

Article

Cannabis Research

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Abstract

The International Cannabis Consortium (ICC) was founded in 2013 by Jacqueline Vink, Nathan Gillespie, Karin Verweij and Eske Derks. The largest contribution to the first meta-analysis was made by Prof. Nick Martin. The ICC has published two primary publications, in *Translational Psychiatry* and *Nature Neuroscience*, and many secondary publications. The study's principal investigators will always be grateful for Nick's contribution to science as they would not have been able to do any of this work without the contributions of Nick and others who collected samples. Nick has made unique contributions to the careers of many junior researchers by supporting their development and growth into senior positions.

Keywords: Professor Nick Martin; cannabis; genetics; large sample size

(Received 19 February 2020; accepted 7 April 2020; First Published online 22 May 2020)

The International Cannabis Consortium (ICC) was founded in 2013 by Jacqueline Vink, Nathan Gillespie, Karin Verweij and Eske Derks. The first meta-analysis of this consortium was published in the journal *Translational Psychiatry*. This meta-analysis included 32,330 subjects (discovery) + 5627 (replication). We did not identify any genome-wide significant single-nucleotide polymorphisms but found four genes to be associated with lifetime cannabis use (Stringer et al., 2016). The supplementary table shows the sample sizes from the 13 individual cohorts; these range from 338 to 6778. Not surprisingly, the largest contribution came from Nick, who shared data from two cohorts, together comprising 7499 samples (23% of the total discovery sample).

You may think 'Who cares about these numbers? It's about the science and the results'. This is not actually true since there would be no science without these numbers. In fact, Nick has made enormous contributions to genome-wide association (GWA) studies of a very wide range of traits and disorders and often was the one contributing the largest sample to a meta-analysis. These days, it may be easy to forget how much time and energy was spent on collecting these samples. As a member of the genetics community, I will always be grateful for Nick's contribution to science as I would not have been able to do any of my work without the contributions of Nick and others (e.g., my PhD supervisor Prof. Dorret Boomsma who also collected very large sample sizes).

Since our first publication, we have been able to further increase sample sizes, and the most recent study of the ICC was published in the influential journal *Nature Neuroscience* (Pasman et al., 2018). This study has revealed important new insights into the genetic risk factors of cannabis use (most notably the influence of the gene *CADM2*, which also impacts other traits, such as risk seeking

behavior and impulsivity). We were also able to investigate the hypothesis that cannabis use leads to schizophrenia. This hypothesis has been generally accepted by the public and the scientific community, but as we all know, correlation does not imply causation. Using Mendelian randomization analysis, we were able to show that in contrast to what many believe, individuals at higher genetic risk for schizophrenia have a higher chance of cannabis use initiation. This suggests that the relation between cannabis use and schizophrenia is more complex than proposed by others, as schizophrenia liability seems to be a precursor of cannabis use. We did not find any evidence for cannabis use causing schizophrenia, but were cautious to make a strong conclusion about a complete lack of causal association in this direction as we had relatively low statistical power to explore this direction of effect. The relationship may still be bidirectional. Our results do show that individuals at higher genetic risk for schizophrenia are more likely to use cannabis, possibly as a form of self-medication.

Our findings are just one example of how genetic data allow investigation of causal relations that are often found to be in unexpected directions. Nick seems to love to challenge old ideas and is unafraid to voice his opposition or propose alternative explanations. Indeed, a print of the following quote by Hans Eysenck is shown in Nick's office and states: 'I always felt that a scientist owes the world only one thing, and that is the truth as he sees it. If the truth contradicts deeply held beliefs, that is too bad. Tact and diplomacy are fine in international relations, in politics, perhaps even in business; in science only one thing matters, and that is the facts'.

We have talked about how Nick has collected large sample sizes, and we have mentioned science. But, we have not yet mentioned Nick's influence on junior researchers by supporting their development and growth into senior positions. This can be exemplified by the ICC, which is led by four senior investigators. Of these four researchers, three are directly connected to Nick. Karin came to

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Cite this article: Derks E, Verweij K, and Gillespie N. (2020) Cannabis Research. *Twin Research and Human Genetics* 23: 129–130, <https://doi.org/10.1017/thg.2020.43>

Nick's group first in 2007 for a 6 months' internship and then again in 2008 to start her PhD under Nick's supervision. A major part of her PhD was on the genetics of cannabis use. She enjoyed this period very much and proceeded with this line of research in future positions. Last year, she was appointed professor at the Amsterdam UMC and Nick flew over from Brisbane to watch her inaugural lecture entitled 'Drugs and Genes', showing their strong scientific and personal bond. Eske started at QIMR Berghofer in 2017 and would not have been in Brisbane without Nick's support. His generosity has given her ample opportunities to set up new studies and publish in influential journals. Nathan completed his PhD under Nick Martin's supervision in 2004 before moving to Richmond, Virginia, where he has worked at the Virginia Institute for Psychiatric and Behavior Genetics (VIPBG) ever since. Incidentally, Nick also undertook postdoctoral training at VIPBG before returning to Australia to establish the Australian Twin Registry. Despite the distance, Nathan has maintained a very active collaboration with Nick over the years and secured NIH funding to collect cannabis data on the Brisbane Longitudinal Twin Study that have been used as part of the ICC meta-analyses.

Following the advent and increased application of GWA scan studies two decades ago, Nick Martin foresaw the need for international consortia as the best means of increasing power to detect alleles for complex behaviors and disorders. He was instrumental in encouraging us to pool our expertise and resources to

establish the ICC in 2013. We are very grateful to have followed his advice.

In summary, Nick Martin has influenced today's science by collecting large and genetically informative data, encouraging and participating in large international consortia, and promoting open science. Nick has not only facilitated our ability to begin unraveling the etiology of so many complex disorders, but in doing so, he has encouraged and fostered many junior researchers to develop themselves into independent researchers and respected leaders of their fields of expertise. It would be premature to call this collection of letters a Festschrift. Nick's motivation and dedication to behavioral genetics are unparalleled and show no signs of slowing down. Given his recent grant success, Nick will continue his pioneering and unprecedented work and we look forward to many more years of collaboration.

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