

# What have we learned about the health effects of cannabis in the last 20 years?

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# Outline

- What sort of evidence was available in 1993?
- What did we conclude about the health effects of cannabis use then?
- What have we learned since about its:
  - Adverse acute effects
  - Adverse chronic effects
- What are the likely effects of any increase in cannabis potency?
- What do we still need to know?

# Acknowledgements

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# Challenges in Assessing Health Risks, 1993

- Limited evidence, much of it quite old
  - Animal studies from late 1970s-early 1980s
  - Human laboratory studies: 7 to 30 days
  - Case-control studies: heavy users vs nonusers
  - Very few epidemiological studies
- Polarised, policy-driven appraisals:
  - Selective use of equivocal evidence
  - To support predetermined policy positions

# A False, Forced Policy Choice

EITHER

- Cannabis use is harmless and should be legalised

OR

- Cannabis use is harmful and should be prohibited
- Evidence refracted through these views:
  - Supporters of status quo focused only on harm to users
  - Reformers focused only on harms from criminal law

# Aims of Our 1993 Review

- Identify
  - probable adverse effects: acute and chronic
  - possible adverse effects deserving of further study
  - high risk groups for any adverse effects
  - advice to current users on harms
- Standard of proof for an adverse effect:
  - Balance of probabilities
  - Rather than beyond reasonable doubt

# Criteria Used to Assess the Evidence

(Hall, Solowij and Lemon, 1994)

- Association between cannabis use & adverse effect
- Clear which comes first:
  - cannabis use or the adverse health effect?
- Longitudinal studies to distinguish effects of cannabis from those of:
  - other drug use: alcohol, tobacco and stimulants .....
  - users': cognitive ability, psychosocial risks, .....
- Comparative assessments for evidential consistency
  - how does the evidence compare with other drugs?
  - what may we expect given similarities to other drugs?

# What has changed in 20 years?

- Much better cohort studies of longer use careers
  - More representative population samples
  - Higher rates of cannabis exposure: dose response
  - Substantial proportions of regular cannabis users
  - Better measurement of health outcomes
  - Better control for potential confounders
- Some of most informative studies from New Zealand
  - Christchurch and Dunedin birth cohorts
  - Inspired similar studies in Australia and elsewhere

# Acute Health Effects:1993 and 2013

- Our view in 1993
  - Low toxicity : No fatal overdoses
  - Anxiety, dysphoria, panic, paranoia
    - especially among naive users
  - Cognitive and psychomotor impairment
    - Potentially increased accident risks
  - Psychotic symptoms with high doses of THC
- What's changed in 2013?
  - Suggestion that adverse effects may be more common
  - Possible role of increased THC and reduced CBD

# Accidental Injury, 1993

- Dose-related impaired performance on:
  - complex psychomotor tasks & simulated driving
- Reduced risk taking in driving simulations:
  - More awareness of impairment
  - Compensatory behaviour change
  - But impaired responses to emergencies
- Problems with the epidemiological evidence
  - measurement of cannabis use vs impairment
  - no per se definition of impairment
  - confounding of cannabis use by alcohol use

# Accidental Injury, 2013

- Better epidemiological studies of fatalities
  - measurement of recent cannabis use
  - larger studies in multiple countries
  - better control for confounding effects of alcohol
- Self-reported accidents in young adults
  - Cannabis users much more likely to report accidents
- Meta-analyses of epidemiological studies
  - RR of accident  $\sim 2$  among cannabis users
  - Risk larger if cannabis affected drivers also use alcohol
- Attributable risk
  - Smaller than alcohol (2.8% vs 28% in France in 2000s)

# Psychosocial Effects of Chronic Cannabis Use

- What do we mean by chronic cannabis use?
  - Daily or near daily use
  - Over months, very often years (mid teens to late 20s)
- Which adverse effects are of most concern?
  - Dependence
  - Use of other illicit drugs
  - Educational under-achievement
  - Poor mental health
    - Psychoses
    - Anxiety, depression and bipolar disorder
    - Suicide

# Cannabis Dependence, 1993

- Diagnosis included in the DSM-III
  - In absence of withdrawal symptoms
- Common disorder in US mental health surveys
  - ECA: 4% lifetime among adults
- But how serious a problem was it?
  - Seen as problem by a minority in surveys
  - Very few users sought treatment
- Debates about the:
  - Existence of a withdrawal syndrome
  - Severity of problems and need for treatment

# Cannabis Dependence 2013

- More epidemiological studies
  - NCS 1 and 2: 4% lifetime
  - NSMWHB in Australia 1997: 2% past year
- More users seeking help
  - in Australia, EU, including Netherlands, & USA
  - Cannabis disorders 2<sup>nd</sup> most common after alcohol
  - withdrawal symptoms reported by these users
- Clinical trials of CBT for cannabis dependence
  - Difficult to achieve enduring abstinence
  - Outcomes very like alcohol dependence

# Risks and Consequences of Cannabis Dependence

- Risks of developing dependence
  - 9% of lifetime users (NCS study in early 1990s)
  - 16% in adolescent initiators
  - 33-50% of daily users
- Health and social consequences reported:
  - respiratory symptoms
  - impaired memory and cognitive performance
  - Impaired work performance
  - strong partner disapproval of use
  - high economic costs of use

# Cannabis as a Gateway Drug, 1993

- Common sequence of drug involvement
  - alcohol & tobacco preceded cannabis &
  - cannabis use preceded heroin & other drug use
- < 5% of cannabis users used “harder” drugs
- But risk much higher in cannabis users
  - who began in mid teens and used > weekly
- Most evidence from cross-sectional surveys
  - Retrospective reports and
  - Poor control of confounding in few prospective studies

# The Gateway Hypothesis, 2013

- Much more prospective evidence
- Gateway pattern remains strong and consistent:
  - Temporal order of cannabis and other drug use
  - ↑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 evidence

# Educational Performance, 1993

- In high school cannabis use associated with:
  - Poor school performance
  - Absenteeism
  - Early school drop out
- Uncertain which was cause and which effect:
  - Were poor school performers more likely to use?
  - Did cannabis use impair school performance?
  - Or were both true?

# Educational Performance 2013

- Longitudinal studies in New Zealand & USA
  - cannabis use predicted school drop out
  - meta-analysis of 3 Australasian studies
- Poor school performers were:
  - more likely to use cannabis
  - affiliate with other cannabis-using peers
- Cannabis use probably has a small direct effect
  - associations persist after statistical adjustment

# Cognitive Impairment 1993

- Adolescents at special risk
  - early users more likely to become heavy users
  - poor school performers likely to be early users
  - chronic cannabis intoxication impairs learning
- Some problem users reported impairment
  - but little evidence of gross impairment
- Subtle effects on attention in lab studies
  - related to duration & frequency of use
- Uncertain how reversible these effects are
  - Mechanism unclear: residue, toxicity, intoxication?

# Cognitive Impairment, 2013

- Case control studies of cognitive impairment
  - More consistent findings in heavy long term users
  - Supportive findings in neuroimaging studies
- In Dunedin cohort an 8 point lower IQ in
  - early cannabis initiators
  - who used cannabis daily throughout 20s into 30s
  - not explained by social class or other confounders

# Cannabis & Schizophrenia, 1993

- Cannabis dependence & schizophrenia associated
  - in the general population: RR ~2 in ECA
  - in clinical populations RR ~ 4
- Clinical reports that cannabis use exacerbated the disorder
  - Reduced compliance or a specific drug effect?
- Unclear whether cannabis use precipitated schizophrenia
  - Evidence from one large longitudinal study in Sweden
  - Any use increased risk 2; heavier use 6 fold risk
  - Unclear if schizophrenia prevalence had changed

# Cannabis & Schizophrenia, 2013

(Zammit et al, 2003)

- 27 year follow up of Swedish cohort (50,000)
  - better register coverage
  - statistical control for more variables
  - covered most of the risk period for the disorder
- Replicated earlier findings:
  - RR = 3 for diagnosis & dose response relationship
  - Persisted after statistical adjustment
  - For whole period, but weakened with time
  - AR of cannabis for schizophrenia: 13%

# Other prospective evidence

- New Zealand birth cohorts:
  - Dunedin (Arsenault et al, 2002) N = 759
  - Christchurch (Fergusson et al, 2003) N=900
  - Both found that cannabis use
    - Predicted psychotic symptoms RR ~ 2
    - Stronger prediction for early onset cannabis use
- Dutch cohort: Van Os et al (2002) 4 year follow up
  - 4848 young Dutch adults
  - increased risk of psychotic symptoms & disorders
  - Attributable risk: 13%; 50% for more severe cases
- German cohort: Henke et al (2004) 4 year follow up
  - N = 2437 German adolescents
  - Cannabis use predicted psychotic disorders
  - Stronger for those with a history of psychotic symptoms

# Cannabis and Schizophrenia:

## Summary

- Reasonable evidence that
  - cannabis use exacerbates schizophrenia
- Consistent evidence that:
  - cannabis use can precipitate schizophrenia
  - Five longitudinal studies in 3 countries
  - consistent RR ~ 2 and AR ~ 13%
- Biological plausibility
  - Cannabinoid-dopamine interaction
  - Provocation studies of THC and psychotic symptoms
- Comparative analysis of evidence
  - Better than for psychotogenic effects of stimulants & alcohol

# Cannabis, Depression and Suicide

- Relationship with depression RR  $\sim$  1.6 in
  - Cross sectional surveys
  - Longitudinal studies
- Correlated with higher suicide risks in some studies
  - Including prospective ones but limited statistical power
- Uncertain how well these studies have
  - controlled for confounding
  - separated cause and effect
- Depression needs attention in cannabis dependent

# Cannabis and other mental disorders

- Higher rates of cannabis use disorders in:
  - Bipolar disorder and anxiety disorders
- Cause and effect less clear:
  - Cross-sectional studies, often in clinical populations
  - Few longitudinal studies: limited control of confounding
  - Self-medication still plausible hypothesis
- Cannabis probably worsens outcomes so:
  - Should screen for cannabis disorders and treat
  - Screen cannabis dependent persons for these disorders

# Adverse Health Effects of Chronic Cannabis Use

- Use during pregnancy
  - Reproductive effects
- Longer term health risks
  - Daily use over decades
    - Respiratory risks
    - Cancer risks
    - Cardiovascular risks

# Reproductive Risks of Regular Cannabis Use During Pregnancy, 1993 and 2013

- Poorer birth outcomes most consistently found
  - Low birth weight and prematurity
- Interpretation complicated by:
  - Measurement issues: rely on self-reported use
  - Confounding by: other drug use, low SES, poor care
- Less certainty about:
  - Birth defects and cognitive impairment in offspring
- Need better studies of effects but in the interim:
  - Prudent to discourage use during pregnancy

# Respiratory Risks of Cannabis Smoking, 1993

- Cannabis primarily smoked
  - smoke similar composition to tobacco smoke
- Clinical evidence from convenience samples of:
  - Increased cough, sputum, wheeze
  - Histopathological changes in lung in MT smokers
  - Impaired immunological responses
- Effects on respiratory function
  - Some studies show impaired function

# Respiratory Risks of Cannabis Smoking, 2013

- Better epidemiological evidence of:
  - Increased cough, sputum, wheeze
  - Increased health service use for respiratory symptoms
- Conflicting evidence on respiratory function
  - Some studies show impaired function
  - Recent studies of long term users have failed to do so
- Suggestive evidence that risks reduced by vaporisers
  - Largely convenience samples
  - Self-report and short term use

# Cannabis Use and Cancer

- Respiratory cancers
  - upper respiratory tract
  - lung cancers
- Childhood cancers
  - leukemia
- Cancers in males
  - Prostate cancer
  - Testicular cancer

# Respiratory Cancers

- Causes for concern in 1993
  - composition of cannabis smoke
  - histopathological changes in lungs of smokers
  - case series of lung cancers in young adults
  - evidence of mutational changes in lung tissue
- Conflicting epidemiological evidence in 2013
  - Mixed findings from case-control studies
  - Positive findings confounded by tobacco smoking
- How convincing is apparent absence of evidence?
  - Given low rates of daily cannabis smoking over decades

# Other Cancers

- Childhood cancers
  - Single studies whose results have not been replicated
  - Cannabis use assessed as possible confounder
  - Inconsistent trends in incidence of these cancers
- Prostate cancer
  - Single cohort study in SFO area: modest RR
  - Confounding likely : cannabis use associated with AIDS
- Testicular cancer
  - Three case-control studies, including two replications
  - Cannabis related to nonseminomas in dose-related way
  - Deserves further study given CB receptors in testes

# Cardiovascular Risks, 1993

- THC a potent cardiovascular stimulant
  - Increases heart rate acutely
  - Complex effects on blood pressure
- Tolerance develops in regular users
  - Especially users who are young and healthy
- More concern about CVD risks in older users
  - Provocation studies in patients with angina
  - Use likely to be more intermittent in older users

# Cardiovascular Risks 2013

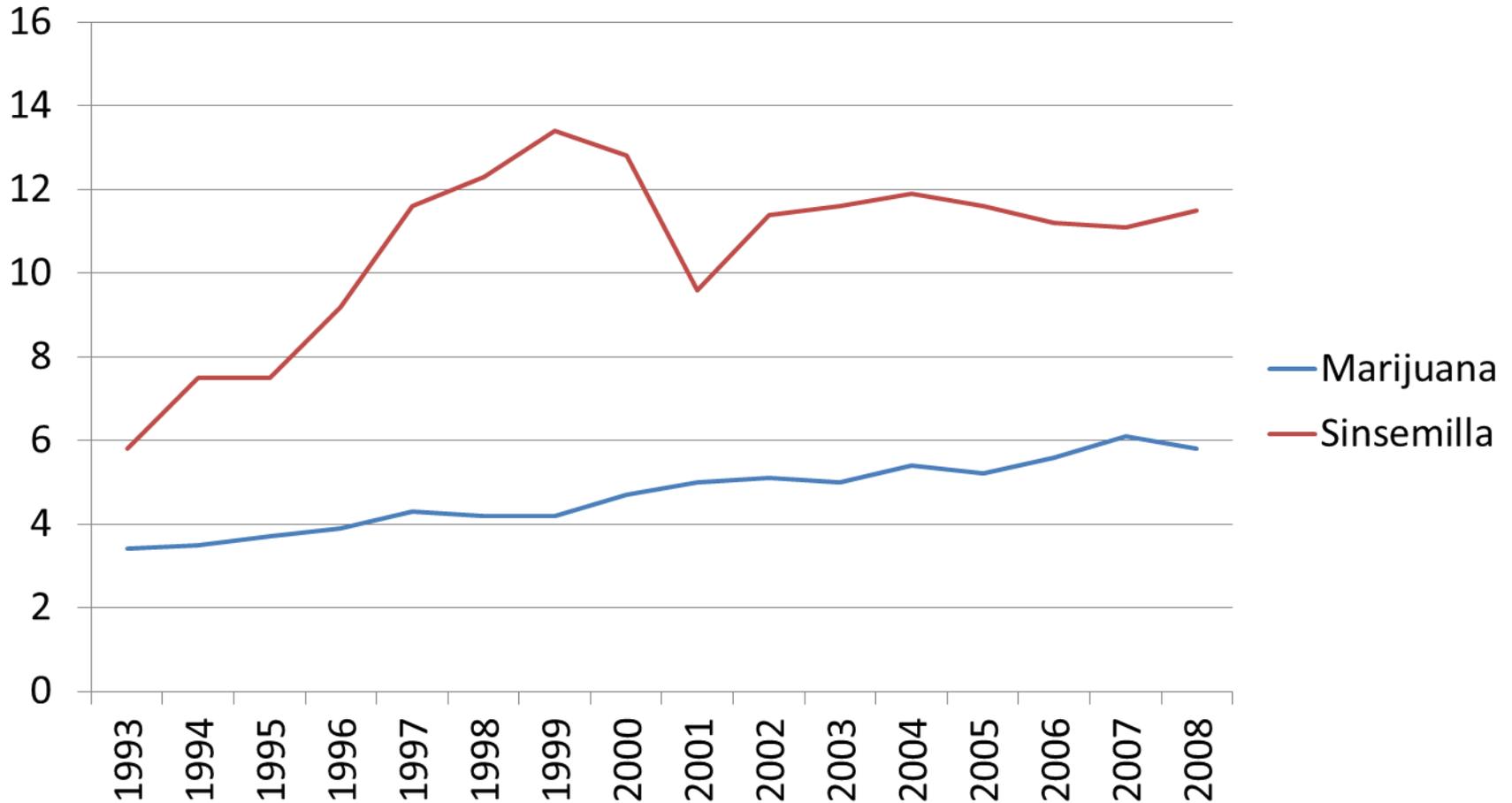
- More reason concern re CVD risks
  - Case reports of MI and strokes in young users
- Many more older cannabis users than in 1993
  - Persisting use among baby boomer cohort?
  - Medical cannabis use among older adults?
- Case-cross over study of myocardial infarction
  - Doubling of MI risk after smoking cannabis
  - Consistent with provocation studies in MI patients
- Longitudinal study of mortality in MI patients
  - Higher CVD mortality in cannabis users

# Cannabis Potency, 1993

- Little data outside USA where THC content
  - Increased between early 1980s and 1990s
- Less clear in Australia and New Zealand
  - Fewer samples of uncertain representativeness
- Confounding effects of changing patterns of use
  - earlier initiation and heavier use
- Debate about significance of increased THC
  - Can users titrate their doses?
  - Do they do so?

# Mean % THC content in US cannabis

Source: Mehmedic et al, 2010



# Cannabis Potency, 2013

- Further increases in THC content in USA
  - THC content now in teens for sinsemilla
  - Market for seeds of plants with higher THC
- Similar findings in Europe in 2000s
  - Markets catering to regular users
  - Who prefer higher potency forms of cannabis
- Is increased THC accompanied by declining CBD?
  - Concerns re possible increased adverse effects
- Still weak evidence for dose titration
  - Laboratory studies suggesting incomplete titration
  - Increased ER mentions of cannabis in USA

# Potential Effects of Increased THC

- For occasional users:
  - more dysphoria & psychotic symptoms?
  - higher rates of discontinuation?
  - higher rates of accidental injury?
- For regular users:
  - lower respiratory risk, if users titrate dose
  - higher risk of dependence?
    - especially among adolescent initiators
  - more cognitive impairment?

# High Risk Groups

- Adolescents
  - who initiate use early (~ 15 years)
  - with poor school performance and conduct disorders
- Pregnant women
- Persons with pre-existing health conditions
  - cardiovascular
  - respiratory
  - psychosis and common mental disorders
  - alcohol & other drug dependence

# Comparisons with tobacco

- Respiratory disease
  - Chronic bronchitis
  - Impaired lung function?
  - Emphysema?
- Cardiovascular disease
  - Acute precipitant of myocardial infarctions
  - Of most concern to older users
- Cancers?
  - Respiratory: as yet unclear for cannabis
  - Increased testicular cancer risk in cannabis users

# Comparisons with alcohol: 1

- Fatal overdose
  - None for cannabis
- Adverse acute psychological effects
  - Perhaps more common than alcohol
  - Probably discourages continued use
- Car crash risk
  - Increased ~ 2 fold
  - Less than comparable doses of alcohol
  - Increased when combined with alcohol

# Comparisons with alcohol: 2

- Dependence
  - Dependence producing
  - Increased treatment seeking
  - Persistent disorders in those who seek help
  - Underappreciated risk among users
- Psychosocial outcomes
  - Underachievement and
  - Occupational performance and life satisfaction
- Mental Health
  - Psychosis: most probable
  - Exacerbation of anxiety and depression

# What We Still Need to Know

- More about adverse effects on:
  - adolescents and young adults'
    - mental health and cognitive development
    - Educational and occupational outcomes
  - Adult physical health:
    - Cardiovascular disease
    - Respiratory diseases and cancers
    - Reproductive effects
- About effects of changes in THC and CBD content
  - Do users titrate their doses of THC?
  - Does CBD reduce adverse effects of THC?

# Better Ways to Reduce Harms

- Car crashes:
  - Is roadside drug testing effective?
- Cannabis dependence
  - better treatment of cannabis dependence and
  - education of users about risks of dependence
- Psychosis and depression:
  - More effective interventions for cannabis use
- Adolescent cannabis users:
  - How best to discourage use & increase cessation?
- Respiratory effects of cannabis use
  - Risks of smoking vs vaporisers

