p_3$	$p_1+p_2+p_4$	$p_1+p_2+p_3+p_4+p_5$	
Risk difference for pain	$(p_1+p_2+p_3)-(p_1)=p_2+p_3$		$(p_1+p_2+p_3+p_4+p_5)-(p_1+p_2+p_4)=(p_3+p_5)$		
Difference in risk differences (DiD)	$(p_3+p_5)-(p_2+p_3)=p_5-p_2$				

Type 5: Synergistic type: the cannabis outcome is present only in individuals exposed to pain ***and*** to the 2012-2013 period

References

1. VanderWeele TJ, Knol MJ: A Tutorial on Interaction. Epidemiol Methods 2014; 3(1):33-72
2. Greenland S: Interactions in epidemiology: relevance, identification, and estimation. Epidemiology 2009; 20(1):14-17
3. Saracci R: Interaction and synergism. Am J Epidemiol 1980; 112(4):465-466
4. Blot WJ, Day NE: Synergism and interaction: are they equivalent? Am J Epidemiol 1979; 110(1):99-100
5. Rothman KJ, Greenland S, Walker AM: Concepts of interaction. Am J Epidemiol 1980; 112(4):467-470
6. Rothman KJ, Greenland S, Lash TL: Modern Epidemiology. Edited by Lippincott WW2012. pp. 71-86.
7. Rothman KJ: Causes. 1976. Am J Epidemiol 1995; 141(2):90-95; discussion 89
8. VanderWeele TJ: On the distinction between interaction and effect modification. Epidemiology 2009; 20(6):863-871
9. VanderWeele TJ, Robins JM: The identification of synergism in the sufficient-component-cause framework. Epidemiology 2007; 18(3):329-339
10. Kaufman JS: Interaction reaction. Epidemiology 2009; 20(2):159-160
11. Knol MJ, VanderWeele TJ: Recommendations for presenting analyses of effect modification and interaction. Int J Epidemiol 2012; 41(2):514-520
12. Kalilani L, Atashili J: Measuring additive interaction using odds ratios. Epidemiol Perspect Innov 2006; 3:5
13. Knol MJ, van der Tweel I, Grobbee DE, et al: Estimating interaction on an additive scale between continuous determinants in a logistic regression model. Int J Epidemiol 2007; 36(5):1111-1118
14. Zou GY: On the estimation of additive interaction by use of the four-by-two table and beyond. Am J Epidemiol 2008; 168(2):212-224
15. Darnton AJ, McElvenny DM, Hodgson JT: Estimating the number of asbestos-related lung cancer deaths in Great Britain from 1980 to 2000. Ann Occup Hyg 2006; 50(1):29-38
16. Bally M, Nadeau L, Brophy JM: Studying additive interaction in a healthcare database: Case study of NSAIDs, cardiovascular profiles, and acute myocardial infarction. PLoS One 2018; 13(8):e0201884
17. Kinsey TL, Sturmer T, Poole C, et al: Changing predictors of statin initiation in US women over two decades. Pharmacoepidemiol Drug Saf 2019; 28(3):305-314
18. Marenholz I, Kerscher T, Bauerfeind A, et al: An interaction between filaggrin mutations and early food sensitization improves the prediction of childhood asthma. J Allergy Clin Immunol 2009; 123(4):911-916
19. Yang X, So WY, Ma RC, et al: Low LDL cholesterol, albuminuria, and statins for the risk of cancer in type 2 diabetes: the Hong Kong diabetes registry. Diabetes Care 2009; 32(10):1826-1832