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Association between non-medical cannabis legalization and emergency department visits for cannabis-induced psychosis

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Abstract

A major public health concern of cannabis legalization is that it may result in an increase in psychotic disorders. We examined changes in emergency department (ED) visits for cannabis-induced psychosis following the legalization and subsequent commercialization (removal of restrictions on retail stores and product types) of non-medical cannabis in Ontario, Canada (population of 14.3 million). We used health administrative data containing the cause of all ED visits to examine changes over three periods; 1) pre-legalization (January 2014 – September 2018); 2) legalization with restrictions (October 2018 – February 2020); and 3) commercialization (March 2020 – September 2021). We considered subgroups stratified by age and sex and examined cocaine- and methamphetamine-induced psychosis ED visits as controls. During our study, there were 6,300 ED visits for cannabis-induced psychosis. The restricted legalization period was not associated with changes in rates of ED visits for cannabis-induced psychosis relative to pre-legalization. The commercialization period was associated with an immediate increase in rates of ED visits for cannabis-induced psychosis (IRR 1.30, 95% CI 1.02-1.66) and no gradual monthly change; immediate increases were seen only for youth above (IRR 1.63, 1.27-2.08, ages 19-24) but not below (IRR 0.73 95%CI 0.42-1.28 ages, 15-18) the legal age of purchase, and similar for men and women. Commercialization was not associated with changes in rates of ED visits for cocaine- or methamphetamine-induced psychosis. This suggests that legalization with store and product restrictions does not increase ED visits for cannabis-induced psychosis. In contrast, cannabis commercialization may increase cannabis-induced psychosis presentations highlighting the importance of preventive measures in regions considering legalization.

82 **Introduction**

83 An increasing number of countries have or are considering legalizing recreational or non-medical
84 cannabis use for adults. A public health concern is that the legalization, and in particular
85 commercialization - allowing widespread cannabis retail access, cannabis marketing and the
86 development of new high potency products - may increase cannabis use and associated health
87 harms, including psychotic disorders.(1)(2) Epidemiological studies have shown a strong link
88 between cannabis use and the development of psychotic disorders.(3)(4)(5)(6)(7)(8) Recent
89 studies using genetically informed methods suggest that at least some of the association between
90 cannabis use and the development of psychotic disorders may be causal.(9)(10)(11)(12)(13)
91 There is also increasing evidence of dose-response relationships with increased risk of both
92 overall development of psychotic disorders and earlier onset psychotic disorders from more
93 frequent cannabis use and use of high-potency cannabis.(14)(15)(6)(8)(7)(16) An estimated
94 12.2% - 50.3% of first-episode psychosis is estimated to be attributable to heavy use of cannabis
95 with high tetrahydrocannabinol (THC) concentrations (>10% THC).(16) This observational
96 evidence is consistent with research on brain functioning and structure. Cannabis use, especially
97 during adolescence, is associated with reduced volume and cortical thickness along with
98 neurofunctional changes of several brain regions linked to the pathogenesis of psychotic
99 disorders.(17–19) Chronic cannabis use is also associated with functional connectivity alterations
100 and executive dysfunction and working memory impairments.(19) Several neurotransmitter
101 systems also appear to be impacted by chronic cannabis use, including acetylcholine,
102 endocannabinoid, dopamine, and glutamate and GABA systems with perhaps the most consistent
103 finding involving altered dopamine synthesis and receptor availability.(20) Critically, despite the
104 known link between cannabis use and psychosis, it is unclear whether the legalization of non-

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105 medical cannabis will impact the frequency and socio-demographic characteristics of cannabis-
106 induced psychosis.

107

108 On October 17, 2018, Canada legalized the sale and use of recreational or non-medical cannabis
109 for adults.(21) Initially, all provinces in Canada were only permitted to sell dried cannabis
110 flowers and seeds. Provinces were allowed to set their own rules regarding the sale of cannabis.
111 Ontario (Canada's most populous province, 2018 population of 14.3 million) set a minimum
112 legal age of purchase of 19 years and, for the first 6 months of legalization, only allowed
113 cannabis sales through an online government-operated website.(22) Beginning in April 2019, the
114 government allowed a limited number of stores to open with a cap of 62 stores (0.55 stores per
115 100,000 individuals aged 15+) placed on the province.(22)(23) Starting in 2020, the legal
116 cannabis retail market in Ontario began to rapidly mature and commercialize. In January 2020,
117 the sale of new cannabis products with high THC content, including concentrates, vapes, and
118 commercially produced edibles, was allowed.(24) Beginning in April 2020, the government cap
119 on cannabis stores was lifted, and by September 2021, there were 1,104 stores (8.86 stores per
120 100,000 individuals aged 15+), representing a 16-fold increase relative to April 2020.(22)(23)

121

122 The rapid commercialization of the legal non-medical cannabis market in Ontario and Canada is
123 unique globally. While a growing number of countries in Europe and Asia have either
124 decriminalized cannabis or legalized cannabis for medical use, to date only Canada, Uruguay,
125 and individual US states have legalized the sale of non-medical cannabis.(25)

126 (26)(27)(21)(28)(29) While Uruguay was the first country to legalize cannabis for non-medical
127 use in 2013, it has done so through a tightly regulated non-commercial model with THC

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128 concentration limits and requirements that individuals who use cannabis register with the
129 government and obtain cannabis from restricted or self-grown sources.(26) Similarly, most US
130 states have not allowed market commercialization, and cannabis remains illegal at the national
131 level.(28) A large body of alcohol-control literature has found that retail store availability is a key
132 predictor of population-level alcohol use and use-related harms.(30) Evidence from Colorado
133 State suggests that greater access to legal cannabis stores is associated with higher rates of ED
134 visits for psychosis.(31) A national US study found that the five US states with legal non-medical
135 cannabis stores had an insignificant trend (Rate Ratio 1.39 95%CI 0.98-1.97) towards greater
136 increases in psychosis-related disorders than states with no legal non-medical cannabis.(27) Prior
137 research from Ontario and Alberta found no impact of legalization on rates of ED visits for
138 cannabis-induced psychosis, but critically only examined changes until December 2019 before
139 market commercialization including the introduction of high potency products.(32)
140 Consequently, little is known about changes in psychosis following legalization in Canada during
141 the period most likely to result in such changes. Evidence from this period has implications not
142 only in Canada but for any country proceeding with allowing a commercial non-medical
143 cannabis market.

144

145 The objective of this study was to evaluate whether legalization and the subsequent
146 commercialization of non-medical cannabis in Ontario were associated with increases in ED
147 visits for cannabis-induced psychosis. As a concurrent control to account for potential COVID-
148 19 pandemic confounding, we examined changes in ED visits for cocaine- and
149 methamphetamine-induced psychosis. We also considered whether changes over time differed by
150 *a-priori* specified subgroups stratified by age (above and below the legal age of purchase) and

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151 sex. We hypothesized that there would be no change in ED visits for cannabis-induced psychosis
152 immediately following legalization during the restricted period, but that visits would increase
153 during the commercialization period.

154

155 **Methods**

156 **Study design Population and Data Sources**

157 We conducted a population-level cohort study of all individuals aged 15-105 years who were
158 eligible for Ontario's Health Insurance Plan (OHIP), which provides universal coverage for all
159 hospital-based care and outpatient physician services, between January 2014 and September
160 2021. Demographic and health care details for each individual, including all ED visits during the
161 study time frame, were accessed through ICES (formerly known as the Institute for Clinical
162 Evaluative Sciences) using six individual-level databases linked using unique coded identifiers,
163 see appendix A for details on database holding and linkage. For each individual in the study we
164 obtained their socio-demographic details, including age, sex, rural residence, and neighborhood
165 income quintile; as well as data and on their healthcare use in the past two years including
166 outpatient mental health visits and ED visits and hospitalizations for mental health and substance
167 use disorders.(33)(34) We then used an interrupted time-series (ITS) design to examine monthly
168 changes in ED visits for cannabis-induced psychosis and control conditions following the
169 legalization of non-medical cannabis.(35)(36) ITS designs use repeated measures before and
170 following an intervention to robustly examine changes and account for pre-intervention
171 trends.(35) The use of the data in this project was authorized under section 45 of Ontario's
172 Personal Health Information Protection Act (PHIPA) and did not require review by a Research
173 Ethics Board.

174

175 **Exposures**

176 We divided our study into three periods: “pre-legalization” (January 2014 – September 2018),
177 “restricted legalization” which included the post-legalization period with limited retail stores and
178 cannabis products (October 2018 – February 2020) and "commercialization" which included the
179 post-legalization period with unlimited retail stores and expanded products which also
180 overlapped with the COVID-19 pandemic (March 2020 – September 2021). These periods were
181 specified *a-priori* and consistent with prior work.(23) During the pre-legalization period in
182 Ontario, there was widespread access to medical cannabis for any individual with authorization
183 from a physician that would therapeutically benefit from medical cannabis.(37) There was also
184 access to an illicit non-medical cannabis market, including physical stores and online delivery
185 services.(38)

186

187 **Outcomes**

188 We identified the diagnostic codes assigned to ED visits using the *International Classification of*
189 *Diseases (ICD) 10th revision* codes. Our primary outcome, an ED visit for cannabis-induced
190 psychosis, was defined when ICD-10 code F12.5 or F12.7 (psychotic disorders, or residual and
191 late-onset psychotic disorder due to the use of cannabinoids) was the main or contributing reason
192 for the visit. As a secondary outcome, we identified first presentation ED visits for cannabis-
193 induced psychosis defined as an incident visit for cannabis-induced psychosis with no ED visits
194 or hospitalizations for any type of substance-induced or non-affective psychosis in the previous
195 two years or two or more outpatient visits to a primary care provider or psychiatrist for psychosis
196 in the previous two years. We examined changes in two control conditions, ED visits for cocaine-

197 induced or methamphetamine-induced psychosis, to account for potential bias from changes in
198 health service use related to the COVID-19 pandemic, which coincided with the start of the
199 commercialization period. We examined changes in all ED visits and first-presentation ED visits
200 for non-affective psychosis and substance-induced psychosis. Finally, we examined the
201 proportion of ED visits requiring admission to the hospital, and length of hospital stay among
202 those admitted as markers of the initial visit severity. See appendix B for details on all outcomes.

203

204 **Statistical Analyses**

205 We present descriptive statistics on the socio-demographic characteristics (e.g. age, sex,
206 neighborhood income quintile), and visit severity (e.g. proportion hospitalized and length of
207 hospital stay) of individuals with ED visits due to cannabis-induced psychosis, as well as the
208 characteristics of members of the general population of Ontario who never had an ED visit for
209 cannabis-induced psychosis. Characteristics and visit severity were captured at the time of the
210 first visit for those with a first presentation visit and at a random visit for those with a prevalent
211 cannabis-induced psychosis ED visit (defined as an individual with an ED visit for cannabis-
212 induced psychosis who in the two years before the ED visit had one or more health care visits for
213 a non-affective psychotic disorder or a substance-induced psychosis). Characteristics of the
214 general population were taken from the first point of cohort eligibility. We described the
215 proportion of total and first-presentation ED visits for non-affective psychosis and substance-
216 induced psychosis caused by cannabis-induced psychosis.

217

218 We used segmented Poisson regression analysis to examine changes in monthly ED visits over
219 the three policy periods (pre-legalization 57 months, restricted legalization 17 months, and

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220 commercialization 19 months). Each month, we identified the number of ED visits for cannabis-
221 induced psychosis and non-affective psychotic disorders and the number of individuals at risk
222 (alive, OHIP eligible during past two years). We analyzed the monthly count of ED visits for our
223 primary and secondary outcome and control conditions with the natural log of the population at
224 risk as an offset. We identified the pre-legalization trend and included two sets of slope and level
225 changes corresponding to a) restricted legalization and b) commercialization to examine
226 immediate and gradual changes in visits relative to the trend in the prior policy period. We
227 included indicators representing the four seasons to account for seasonal variation, and all
228 analyses included first-order autocorrelation. We ran stratified models comparing changes in ED
229 visits for cannabis-induced psychosis for pre-specified subgroups, including men vs women and
230 individuals aged 15-18 (youth below legal age), 19-24 (youth above legal age), and 25+ years.
231 As a sensitivity analysis, we repeated our segmented regression analyses for our primary and
232 secondary outcomes, including an indicator variable for each of the first two months of the
233 pandemic, consistent with prior work, during which all-cause ED visits declined relative to 2019
234 (-23.8% in March 2020 and -46.0% in April 2020).(14) Each interruption's immediate and
235 gradual changes were expressed as Incidence Rate Ratios (IRR) with 95% Confidence Intervals.
236 All statistical analyses were completed using in SAS Enterprise Guide 7.1 (SAS Institute, Cary,
237 NC).

238

239 **Results**

240 During our 8.5-year study, we included 14,015,365 individuals of whom 5,374 had one or more
241 ED visits for cannabis-induced psychosis, see **supplement Figure 1** for cohort flow and
242 exclusions. The mean (SD) age at the time of the ED visits for cannabis induced-psychosis was

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243 28.5 years (10.5), 4,074 (75.8%) were men, and 1,719 (32.0%), lived in neighborhoods with the
244 lowest income quintile. Over the same period, 3,181 (59.2%) individuals had a first presentation
245 ED visit for cannabis-induced psychosis. The majority of individuals (n=4,269, 79.4%) had an
246 outpatient visit (n= 3,934, 73.2%) or an ED visit or hospitalization for a mental health condition
247 (n=2,981, 55.5%) or substance use (n=1,622, 30.2%) in the two years before their ED visit for
248 cannabis-induced psychosis. Cannabis (n=597, 11.1%) and anxiety (n=1,273, 23.7%) were the
249 most common substance and non-psychotic mental health diagnoses associated with these visits,
250 **Table 1.** Compared to the general population, individuals with ED visits for cannabis-induced
251 psychosis were younger, more likely to be male, live in the lowest income quintile, and have had
252 an outpatient, ED visit or hospitalization for a mental health condition or substance use in the
253 past two years.

254

255 **Table 2** shows the total and mean rates of all-cause ED visits, ED visits for non-affective
256 psychotic disorders, and ED visits for cannabis-induced psychosis. During the entire observation
257 period, there were 231,024 ED visits for non-affective psychotic disorders or substance-induced
258 psychosis, of which 6,300 (2.6%) were for cannabis-induced psychosis. Of the 6,300 ED visits
259 for cannabis-induced psychosis, 3,450 (n=54.8%) were first-episode presentations. The rate of
260 total psychosis ED visits (non-affective and substance-induced psychosis) increased over time
261 from a monthly mean of 19.5 visits per 100,000 individuals pre-legalization to 23.4 visits per
262 100,000 individuals during the commercialization period. In addition, the proportion of ED visits
263 for non-affective or substance-induced psychosis with a diagnostic code for cannabis-induced
264 psychosis increased from 2.1% pre-legalization to 3.9% during the commercialization period.
265 Cannabis also increased as a cause of first-presentation non-affective or substance-induced

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266 psychosis ED visits over time. By the end of the study, 8.1% of total first-presentation psychosis
267 visits to the ED had a diagnostic code for cannabis-induced psychosis. Rates of ED visits for
268 cannabis-induced psychosis were greater in men compared to women, highest in individuals
269 aged 19-24 years and for individuals living in the lowest income quintile neighborhoods. Over
270 half (n=60.1%, n=3784) of ED visits for cannabis-induced psychosis required hospitalization
271 with a mean (SD) length of stay of 13.4 (20.8) days.

272 **Figures 1a, 1b** display rates of ED visits for cannabis-induced psychosis over the observation
273 period. Overall, between 2014 and 2021, the mean annual rate of ED visits for cannabis-induced
274 psychosis per 100,000 individuals aged 15+ years increased by 220.7% (0.29 to 0.93 per
275 100,000). Pre-legalization rates of ED visits per capita for cannabis-induced psychosis increased
276 by 2% per month (IRR 1.02 95%CI 1.01-1.02). Legalization was not associated with an
277 immediate (intercept) change in rates of visits and was associated with a decrease in the change
278 in slope of 2% (IRR 0.98 95%CI 0.96-1.00). After commercialization and at the onset of the
279 COVID-19 pandemic, there was an immediate increase of 30% (IRR 1.30 95%CI 1.02-1.66) in
280 rates of cannabis-induced psychosis per capita and an insignificant increase in slope (IRR 1.01
281 95%CI 0.99-1.04), see Figure 1 panel A and Table 3. In our sensitivity analysis which included
282 an indicator for March 2020 and April 2020, there was an immediate increase of 53% (IRR 1.53
283 95%CI 1.21-1.95) in rates of cannabis-induced psychosis during the commercialization, see
284 appendix Table 1. Similar trends were observed for first-episode presentations for cannabis-
285 induced psychosis.

286

287 Changes in monthly rates of ED visits for cannabis-induced psychosis following legalization
288 differed by age, **Figure 1 panel b**. Legalization was not associated with an immediate change in

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289 rates of visits per capita for any age group. It was associated with a decrease in slope for youth
290 aged 19-24 and individuals aged 25+ years. However, commercialization was associated with an
291 immediate increase in rates of ED visits for cannabis-induced psychosis in youth aged 19-24
292 years (IRR 1.63 95%CI 1.27-2.08) and not associated with an immediate change in rates for
293 youth aged 15-18 years (IRR 0.73 95%CI 0.42-1.28) or people aged 25+ years (IRR 1.30 (0.93-
294 1.81), figure 1 panel b, supplement table 1.

295

296 When examining our control conditions, ED visits for cocaine- and methamphetamine-induced
297 psychosis, the cannabis commercialization period was not associated with any immediate or
298 gradual changes; see **Figure 2**, Table 3 for segmented regression outputs for all outcomes.

299

300 **Discussion**

301 This study examined changes in ED visits for cannabis-induced psychosis following the
302 legalization and subsequent commercialization of non-medical cannabis in Ontario, Canada. Our
303 first key finding was that strictly regulated legalization of non-medical cannabis was not
304 associated with initial changes in cannabis-induced psychosis. Rather visits increased following
305 market commercialization, which included the introduction of new high THC-concentration
306 products and a 16-fold increase in legal cannabis retail stores. We observed similar changes for
307 individuals with a history of psychosis and those without, suggesting both a trigger of psychotic
308 episodes among people with pre-existing psychotic disorders and the potential development of
309 new psychoses. Our second key finding was that visits for cannabis-induced psychosis increased
310 specifically in youth above the minimum legal age of cannabis purchase (19-24 years) and did
311 not for youth below the legal age (15-18 years). Collectively, our findings highlight that non-

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312 medical cannabis legalization, and in particular, commercialization may result in important
313 population-level increases in cannabis-induced psychosis.

314

315 Although we observed an association between the period of commercialization of the legal
316 cannabis market in Ontario and increases in ED visits for cannabis-induced psychosis, our design
317 does not establish a causal relationship between these events. A key challenge is that the COVID-
318 19 pandemic overlapped closely with the commercialization of the market. However, three
319 points support a link between commercialization and increases in cannabis-induced psychosis.

320 *First*, we observed large differences in changes in ED visits for cannabis-induced psychosis
321 based on the minimum legal age of cannabis purchase. Youth below the legal age of cannabis
322 purchase in Ontario (19+ years) did not experience increases in visits. In contrast, young adults
323 just above the legal age experienced the largest increase, which suggests that access to legal
324 cannabis is a risk factor for cannabis-induced psychosis. *Second*, daily cannabis use and greater
325 potency (THC concentration) of cannabis products have been linked to an increased risk of
326 psychosis.⁽¹⁵⁾⁽⁶⁾ The observed increase in visits for cannabis-induced psychosis are consistent
327 with increases in self-reported daily or near-daily cannabis use from population-representative
328 surveys in Ontario (4.9% in Q1 2018 to 9.3% in Q4 2020) and with data showing that the
329 potency (e.g. THC concentration) of legal cannabis has been increasing over time in Ontario.

330 ⁽³⁹⁾⁽⁴⁰⁾⁽⁴¹⁾ ⁽⁹⁾⁽²⁸⁾ *Finally*, our analyses showed that increases in ED visits for cannabis-
331 induced psychosis during the commercialization period were greater than increases in visits for
332 cocaine- or methamphetamine-induced psychosis, conditions unrelated to cannabis-legalization
333 but that could similarly increase in response to COVID-19 stressors. This finding suggests that

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334 increases in cannabis-induced psychosis are less likely related to changes in substance use or
335 health service use for psychotic disorders during the pandemic.

336

337 Our findings suggest several areas of further inquiry and preliminary evidence for policymakers.

338 First, we observed that ED visits for cannabis-induced psychosis were increasing in the lead-up

339 to legalization. During Ontario's pre-legalization period, there was increasing access to medical

340 cannabis and illegal non-medical cannabis dispensaries and online delivery services.(42)(43)

341 Data from regions without liberalized cannabis policies estimate that a growing proportion of

342 schizophrenia diagnoses are attributable to heavy cannabis use.(44) Further research examining

343 the contribution of increased medical cannabis and illicit cannabis access on changes in

344 cannabis-induced psychosis is needed. *Second*, the absence of an increase in cannabis-induced

345 psychosis during the restricted legalization period offers cautious support that legalization with

346 public-health oriented regulations may not increase cannabis-induced psychosis. These findings

347 are consistent with growing evidence showing that the initial period of restricted legalization did

348 not result in large changes in cannabis use or healthcare visits caused by cannabis.(45,46)(24)

349 Importantly, given the already established medical and illegal non-medical cannabis market in

350 Ontario, the lack of increase in visits during stringent legalization period that we observed may

351 not generalize to other regions without legal medical cannabis or less illicit market access. *Third*,

352 the impact of cannabis commercialization on changes in psychotic disorders remains unclear. A

353 prior cross-sectional study from the US found that in states with more permissive medical or

354 non-medical cannabis policies a higher proportion of hospitalizations for psychosis involve

355 cannabis.(47) A national US study found no statistically significant association between different

356 levels of cannabis commercialization and increases in psychosis-related disorders. Importantly,

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357 the study did report relatively large effect sizes that approached significance and did not examine
358 first presentations for psychotic disorders or cannabis-involvement in psychosis.(27) A prior
359 meta-analysis found a mean of six years between the initiation of regular cannabis use and the
360 onset of psychotic disorders which suggests that longer-term monitoring may be needed for
361 studies examining changes in overall rates of psychosis.(48) While our study offers caution that
362 the commercialization of non-medical cannabis in Ontario may have been associated with
363 increased cannabis-induced psychosis, further research is urgently indicated. *Finally*, consistent
364 with a robust alcohol literature, our findings suggest that being below the minimum legal age of
365 cannabis purchase may be protective against severe cannabis-related harms.(30) Additional
366 research is required to clarify the health impacts of different minimum legal ages and whether
367 setting a higher age would protect this vulnerable population.

368

369 Our findings also have implications for healthcare costs and health service planning. ED visits
370 for cannabis-induced psychosis were high acuity events, with over half requiring hospitalization
371 with an average length of stay of almost two weeks. Over half of the individuals with an ED visit
372 for cannabis-induced psychosis had no history of outpatient, ED, or hospital-based care for an
373 affective, non-affective, or substance-induced psychosis in the past two years. A prior meta-
374 analysis estimated that 34% (95%CI 30-43) of individuals with a first episode of cannabis-
375 induced psychosis would subsequently transition to schizophrenia over several years.(49) These
376 findings raise concerns that recent increases in ED visits for cannabis-induced psychosis
377 following non-medical cannabis legalization in Ontario could translate into future population-
378 level increases in chronic psychotic disorders, which in turn result in substantial morbidity and
379 mortality and burden on the mental health system.(50) (51)

380

381 Our study has limitations. First, this is an observational study, and while our interrupted time
382 series design accounts for pre-legalization trends, it does not exclude competing events. While
383 several arguments support the role of legalization in these increases, the overlap of the COVID-
384 19 pandemic with its disruption of routines and strain on mental health could also contribute to
385 changes in cannabis-induced psychosis.⁽⁵²⁾ Second, the observed increases could be from a
386 greater willingness of patients to disclose use of a now legal substance or increased awareness
387 and sensitivity to cannabis use by a physician following legalization. Importantly, while these
388 biases could explain increases following legalization, their influence would be expected to begin
389 immediately following legalization. Therefore, they are less likely to explain the large increase
390 observed 18 months after legalization. In addition, overall rates of ED visits for psychosis have
391 increased over time in Ontario which argues against simple changes in detection or reporting of
392 cannabis use. Third, we lacked data on patterns of cannabis use and the cannabis products used
393 by individuals with cannabis-induced psychosis. While our results are consistent with increases
394 in self-reported daily cannabis use following legalization in Ontario, further research, such as
395 chart reviews, which can capture individual-level patterns of cannabis use following legalization
396 among individuals with psychosis, is indicated.⁽³⁹⁾⁽⁴⁰⁾⁽⁵³⁾ Fourth, while coding for cannabis-
397 induced psychosis has been used in multiple prior studies it has not been chart validated in
398 Ontario, and may over or underrepresent cases of cannabis-induced psychosis.⁽⁵⁴⁾ Finally,
399 despite the large retail expansion during our study period, the legal market in Ontario had still
400 not reached maturity. Consequently, our results may underestimate the full impact of mature
401 markets following legalization.

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402

403 The findings of this study suggest that legalization of non-medical cannabis with tight
404 restrictions on product types and the number of retail stores was not associated with increases in
405 ED visits for cannabis-induced psychosis. In contrast, a period of commercialization of legal
406 cannabis markets, which overlapped with the COVID-19 pandemic, was associated with
407 increased ED visits for cannabis-induced psychosis, particularly for youth just above the legal
408 age of purchase. Although causation cannot be inferred, these results caution that current global
409 trends towards non-medical cannabis legalization, particularly the commercialization of
410 cannabis, may result in increases in psychotic disorders in the absence of additional preventive
411 measures and market restrictions.

412

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435 are solely those of the authors and do not reflect those of the funding or data sources; no
436 endorsement is intended or should be inferred.

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442 provided by the Canadian Institute for Health Information and the Ontario Ministry of Health.

443
444 Data Sharing Statement: The dataset from this study is held securely in coded form at ICES.
445 While legal data sharing agreements between ICES and data providers (e.g., healthcare
446 organizations and government) prohibit ICES from making the dataset publicly available, access
447 may be granted to those who meet pre-specified criteria for confidential access, available at
448 www.ices.on.ca/DAS (email: das@ices.on.ca). The full dataset creation plan and underlying
449 analytic code are available from the authors upon request, understanding that the computer
450 programs may rely upon coding templates or macros that are unique to ICES and are therefore
451 either inaccessible or may require modification.

452
453 **Conflict of Interest**

454 Marco Solmi has received honoraria/has been a consultant for Angelini, Lundbeck, Otsuka.

455

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Figure Legends

Panel Figure 1. Observed and predicted rates of ED visits during different phases of non-medical cannabis legalization in Ontario. Panel 1a shows cannabis-induced psychosis, and first presentation cannabis-induced psychosis ED visits per 100,000 individuals, Panel 1b shows cannabis-induced psychosis ED visits per 100,000 individuals aged 15-18, 19-24, 25+ years. Shaded regions represent 95% confidence intervals.

Figure 2. Observed and predicted rates of ED visits per 100,000 individuals during different phases of non-medical cannabis legalization in Ontario for cannabis- cocaine- and methamphetamine-induced psychosis. Shaded regions represent 95% confidence intervals.

Legalization and Cannabis-Induced Psychosis

618 **Table 1.** Characteristics of individuals with an emergency department visit for cannabis-induced
 619 psychosis and the general population of Ontario, Canada between January 2014 and September
 620 2021.

		Prevalent Cannabis-Induced Psychosis ^{1,2}	First-Presentation Cannabis-Induced Psychosis ³	Any Cannabis-Induced Psychosis ²	General Population of Ontario ⁴
		N (%)			
Total		2,193	3,181	5,374	14,009,991
Sex	Women	499 (22.8)	801 (25.2)	1,300 (24.2)	7,114,128 (50.8)
	Men	1,694 (77.2)	2,380 (74.8)	4,074 (75.8)	6,895,863 (49.2)
Age	Mean (SD)	28.62 (9.59)	28.44 (11.03)	28.47 (10.48)	43.0 (19.9)
	15-18 years	151 (6.9)	401 (12.6)	565 (10.5)	1,940,142 (13.8)
	19-24 years	771 (35.2)	1,100 (34.6)	1,871 (34.8)	1,202,085 (8.6)
	25-44 years	1,090 (49.7)	1,362 (42.8)	2,439 (45.4)	4,429,799 (31.6)
	45+ years	181 (8.3)	318 (10.0)	499 (9.3)	6,437,965 (46.0)
Rurality	Rural	148 (6.7)	223 (7.0)	373 (6.9)	136,7631 (9.8)
	Urban	2,019 (92.1)	2,938 (92.4)	4,957 (92.2)	12,602,107 (90.0)
	Missing	26 (1.2)	20 (0.6)	44 (0.8)	40,253 (0.3)
Neighborhood Income Quintile	1 (poorest)	801 (36.5)	914 (28.7)	1,719 (32.0)	2,918,983 (20.8)
	2	472 (21.5)	698 (21.9)	1,169 (21.8)	2,816,266 (20.1)
	3	369 (16.8)	629 (19.8)	993 (18.5)	2,752,749 (19.6)
	4	282 (12.9)	466 (14.6)	753 (14.0)	2,694,356 (19.2)
	5 (Richest)	243 (1.1)	454 (14.3)	696 (13.0)	2,782,654 (19.9)
	Missing	26 (1.2)	20 (0.6)	44 (0.8)	44,983 (0.3)
Substance Use ED visit or Hospitalization in Past 2 Years	Any	1,268 (57.8)	403 (12.7)	1,622 (30.2)	76,843 (0.5)
	Alcohol	196 (8.9)	131 (4.1)	325 (6.0)	50,295 (0.4)
	Opioids	78 (3.6)	21 (0.7)	99 (1.8)	7,345 (0.1)
	Cannabis	521 (23.8)	142 (4.5)	597 (11.1)	4,427 (0.0)
	Other	799 (36.4)	166 (5.2)	940 (17.5)	18,718 (0.1)
Mental Health ED visit or Hospitalization in Past 2 Years	Any	2,193 (100.0)	781 (24.6)	2,981 (55.5)	287,749 (2.1)
	Anxiety Disorder	763 (34.8)	513 (16.1)	1,273 (23.7)	133,600 (1.0)
	Mood Disorder	635 (29.0)	315 (9.9)	938 (17.5)	85,412 (0.6)
	Non-Affective Psychosis	2,193 (100.0)	0 (0.0)	2,202 (41.0)	80,785 (0.6)
	Other	1,110 (50.6)	142 (4.5)	1,235 (23.0)	46,333 (0.3)

Legalization and Cannabis-Induced Psychosis

Outpatient Substance Use or Mental health Visits in Past 2 Years	Family Medicine/ General practice	1,689 (77.0)	1,718 (54.0)	3,402 (63.3)	2,798,075 (20.0)
	Psychiatry	1,665 (75.9)	815 (25.6)	2,469 (45.9)	586,467 (4.2)
Any ED visit or Hospitalization in past month	ED visit	1,113 (50.8)	734 (23.1)	1,844 (34.3)	355,144 (2.5)
	Hospitalization	549 (25.0)	83 (2.6)	616 (11.5)	75,182 (0.5)

621 ¹Individuals with cannabis-induced psychosis and at the time of the ED visits cannabis-induced
 622 psychosis had received care for a non-affective or substance-induced psychotic disorder in past 2
 623 years

624 ²Characteristics taken at the time of random visit,

625 ³Characteristics taken at time of first visit

626 ⁴Characteristics taken at first point of cohort eligibility

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Table 2 Types of ED visits in Ontario during the pre-legalization, legalization and commercialization.

		Pre-Legalization	Restricted Legalization	Commercialization
		Jun 2014 – Sept 2018	Oct 2018 – Feb 2020	Mar 2020 - Sept 2021
		(57 months)	(17 months)	(19 months)
Total Visits, N (%)	All-Cause ED visit	23,514,026	6,772,318	6,917,821
	Any Non-Affective or Substance-Induced Psychosis (% of All-Cause ED visits)	131,218 (0.56)	44,667 (0.66)	55,139 (0.80)
	Any Cannabis-Induced Psychosis (% of total psychosis ED visits) ¹	2,769 (2.11)	1,396 (3.13)	2,135 (3.87)
	First Presentation Non-Affective or Substance-Induced Psychosis (% of All-Cause ED visits)	33,114 (0.14)	11,201 (0.17)	14,336 (0.21)
	First Presentation Cannabis-Induced Psychosis (% of first-presentation total psychosis ED visits)	1,525 (4.61)	768 (6.86)	1,157 (8.07)
ED Visits per 100,000 individuals Monthly mean rate (SD)	Any Non-Affective or Substance-Induced Psychosis	19.47 (1.81)	21.38 (1.02)	23.4 (1.25)
	Any Cannabis-Induced Psychosis	0.41 (0.14)	0.67 (0.09)	0.91 (0.16)
	First Presentation Non-Affective or Substance-Induced Psychosis	4.91 (0.46)	5.36 (0.39)	6.08 (0.49)
	First presentation Cannabis-Induced Psychosis	0.23 (0.08)	0.37 (0.05)	0.49 (0.11)
Cannabis-Induced Psychosis Visits per 100,000 individuals Monthly mean rate (SD)	Women	0.16 (0.08)	0.32 (0.08)	0.47 (0.10)
	Men	0.67 (0.21)	1.03 (0.14)	1.36 (0.26)
	Age 15-18 years	1.01 (0.45)	1.28 (0.54)	1.16 (0.36)
	Age 19-24 years	1.77 (0.64)	2.57 (0.52)	3.77 (0.63)
	Age 25+ years	0.23 (0.11)	0.44 (0.07)	0.62 (0.15)
	Neighborhood Income Q1	0.68 (0.24)	1.10 (0.2)	1.40 (0.29)
	Neighborhood Income Q5	0.25 (0.12)	0.43 (0.14)	0.60 (0.17)
ED visits for cannabis-induced psychosis requiring Hospitalization, N(%)	Cannabis-Induced Psychosis	1,626 (58.7)	814 (58.3)	1,344 (63.0)
	Mean length of stay in hospital, days (SD)	14.1 (23.5)	13.1 (16.8)	11.9 (17.3)

¹Total Psychosis ED visits include visits for non-affective- or substance-induced psychosis

Table 3. Interrupted time series analysis of ED visits for cannabis-induced psychosis and cocaine- and methamphetamine-induced psychosis following non-medical cannabis legalization and commercialization.

	Any Cannabis-Induced Psychosis	First Presentation Cannabis-Induced Psychosis	Cocaine-Induced Psychosis	Methamphetamine-Induced Psychosis
	Incidence Rate Ratio (95% CI)			
Pre-Legalization Monthly Slope	1.02 (1.01-1.02)	1.02 (1.01-1.02)	1.02 (1.02-1.03)	1.04 (1.03-1.04)
Restricted Legalization Immediate Change	1.11 (0.88-1.39)	1.04 (0.79-1.36)	0.83 (0.65-1.06)	0.97 (0.81-1.17)
Restricted Legalization Gradual Change	0.98 (0.96-1.00)	0.98 (0.96-1.00)	0.99 (0.97-1.01)	0.98 (0.97-1.00)
Post Restricted Legalization Monthly Slope	1.00 (0.98-1.02)	1.00 (0.98-1.02)	1.01 (0.99-1.03)	1.02 (1.00-1.03)
Commercialization				
Commercialization Immediate Change	1.30 (1.02-1.66)	1.26 (0.95-1.68)	0.90 (0.69-1.17)	1.04 (0.86-1.25)
Commercialization Gradual Change	1.01 (0.99-1.04)	1.00 (0.97-1.04)	1.00 (0.98-1.03)	0.98 (0.96-1.00)
Post Commercialization Monthly Slope	1.01 (0.99-1.02)	1.00 (0.99-1.02)	1.02 (1.00-1.03)	1.00 (0.99-1.01)

Figures

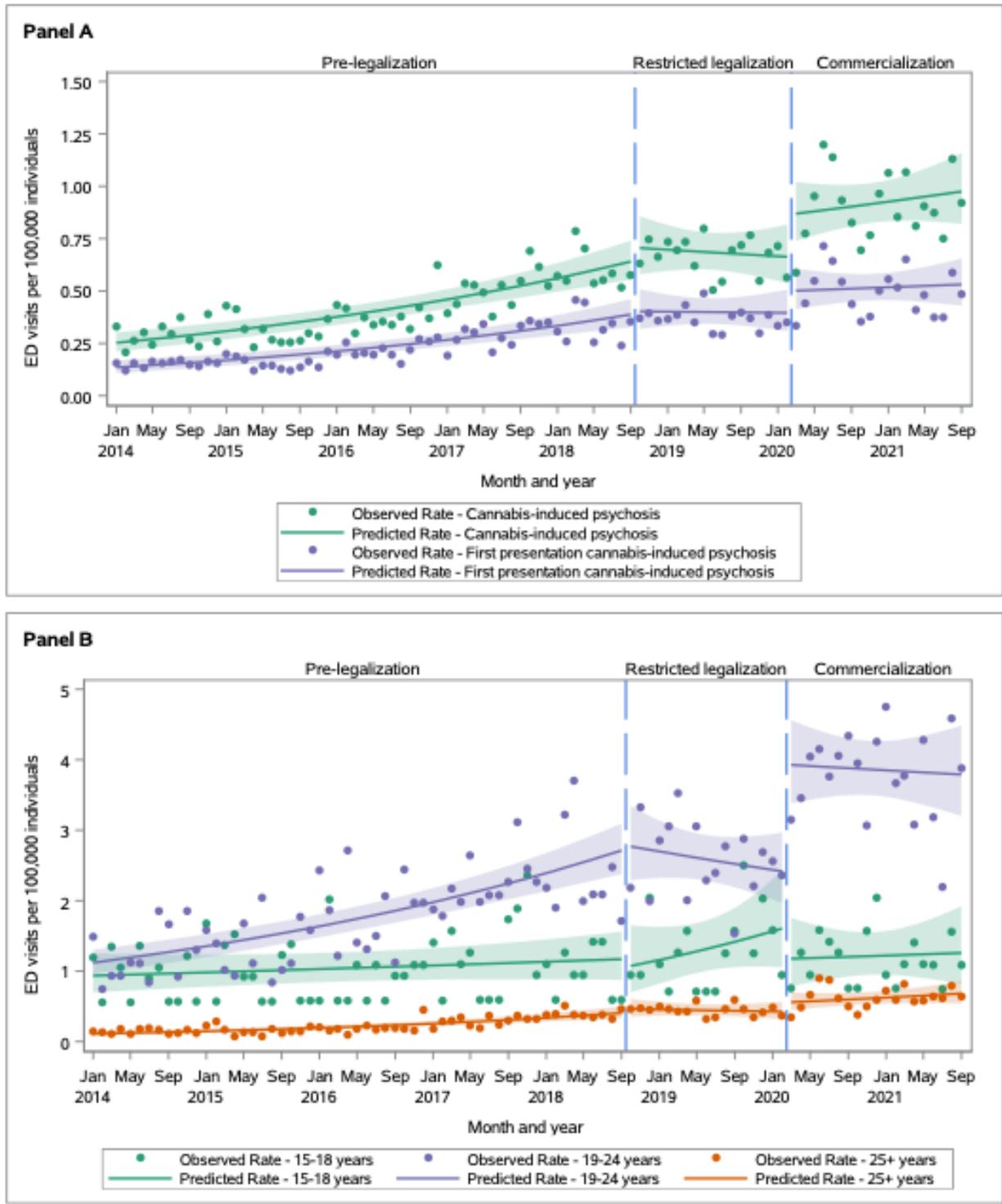


Figure 1. Observed and predicted rates of ED visits during different phases of non-medical cannabis legalization in Ontario. Panel 1a shows cannabis-induced psychosis, and first presentation cannabis-induced psychosis ED visits per 100,000 individuals, Panel 1b shows cannabis-induced psychosis ED visits per 100,000 individuals aged 15-18, 19-24, 25+ years. Shaded regions represent 95% confidence intervals.

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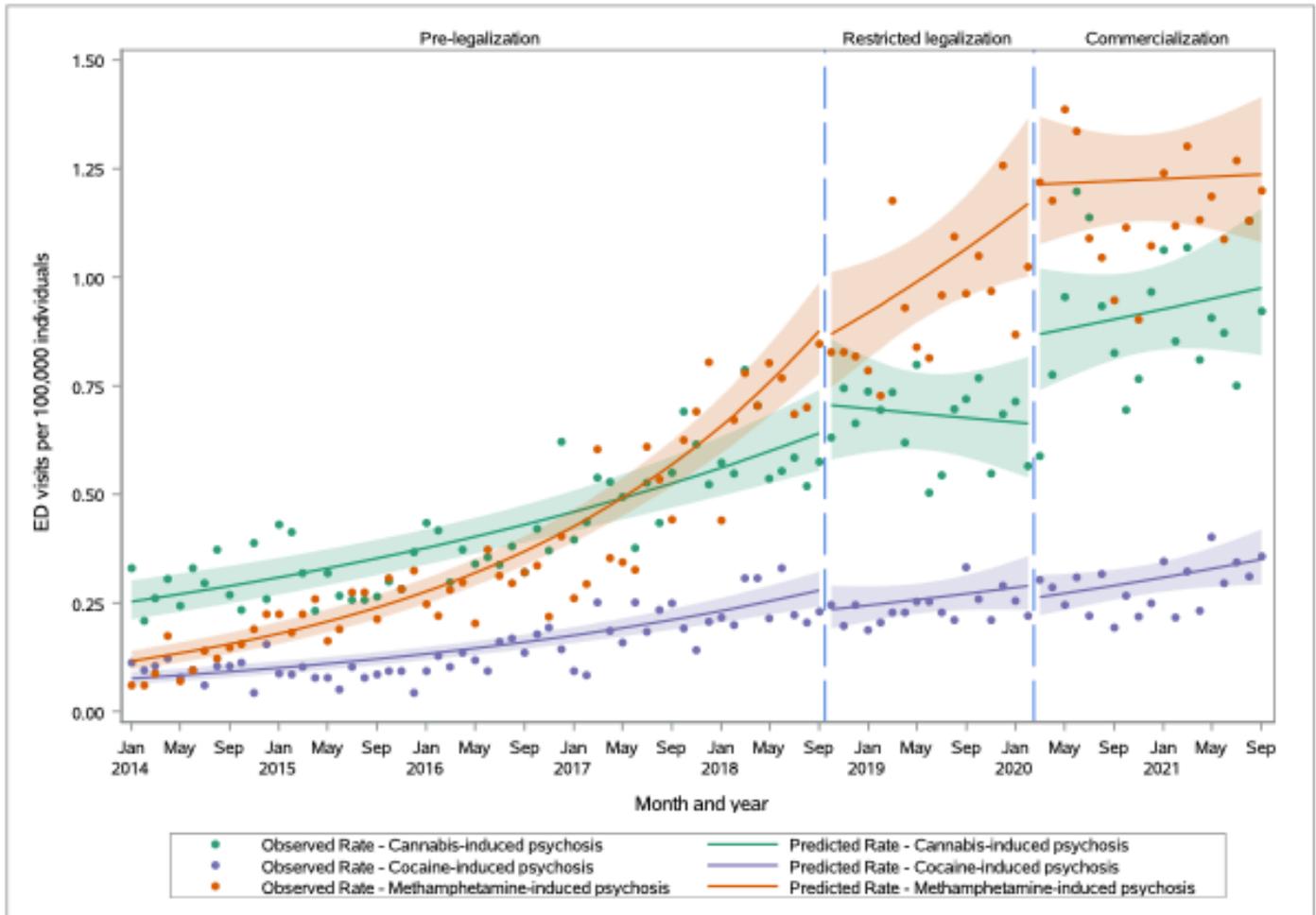


Figure 2. Observed and predicted rates of ED visits per 100,000 individuals during different phases of non-medical cannabis legalization in Ontario for cannabis- cocaine- and methamphetamine-induced psychosis. Shaded regions represent 95% confidence intervals.