What are the adverse health effects of cannabis?

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Outline

- My approach to assessing the adverse effects of cannabis
  - Political challenges of polarized views
  - Making causal inferences from observational data
- A summary of epidemiological evidence on
  - Acute and chronic adverse effects of cannabis use
  - Acknowledging uncertainties
- Assessing the population level impacts of cannabis use
  - the effects to date of cannabis legalisation in USA
  - what effects we may expect to see in the future

Assessing the adverse effects of cannabis

- Polarised opinions and policy-driven appraisals:
  - Selective use of evidence to support predetermined positions
- An implicit policy simplification: cannabis use is
  - Harmful → and so should be prohibited

    OR
  - Harmless → and so should be legalized
- Consequences:
  - Harms amplified by supporters of prohibition
  - Harms discounted by advocates of legalization
  - Similar challenges in assessing the benefits of medical use

Causal inferences about cannabis harms

- Cannabis use & the adverse effect are associated
- Evidence on which comes first:
  - cannabis use or the adverse effect?
- Separating the effects of cannabis from those of:
  - other drugs: alcohol, tobacco and stimulants….
  - users' cognitive ability, psychosocial risks….
  - genetic risks of cannabis use and outcomes
- Is a causal relationship biologically plausible?
- How do the harms of cannabis compare with other drugs?

Acute adverse health effects

- Low acute toxicity:
  - No fatal overdoses: no respiratory depression unlike opioids
  - heart attacks and strokes in heavy smokers??
- Anxiety, dysphoria, panic, paranoia
  - Common among naive users and
  - experienced users who take more than planned e.g. oral doses
- Cognitive and psychomotor impairment
  - Potential for accidental injuries while intoxicated
- Psychotic symptoms with high doses of THC
  - More common in persons with psychoses

Accidental Injury

- Dose-related impaired psychomotor performance on:
  - complex laboratory tasks & simulated driving studies
  - small number of on-road driving studies
- Epidemiological studies of fatalities
  - measures of recent cannabis use in larger studies
  - controlling for confounding effects of alcohol
- Meta-analyses of case control and culpability studies
  - RR of accident ~ 1.3-2.1 among recent cannabis users
  - Risk larger is if cannabis affected drivers also use alcohol
- Contribution to fatal accidents (attributable risk)
  - Much smaller than alcohol (2.8% vs 28% in France, 2000s)

Adverse effects of long-term regular use

- What do we mean by longer term regular use?
  - Daily or near daily use
  - Over months and often years
  - Most studied: daily use from teens to early 30s

- What adverse effects are of concern?
  - Dependence syndrome
  - Impaired adolescent psychosocial outcomes
  - Poorer mental health: psychoses, anxiety and depression
  - Cancers caused by smoking
  - Cardiovascular disease
  - Reproductive outcomes from use in pregnancy

Cannabis dependence

- Increased numbers of cannabis users seeking help
  - in Australia, EU, USA and Netherlands
  - Cannabis 2nd only to alcohol in Australian treatment seekers
- Epidemiological studies of risk:
  - 9% of lifetime users (in early 1990s in USA)
  - 16% in adolescent initiators; 33-50% of daily users
  - Leung et al meta-analysis confirmed these risk estimates
- Health and social consequences of dependence:
  - respiratory symptoms
  - impaired cognitive and work performance
  - partner disapproval and cost of heavy use
  - concern about setting a bad example for their children

Correlates of cannabis dependence

- More likely to use other more harmful illicit drugs:
  - Amphetamines, cocaine and heroin
- Poor school outcomes:
  - Early school leaving and welfare dependence in adulthood
- Poorer mental health:
  - Cognitive impairment
  - Schizophrenia and other psychoses
  - Depression and suicide
  - Anxiety disorders
- Debate about which are:
  - Causes or consequences of dependence e.g. depression?
  - Reflect common causes e.g. school leaving & other drug use?

Is cannabis a "gateway drug"?

- Common sequence of drug involvement
  - alcohol & tobacco → cannabis → other illicit drugs
- This pattern is strong and consistent in prospective studies:
  - Temporal order of alcohol, tobacco, cannabis and other drugs
  - ⇧RR of illicit drug use in early & regular users
- Partially explained by common causes:
  - Selective recruitment & genetic vulnerability
- Some support for causal roles for:
  - Peer affiliation & greater access via drug markets
- Pharmacological sensitization?
  - Suggestive animal models: effects of pubertal exposure

Poor educational outcomes

- In high school cannabis use is associated with:
  - Poorer school performance & early school drop out
- Which is cause and effect?
  - poor school performers → use cannabis
  - cannabis → impairs school performance?
  - Both are true?
- A meta-analysis of 3 Australasian studies found
  - cannabis use predicted school drop out
  - Poor school performers
    - more likely to use cannabis & affiliate with cannabis-users
- Cannabis use probably has a small effect
  - associations persist after statistical adjustment
  - biologically plausible:
    - Daily use impairs cognitive performance

Cognitive impairment

- Impaired performance in cognitive tasks in lab:
  - related to duration and frequency of use
- Case-control studies of cognitive impairment
  - More impairment in long-term daily users
  - Support from neuroimaging studies
- Evidence in longitudinal studies
  - Dunedin cohort an 8-point IQ decline
  - Early users who used daily throughout 20s into 30s
- Still uncertain about:
  - how reversible these effects are
  - mechanisms: intoxication, residual effect, toxicity?

Cannabis use and schizophrenia

- 27 year follow up of Swedish cohort (N = 50,000)
  - RR = 3, dose response that persisted after adjustment; AR: 13%
- Cohort studies in Australia, New Zealand, Netherlands, and Germany
  - Regular cannabis use associated with more psychotic symptoms
  - Meta-analysis: RR=3.9 in those who use higher THC cannabis
- Systematic review of genetically informative studies
  - Shared genetic risks for cannabis use and psychosis
  - Association not wholly explained: a small causal role
- Biologically plausible causal relationship
  - Cannabinoid-dopamine interaction
  - provocation studies using THC in normal and affected persons
- Comparative evaluation: better evidence than alcohol and stimulants

Long term adverse health effects

- Reproductive effects of use in pregnancy
  - Childbirth outcomes
  - Child development
- Respiratory diseases
  - Bronchitis
  - Emphysema
  - Lung and other URT cancers from smoking
- Cardiovascular diseases
  - Myocardial infarction
  - Stroke

Cannabis use during pregnancy

- Most consistent: lower birth weight and increased prematurity
- Limitations of these studies:
  - Most rely on self-reported cannabis use
  - Confounding by other drug use, low SES, antenatal care
- Uncertainty about:
  - Birth defects: low statistical power in most studies
  - Cognitive impairment in childhood and adolescence
- Need larger better controlled studies but:
  - Prudent to discourage cannabis use during pregnancy

Respiratory effects of cannabis smoking

- Cannabis has been primarily smoked
  - Cannabis smoke similar tobacco smoke
- Epidemiological studies of heavy users of:
  - Increased cough, sputum, wheeze
  - Histopathological changes in lung
  - Impaired immunological responses
- Conflicting evidence on respiratory function
  - Impaired function in some prospective studies
  - But larger studies have failed to find it
- Suggestive evidence of reduced risk with vaporisers:
  - Self-report and short-term use
- Use of ingestible cannabis eliminates respiratory risks

Respiratory cancers

- Reasons for concern
  - composition of cannabis smoke: tar, carcinogens and particulates
  - histopathological changes in lungs of smokers
  - case reports of lung cancer in young adults
- Conflicting epidemiological evidence
  - mixed findings from case-control studies
  - positive findings confounded by tobacco smoking
- How convincing is an absence of evidence?
  - Few cannabis users smoke as often as tobacco smokers
  - Very low rates of daily cannabis smoking over decades
  - May these change with legalization?

Other cancers

- Childhood cancers
  - Old case control studies of 3 different cancers
  - Cannabis use measured as a possible confounder
  - Results not replicated and no trends in their incidence
- Prostate cancer
  - Single cohort study in SFO area: modest RR
  - Confounding a risk: AIDS deaths in cohort
- Testicular cancer
  - Three case-control studies and two replications
  - Cannabis use and dose related risk of nonseminomas
  - Further studies needed: CB receptors in testes

Cardiovascular effects

- THC is a potent cardiovascular stimulant
  - Increases heart rate acutely and has complex effects on BP
  - Tolerance in young and healthy regular users
  - Case reports of MI and strokes in young users
- Concern about CVD risks in older cannabis users
  - Small provocation studies in patients with angina
  - Intermittent cannabis use in older users and medical users
- Case-crossover study of myocardial infarction
  - Doubling of MI risk in hours after ***smoking*** cannabis
  - Consistent with provocation studies in MI patients
- Longitudinal study of mortality in MI patients
  - Higher CVD mortality in cannabis ***smokers***

High risk groups

- Adolescents
  - who initiate use early (~ 15 years)
  - with poor school performance and conduct disorders
- Pregnant women and women planning a pregnancy
- Persons with pre-existing conditions
  - cardiovascular disease especially older adults
  - respiratory disease e.g. asthma
  - Psychoses, depression and anxiety disorders
  - alcohol and drug dependence

Comparisons with tobacco

- Respiratory diseases
  - Chronic bronchitis
  - Impaired lung function?
  - Emphysema?
- Cardiovascular disease
  - Acute precipitant of myocardial infarctions?
  - Concerns about increased use among older users
- Cancers?
  - Respiratory: unclear for cannabis smoking
  - Testicular cancer risk in cannabis users?

Comparisons with alcohol

- Fatal overdose
  - Can occur with alcohol; extremely low risk for cannabis
- Adverse acute psychological effects
  - more common than alcohol?
- Car crash risk
  - ~ 2 fold increase, less than alcohol; higher if combined with alcohol
- Dependence
  - Increased treatment seeking; persistent in those who seek help
- Psychosocial outcomes
  - Underachievement, occupational performance and low life satisfaction
- Mental Health
  - Probably exacerbates psychoses, anxiety and depression
  - May precipitate psychosis in vulnerable persons
  - May increase suicide risk in depressed persons

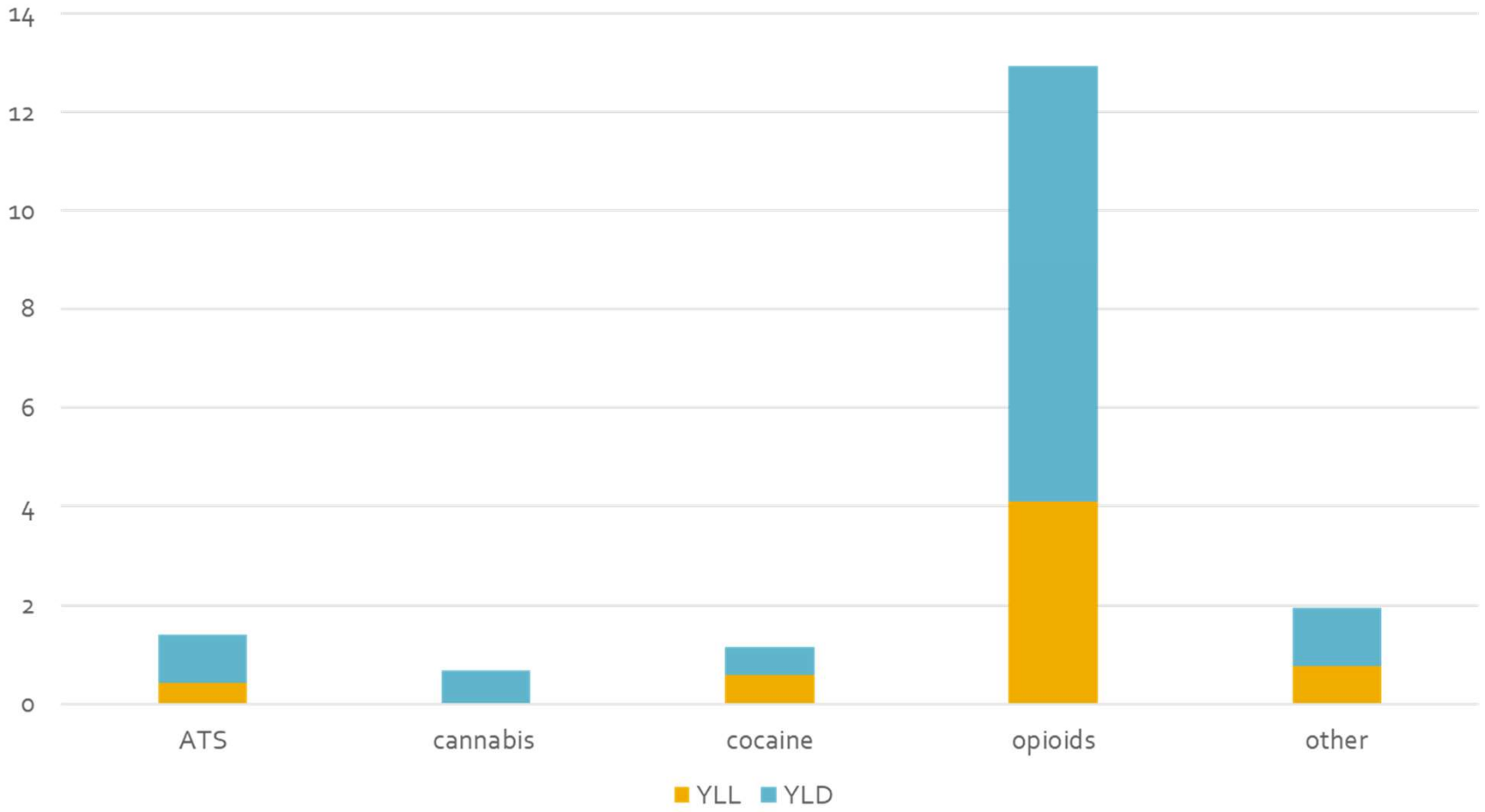
Cannabis and the Global Burden of Disease, 2016

- The GBD study estimated the contribution of problem:
  - Amphetamine, cannabis, cocaine, opioid and other drugs to
  - Life years lost from premature death (YLL)
  - Life years lived in disability (YLD)

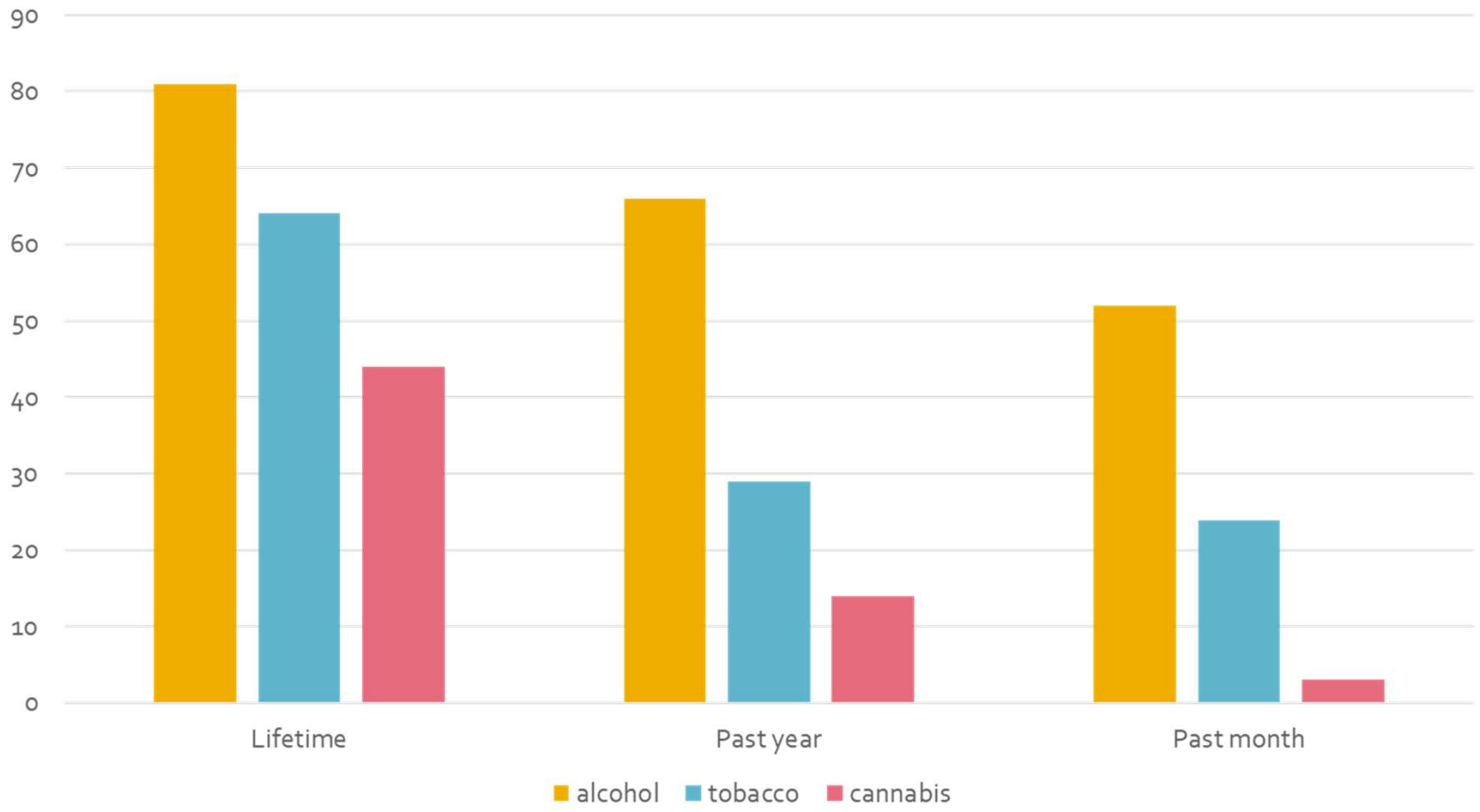
- Illicit drugs accounted for 1.3% GBD in 2019 compared with
  - 7.9% tobacco smoking
  - 3.7% alcohol

- Contributions of specific drugs to GBD
  - Opioids accounted for 71.3% of DALYs
  - Cannabis accounted for 3.8% of DALYS
    - all via the effects of CUD on YLDs

Millions years of life lost and years lived with disability attributable to drug use disorders in GBD 2019



Alcohol, tobacco and cannabis use in USA, 2016



What are the implications of higher THC cannabis?

- The THC content of cannabis has increased in:
  - In USA since 1990s; sharply since 2014: extracts with >70% THC
  - EU and Netherlands in 2010s: cannabis flower now 15% THC
- Increasing THC has been accompanied by declining CBD:
  - More adverse effects from High THC/low CBD cannabis?
  - Suggestive evidence from laboratory studies
- What is the health impact of higher THC cannabis?
  - Are users able to titrate their THC doses?
  - How well do they do titrate doses?

Evidence on cannabis dose titration

- Systematic review of evidence on titration
  - Laboratory evidence for incomplete titration
  - Observational studies suggest incomplete titration
- Survey evidence:
  - Some users report that they do titrate doses
  - But more potent cannabis users report more adverse effects
- Possible effects on infrequent cannabis users:
  - more dysphoria & psychotic symptoms?
  - More discontinuation by naïve users?
  - higher rates of accidental injury?
- Potential effects of higher potency on regular cannabis users:
  - lower respiratory risk, if users titrate dose?
  - A higher risk of dependence?
  - more cognitive impairment?
  - more psychotic symptoms?

Cannabis legalisation in practice

- In US 15 states, Canada and Uruguay have legalised cannabis
  - 13 US states now allow retail sales and more soon will
- Commercialisation of cannabis retail sales
  - Has created a legal industry with an interest in promoting cannabis use
  - Allows adults to use any type of cannabis for any reason
  - Focus on demands of daily users who account for 80% of use
- Most US states use alcohol as a regulatory model:
  - License companies to produce and sell cannabis for a profit
  - Vary in licensing: growers, processers, suppliers and retail sellers
  - Minimum legal age 21 years in USA; lower in Canada
  - cannabis-impaired driving an offence but enforced in various ways

Effects of cannabis commercialisation

- Substantially reduced retail prices:
  - No need to compensate illicit producers and sellers for risk of arrest
  - Production no longer small scale or clandestine
  - Growers can increase production, reduce costs, and lower prices

- Increased diversity of cannabis products:
  - flower of higher potency than before legalisation
  - high-potency cannabis extracts (wax, shatter) with 70% + THC
  - edibles (e.g., gummy bears, candy and chocolates) and beverages

- Increased access, social marketing and visibility of use
  - Likely to make adult use more socially acceptable and
  - May increase duration of cannabis use in adulthood

Effects of legalisation on cannabis use

- Lower prices → increased frequency of use among users
  - In surveys frequency of use has increased among adults in legalised states
- In CO and WA mixed impacts on adolescent cannabis use:
  - Increase among students after legalization in WA but a decrease in CO
  - No changes in youth use in Washington State 2002-2016 or 2013-2015
  - No increase in youth use in 4 years before & 3 years after legalization
- In NSDUH past 30 day cannabis use and cannabis use
  - No increase among adolescents and young adults in legalisation states
- A small increase in 12-17 years but no large effect in 18-25 years
  - small increases could be due to unmeasured confounding
  - Countervailing trends in alcohol, tobacco and cannabis use?

Cannabis-related hospitalizations

- In Colorado hospitalisations increased after legalization of
  - Medical use in 2008 and recreational use in 2014
  - For CUDs, car crashes and other injuries
- More hyperemesis cases in EDS after medical use was legalised in 2000
  - Another increase after recreational use was legalized in 2014
  - 46% increase in cyclic vomiting 2010-2014 in CO State Inpatient Database
- More cannabis-related ED cases after legalization in Colorado:
  - Childhood poisonings and distress and vomiting in adults
  - Mental illnesses with cannabis co-diagnoses: 5 X increase 2012-2014
  - Schizophrenia, psychoses, suicide, self-harm, & mood disorders
- More unintentional poisonings after medical & recreational legalisation
  - Not reduced by limiting package and serving sizes of edibles
  - More poisonings of children in MA after legalization of medical use

Effects on road crashes

- Mixed evidence from epidemiological studies
  - Aydelotte et al:
    - no more traffic fatalities in WA and CO than in states that did not legalize
  - Sevigny FARS data (1993-2014)
    - No differences in prevalence of cannabis-positive cases after legalization
  - Lane and Hall:
    - short-term, monthly increase in fatalities in CO, WA and OR
  - Chung et al more hospital admissions in CO hospitals
    - for traumatic injuries who were cannabis + 2012-2015.
    - No increases in neighbouring states that did not legalize cannabis
- Major caveats on these studies:
  - Short-term assessments; longer-term effects are needed
  - Confounded by increased cannabis testing after legalisation in many states
  - Challenging to identify which drivers were cannabis-impaired

Treatment for CUDS

- Darnell and Bitney compared
  - treatment seeking for CUDS in WA in national treatment data
  - in the first two years after legalization in WA
  - Compared WA to states that had not legalized
  - Treatment seeking declined at same rate in WA as in other states

- *Caveats*
  - Variable quality of data on treatment seeking in different states
  - Variation in treatment provision between states

The effects of cannabis legalisation to date

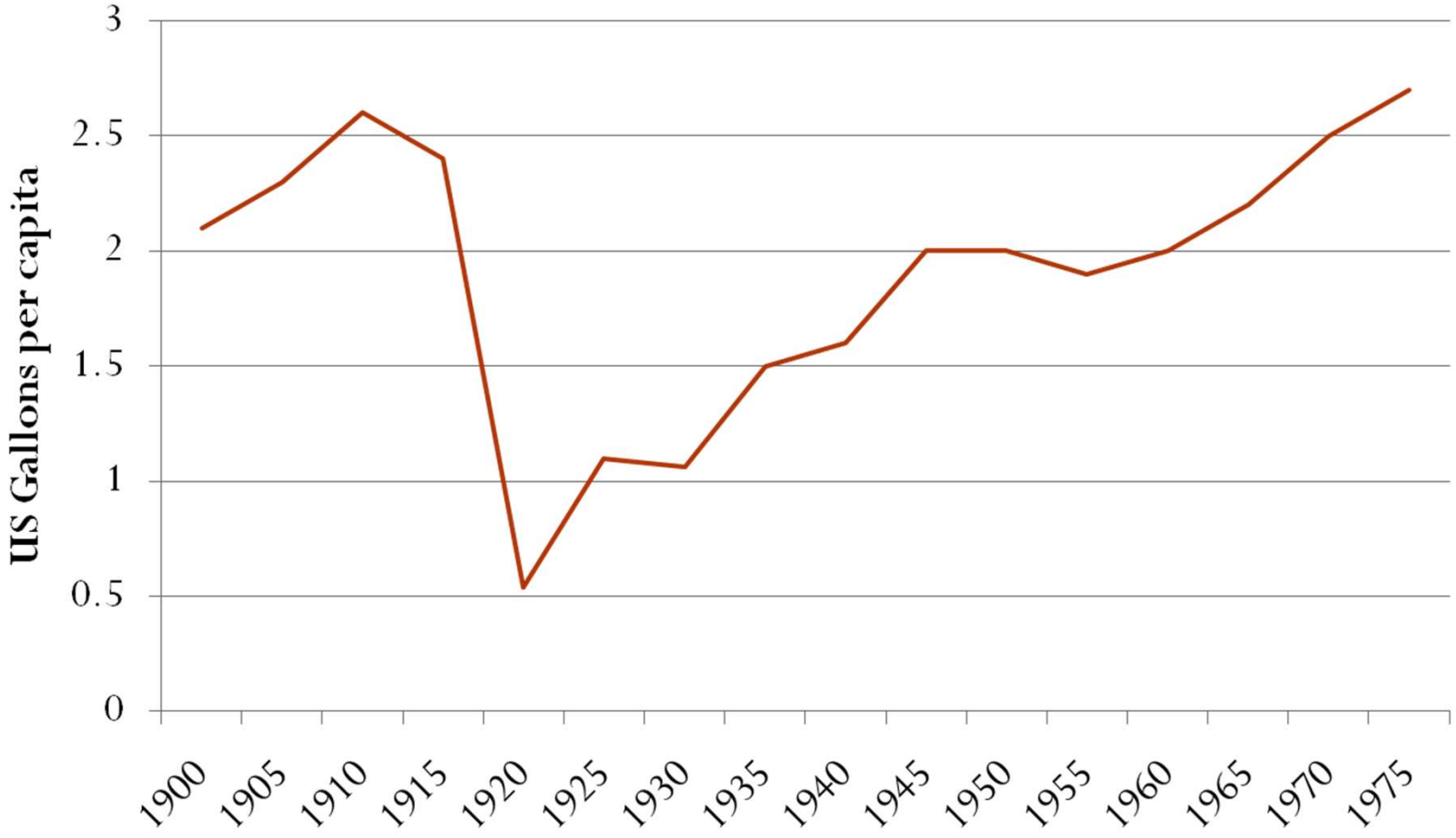
Only short term effects

- Legalization of adult use
  - only six years old in Washington State and Colorado
  - Taken time for legal market to develop
- Too soon to judge the full effects of cannabis legalization
  - It takes time to produce dependable cannabis supplies
  - Limited N of retail outlets in few locations in many states
  - Poor indication of the impacts on public health after a decade or more
- Major constraints of Federal cannabis prohibition
  - Limits on commercialisation, investment and ability to promote use
  - No interstate cannabis commerce

When may we see the full effects?

- Repeal of National Alcohol Prohibition in 1932 showed:
  - It takes time to scale up legal production
  - Social attitudes towards use change slowly
- Cannabis legalisation has been slowly implemented:
  - Limited N of licensees to make regulation easier
  - Local option has restricted where cannabis can be sold
  - Social norms are changing slowly
  - Lag between increased use and adverse effects
    - Especially in new users but probably also in current users
- In the short term:
  - Evidence of harm equivocal and contested
    - Adverse effects on youth amplified by critics
    - Debunked by supporters of legalisation

US per capita alcohol use 1900-1975
(including best estimates during NAP)



Conclusions

- Adverse effects of cannabis are not well understood:
  - Used for shorter time and on smaller scale than alcohol and tobacco
  - Few users have used cannabis near daily for decades
  - Also under-studied compared to opioids and stimulants
  - Measuring cannabis dose a challenge: frequency of use as proxy

- On current patterns of use, major adverse effects for users
  - Accidental injury
  - Dependence
  - Poorer outcomes in young adults especially educational
  - Impaired reproductive outcomes
  - Worsening of mental health
  - Longer term physical health effects probable but unclear

Conclusions

- Public health impact of current cannabis use is modest
  - reflecting the ow prevalence of long term daily use
  - Could change after full-scale legalisation

- Major cannabis policy experiments are underway in USA
  - Legalisation and commercialisation of cannabis markets
    - alcohol as model in which public health given a low priority
  - On alcohol experience, legalisation is likely to increase heavy use
  - Diversification of cannabis products to attract new users

- It will take time to evaluate its effects on:
    - Rates of cannabis use among youth and adults
    - Cannabis related harm among current and new users
    - Effects on alcohol and other drug-related harm