Institution: Cardiff University

Unit of Assessment: UoA4

Title of case study: Informing and transforming the international policy and debate on cannabis use and psychosis

1. Summary of the impact (indicative maximum 100 words)

Cardiff University research quantifying the association between cannabis use and increased risk of psychosis has transformed the global debate on cannabis use and continues to shape governmental policies, guidelines and public attitude internationally. Cardiff's findings regarding the effects of cannabis use on mental health are both widely cited in the media and commonly used worldwide as information sources when delivering public health educational material. Cardiff research demonstrated that cannabis use is the only individual-specific, modifiable risk factor known for schizophrenia. Results were used to calculate that, in the UK alone, approximately 15% of cases of schizophrenia are preventable if cannabis were to be eliminated from the population.

2. Underpinning research (indicative maximum 500 words)

The body of underpinning research examined the complex relationship between cannabis use and its long-term effects on mental health, in particular its influence on the risks of psychotic disorders such as schizophrenia. It took place in Cardiff in the period from 1998, initially as the focus of Dr Stanley Zammit's MRC-funded PhD Fellowship from 2000-2003 (supervisors: Mike Owen [Professor in Cardiff]; Glyn Lewis [Professor in Cardiff until moving to Bristol in 2002] and later continued within the context of Dr Zammit's NHS-funded Senior Clinical Fellowship in Cardiff from 2005-2009, again supervised by Owen and Lewis. (Zammit has always been employed full-time in Cardiff and has also had an honorary appointment in Bristol that reflects continuing collaboration since Lewis' move).

Approach

The focus of Zammit's work was a secondary analysis, with extended follow-up, of data from a large Swedish conscript cohort of 50,000 men that had originally been published in 1987.[3.1] Zammit was able to address earlier methodological criticisms and demonstrated that individuals who used cannabis regularly had a substantially increased risk of schizophrenia (odds ratios 3-5; statistical significance: $p<0.001$) compared to those who did not use this drug. Importantly, by addressing reverse causation the Cardiff team found that the data were consistent with cannabis consumption having a causal effect on psychosis. Further, Zammit also demonstrated that the causal relationship was a dose-response effect, persisting even after statistically controlling for the effects of other drug use and other potential confounding factors.

Scope

This research provided compelling support for other studies that had suggested the possibility of a long-term effect of cannabis on risk of chronic psychotic disorders (as distinct from a short-term, transient psychotic experience that occurs during cannabis intoxication). Zammit has, along with other studies since the original longitudinal study,[3.1, 3.2] demonstrated through systematic review[3.3] a similar effect for other types of psychosis, not just schizophrenia. However, given the global burden of disease associated with schizophrenia, the effect of cannabis on risk of this disorder is likely to remain as the primary focus of public health investigations.

Quantified potential impact on patient health

Cardiff research[3.1, 3.3] has also been used to describe the likely impact of cannabis use on risk of schizophrenia at a population level, in addition to demonstrating the limited impact that current strategies for reducing cannabis use in the population have on reducing the incidence of schizophrenia. For example, in the UK alone approximately 15% of cases of schizophrenia are preventable by eliminating cannabis from the population.[3.1-3.4] This makes cannabis the only clearly modifiable risk factor in the prevention of schizophrenia.

3. References to the research (indicative maximum of six references)

Key publications

1. **Zammit, S.**, Allebeck, P., Andreasson, S., Lundberg, I., Lewis, G. (2002). Self-reported

cannabis use as a risk factor for schizophrenia in Swedish conscripts of 1969: Historical cohort study. *British Medical Journal, 325*, 1199-1201. [246 citations, *Web of Science*, Jan 2013] http://dx.doi.org/10.1136/bmj.325.7374.1199

2. **Zammit, S.** (2004). *An investigation into the use of cannabis and tobacco as risk factors for schizophrenia. In Psychological Medicine*. PhD Thesis. Cardiff: Cardiff University [available on request from HEI].

3. Moore, T.H., **Zammit, S.**, Lingford-Hughes, A., Barnes, T. R., Jones, P. B., Burke, M., et al. (2007). Cannabis use and risk of psychotic or affective mental health outcomes: A systematic review. *Lancet*, *370*, 319-28. [311 citations, *Web of Science*, Jan 2013] http://dx.doi.org/10.1016/S0140-6736(07)61162-3

4. Hickman, M., Vickerman, P., Macleod, J., Lewis, G, **Zammit, S**, Kirkbride, J., & Jones, P (2009). If cannabis caused schizophrenia--how many cannabis users may need to be prevented in order to prevent one case of schizophrenia? England and Wales calculations. *Addiction*, *104*, 1856-1861. http://dx.doi.org/10.1111/j.1360-0443.2009.02736.x

Key grants

2000-2003: Investigating cannabis and tobacco use as risk factors for schizophrenia using genetic and epidemiological studies. **Prof G. Lewis, Prof M.J. Owen**, Clinical Training Fellowship, MRC (£130,000).
2005 – 2009: Investigating genetic and epidemiological risk factors for sub-clinical psychosis-like symptoms in a birth cohort study. **S. Zammit**, G. Lewis, **M.J. Owen**. Clinician Scientist Award to **S. Zammit**, Welsh Assembly Government (£688,000).

4. Details of the impact (indicative maximum 750 words)

Cardiff research on this issue has had significant global impact on public policy and services. Both the content and tone of global discourse, policy and public and professional education have changed substantially as a direct result of Zammit's research.

As the only clearly modifiable risk factor in the prevention of schizophrenia, elimination of cannabis is particularly significant. The greatest reduction in risk will be in those who are at highest risk by virtue, for example, of having a parent or sibling with schizophrenia. Nationwide elimination offers the potential to prevent approximately 15% of cases in the UK.

Situation before the underpinning research
Schizophrenia and other psychotic disorders are major worldwide causes of morbidity and mortality and are associated with a major burden on societies through high usage of health services and lost productivity. Identifying modifiable risk factors is an essential strategy for improving global public health.

Before the underpinning research carried out by Cardiff, cannabis was known to cause acute, short-term psychotic states but there was insufficient evidence supporting a causal relationship between cannabis and chronic psychotic disorders. For example, the 1998 UK House of Lords Select Committee Report (Cannabis: the Scientific and Medical Evidence) concluded, *"…cannabis is neither poisonous nor highly addictive, and we do not believe that it can cause schizophrenia in a previously well user with no predisposition to develop the disease."*
Textbooks for psychiatrists made little or no mention of cannabis as a potential aetiological agent for schizophrenia. Similarly, information books/leaflets for sufferers, carers and the public did not link cannabis use and psychosis risk.

Transformative effect of the underpinning research
Since their publication in 2002[3.1] and 2004[3.2] Cardiff research findings have informed global policy debate through both traditional academic routes (>500 citations of refs[3.1, 3.2]) and global media interest and coverage. During the REF assessment period Cardiff research findings have influenced populations, groups and governments across the world, as described below.

Impacting government policy and guidelines across the globe

UK: In its 2008 Submission to the Advisory Council on the Misuse of Drugs (ACMD) Cannabis Classification Review, "Bringing evidence and analysis together to inform UK drug policy," the UK Drug Policy Commission cited Cardiff research results and concluded that; "*the risks [of a long-term psychotic illness resulting from cannabis use] are real and the consequences can be serious for individuals and their families*" (p.4).
(http://www.ukdpc.org.uk/wp-content/uploads/Briefing - Submission to the ACMD cannabis classification review.pdf).
As a result, the 2008 ACMD advice to UK government regarding legal classification of cannabis[5.1] requests further studies to assess the links between cannabis and psychosis, and notes that "*Only one study [Zammit et al., 2002] has had the statistical power to assess whether cannabis use precedes the onset of an illness that meets the full diagnostic criteria for schizophrenia*" (p.17; recommendation 16).

US: In 2010, the White House Office of National Drug Control Policy (ONDCP) contribution to the debate[5.2] on legalization of cannabis referred to a systematic review, based on Cardiff work, to support the statement; "*Studies have shown an association between chronic marijuana use and increased rates of anxiety, depression, suicidal thoughts, and schizophrenia*."
Since then, the impact of Zammit's work can be seen repeatedly supporting state-level and nationwide policy and guidelines:
"*Research indicates an association exists between early marijuana use and the development and worsening of symptoms of schizophrenia*" (p. 6). 2012 White Paper on State-Level Proposals to Legalize Marijuana. American Society of Addiction Medicine http://www.asam.org/docs/publicy-policy-statements/state-level-proposals-to-legalize-marijuana-final2773DD668C2D.pdf?sfvrsn=2
"*Although the mechanism is unknown, repeated studies have shown that cannabis use is correlated with an increase in the risk of manifesting schizophrenia, an illness that affects approximately 1% of the global population*" (p. 3). 2011 Guidelines of the Council on Scientific Affairs Subcommittee on Medical Marijuana Practice Advisory: California Medical Association, Government of California, http://www.mbc.ca.gov/medical_marijuana_cma-recommend.pdf
"*…adolescent marijuana users are more likely than adult users to develop marijuana dependence, and their heavy use is associated with increased incidence and worsened course of psychotic, mood, and anxiety disorders*." AACAP Medical Marijuana Policy Statement.[5.7]

EU: In both 2010 and 2011, The European Monitoring Centre for Drugs and Drug Addiction also cited Zammit's work when advising the European Union in The State of the Drugs Problem in Europe: "*Regular cannabis use in adolescence might adversely affect mental health in young adults, with evidence of an increased risk of psychotic symptoms and disorders that increase with frequency of use*." http://www.emcdda.europa.eu/online/annual-report/2010/boxes/p47
http://www.emcdda.europa.eu/online/annual-report/2011/boxes/p47

Australia: In 2008, Australia's Cannabis and Mental Health National Drug Strategy (NDS)[5.3] also noted that Zammit's (2002) study is the only one to find a relationship between cannabis and hospitalisation for schizophrenia: "*Those who had used cannabis at least 50 times by age 18 were about three times more likely to be hospitalised for schizophrenia by the age of 45 than those who had not used cannabis. Overall, these studies showed that cannabis use during adolescence was associated with an increased risk of being hospitalised for schizophrenia over the next 27 years."*

Impacting educational material and patient information sheets across the globe
Cardiff findings are also commonly referred to in educational material about cannabis and mental health by: **Government bodies** in the UK (*Cannabis: A Handbook*. City of London Drug Action Team (www.cityoflondon.gov.uk) 2009; *Talk to FRANK*. Home Office, UK Government (www.talktofrank.com) 2012) and other countries (*Marijuana Abuse*. National Institute of Drug Abuse, NIH, USA, http://www.drugabuse.gov 2010). **Professional bodies** in the UK[5.4, 5.5] (e.g., *Cannabis use and abuse*. Patient.co.uk http://www.patient.co.uk 2011) and in other countries.[5.6]

Mental health charities and numerous drug information and young people **websites** worldwide: In

contrast to information disseminated before this research was undertaken, educational leaflets about schizophrenia published during the REF assessment period now consistently warn about the risk of psychotic disorders such as schizophrenia related to cannabis use both in the UK (e.g., RETHINK[5.8]; MIND, http://www.mind.org.uk; DRUGSCOPE www.drugscope.org.uk; KNOW CANNABIS www.knowcannabis.org.uk; HIT www.hit.org.uk; Know the Score www.knowthescore.info; Talking about cannabis www.talkingaboutcannabis.com) and other countries worldwide (e.g., Prevent Teen Drug Use www.preventteendruguse.org; DrugInfo www.druginfo.adf.org.au).

Professional training: Textbooks and other educational material for psychiatrists published during the REF assessment period typically include information, based on this work, on the role of cannabis in the aetiology of schizophrenia. See, for example, the latest editions of *Companion to Psychiatric Studies*,[5.9] and the *Shorter Oxford Textbook of Psychiatry*, p. 275.

5. Sources to corroborate the impact (indicative maximum of 10 references)

Government bodies

1. Evidence of impact on UK policy can be found in *Cannabis: Classification and Public Health. Advisory Council on the Misuse of Drugs*. Home Office Report; 2008, https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/119174/acmd - cannabis-report-2008.pdf [saved as pdf on 25/07/13 and available on request from HEI].
2. Evidence of impact on US policy can be found in *Marijuana Fact Sheet: White House Office of National Drug Control Policy (ONDCP)*, Executive Office of the President http://www.whitehouse.gov/sites/default/files/ondcp/Fact_Sheets/marijuana_legalization_fact_sheet_3-3-11.pdf 2010, p.2. [saved as pdf on 25/07/13 and available on request from HEI].
3. Evidence of impact on Australian policy can be found in *Cannabis and Mental Health: put into context*. National Drug Strategy, Australian Government http://ncpic.org.au/static/pdfs/young-people-training-package/cannabis-and-mental-health-put-into-context.pdf 2008, pp.1, 23, 28, 29, 31, 33 of full report. [saved as pdf on 18/11/13 and available on request from HEI].

Professional Bodies

4. Evidence of impact on Royal College of Psychiatrists advice can be found in Cannabis and Mental Health: The Royal College of Psychiatrists, 2013. http://www.rcpsych.ac.uk/expertadvice/problemsdisorders/cannabis.aspx. [saved as pdf on 25/07/13 and available on request from HEI].
5. Evidence of impact on NHS advice can be found in Schizophrenia: NHS Choices, 2012. http://www.nhs.uk/Conditions/Schizophrenia/Pages/Causes.aspx 2012. [saved as pdf on 25/07/13 and available on request from HEI].
6. Evidence of impact on Australian General Practice. GP Factsheet: Cannabis and Mental Health. National Cannabis Prevention and Information Centre, Department of Health and Ageing, Australian Government, 2012. http://ncpic.org.au/workforce/gps/factsheets-for-gps-and-patients/pdf/cannabis-and-mental-health-for-gps. [saved as pdf on 25/07/13 and available on request from HEI].
7. Evidence of impact on US Child Psychiatry advice can be found in American Academy of Child and Adolescent Psychiatry: AACAP Medical Marijuana Policy Statement, 2012. http://www.aacap.org/AACAP/Policy_Statements/2012/AACAP_Medical_Marijuana_Policy_Statement.aspx. [saved as pdf on 25/07/13 and available on request from HEI].

Mental Health Charities, Drug Information, and Young People Organisations

8. Evidence of impact on UK charity advice can be found in RETHINK http://www.rethink.org/diagnosis-treatment/conditions/substance-abuse-mental-illness-dual-diagnosis/causes [saved as pdf on 25/07/13 and available on request from HEI].

Professional training: Standard textbook

9. Evidence of impact on UK psychiatry textbook can be found in *Companion to Psychiatric Studies*, 8th edition, p.404 [copy available from HEI].

Referee

10. The Deputy Director of the University of Queensland Centre for Clinical Research can verify the impact of this work on the international debate on cannabis use and psychosis.