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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

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ABSTRACT

Background We consider how many cannabis users may need to be prevented in order to prevent one case of schizophrenia or psychosis [defined as number needed to prevent (NNP)]. **Method** Calculation for England and Wales using best available estimates of: incidence of schizophrenia; rates of heavy and light cannabis use; and risk that cannabis causes schizophrenia. **Results** In men the annual mean NNP for heavy cannabis and schizophrenia ranged from 2800 [90% confidence interval (CI) 2018–4530] in those aged 20–24 years to 4700 (90% CI 3114–8416) in those aged 35–39. In women, mean NNP for heavy cannabis use and schizophrenia ranged from 5470 (90% CI 3640–9839) in those aged 25–29 to 10 870 (90% CI 6786–22 732) in 35–39-year-olds. Equivalent mean NNP for heavy cannabis use and psychosis were lower, from 1360 (90% CI 1007–2124) in men aged 20–24 and 2480 (90% CI 1408–3518) in women aged 16–19. The mean and median number of light cannabis users that would need to be prevented in order to prevent one case of schizophrenia or psychosis per year are four to five times greater than among heavy users. **Conclusions** The number of young people who need to be exposed to an intervention to generate NNP and prevent one case of schizophrenia will be even larger. The public health importance of preventing cannabis to reduce schizophrenia or psychosis remains uncertain. More attention should be given to testing the hypothesis that cannabis is related causally to psychotic outcomes, and to considering what strategies will be the most effective in reducing heavy cannabis use among young people.

Keywords Cannabis, models, number needed to prevent, prevention, psychosis, schizophrenia.

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INTRODUCTION

There is no question that cannabis use is a public health problem, yet the risks associated with cannabis use and the most appropriate policy response are controversial and contested [1]. A key concern and influence on the UK Government's decision to reclassify cannabis from class C back to class B is whether cannabis causes schizophrenia and persistent psychosis. The difference in class refers to the maximum penalty for possession: 2 years for Class C and 5 years for Class B [2]. The evidence, however, is inconsistent. Several longitudinal surveys report that cannabis exposure is associated with an increased risk of a schizophreniform disorder [3–5]. One systematic review interpreted this evidence as weak because of measurement problems and confounding [6], while the most recent systematic review concluded that, given the inevitable uncertainty in determining causality, the evidence was strong enough to advise people about the potential risk that heavy cannabis users may have a twofold risk of a psychotic outcome compared to non-users [7]. In the United Kingdom, as in many other countries, cannabis exposure is very common among young people and over the last 30 years there has been a substantial increase in

the population exposed to cannabis [8,9]. Yet the evidence of any increase in schizophrenia diagnoses is either absent in part because of a lack of robust data (UK) or does not support a direct causal relationship (Australia) [10]. Here we consider the number of cannabis users who may need to be prevented from using for a particular year [number needed to prevent (NNP)] in order to prevent one case of schizophrenia *if* cannabis causes schizophrenia.

METHODS

Exposure

The risk of cancer persists after tobacco consumption [11]. It is unclear, however, whether or for how long any elevated risk of schizophrenia or pyschosis persists after light or heavy cannabis use. Longitudinal studies tend to measure cannabis use at specific periods of time, but measure schizophrenia and psychosis over a longer period. In order to be consistent with these studies, we used estimates of 12-month cannabis dependence from the Office of National Statistics Survey of Psychiatric Morbidity, which adopted a low threshold for classifying dependence equating often to heavy use [12], and non-dependence as 'light use'. We assumed that any elevated risk occurred during or within 12 months of exposure, and in the Discussion consider the impact if this risk persisted for 10 years after exposure. Estimates of cannabis use for men and women (blue and pink lines) and light and heavy use (full and dotted lines) with 95% confidence interval (CI) are shown in Fig. 1.

Outcome

Estimates of schizophrenia and psychosis incidence from 1997 to 1999 were based on the largest and most recent comprehensive population-based survey of clinically relevant first-onset psychotic syndromes [the Aetiology and Ethnicity in Schizophrenia and Other Psychoses study (ÆSOP)] [13]. ÆSOP was conducted in 1997–99 in three centres (Southeast London, Nottingham and Bristol) and used World Health Organization Psychosis Screen and Schedules for Clinical Assessment in Neuropsychiatry to classify all DSM-IV psychotic syndromes and subclasses of schizophrenia [13]. We assumed that the pooled data across these three sites was representative of England and Wales incidence. Figure 2 shows the estimates (with 95% CI) by 5-year age group for men and women aged 16–19 to 35–39 years. Schizophrenia incidence was higher among men than women and shows greater variation by age group for men compared to women. All psychosis incidence is higher than schizophrenia, but with less difference between men and women.

Risk

We incorporated the findings from the recent meta-analysis which report an adjusted risk ratio (RR) of 2.1 (95% CI 1.5–2.8) between 'heavy cannabis use' and psychosis outcome compared to non-users [7]. In addition, we derived an estimate of the risk of developing a psychosis outcome for 'light cannabis use' from the studies in the meta-analysis based on information provided on 'ever cannabis use', 'heavy cannabis use' and number of cannabis users. The adjusted odds ratio for light use was 1.3 (95% CI 1.01–1.59).

Calculated estimates

We assume that the observed ÆSOP schizophrenia incidence I_{sch} (or all-cause psychosis, I_{psych}) is a combination of the incidence among people exposed to heavy (I_h) and light cannabis use (I_l) and unexposed (I_u) to cannabis. Therefore, given information on the prevalence of light and heavy exposure (p_h and p_l) and RR of schizophrenia among the population exposed due to light and heavy cannabis use (RR_l and RR_h) we can

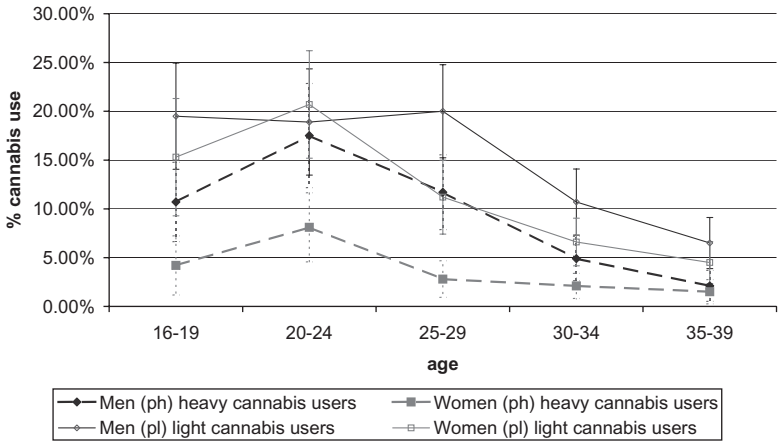

Figure 1 Estimated prevalence of heavy and light cannabis use by men and women aged 16–39 years

estimate $I_{sch} = I_h \times p_h + I_l \times p_l + I_u \times p_u$, where prevalence of non-cannabis use is $p_u = 1 - p_h - p_l$, $I_h = RR_h \times I_u$ and $I_l = RR_l \times I_u$. Therefore, estimates of I_u can be calculated by re-arranging the first equation: $I_u = \frac{I_{sch}}{1 + p_h[RR_h - 1] + p_l[RR_l - 1]}$.

I_h and I_l can then be calculated as shown above and we can estimate the NNP among heavy and light cannabis users as $NNP_h = 1/(I_h - I_u)$ and $NNP_l = 1/(I_l - I_u)$, i.e the number of heavy or light cannabis users who would need to be prevented from using in that year in order to prevent one incident case of schizophrenia or psychosis per year. We calculated NNP for men and women by age group.

Each of the separate components (I_{sch}, I_{psych}, p_h, p_l, RR_h and RR_l) in the calculation have uncertainty associated with them (see Fig. 1 and RR above). In order to reflect this and generate median and 90th per centiles for the NNP we sampled randomly 10 000 different parameter sets from the uncertainty distributions for schizophrenia and psychosis incidence (Poisson distribution), prevalence of light/heavy cannabis users (binomial distribution) in each age/sex band and the RR effect of light/heavy cannabis use on schizophrenia incidence (log-normal distribution). For each parameter set sampled from the uncertainty distributions, the NNP was estimated and so the uncertainty distribution and confidence bounds for the NNP could be ascertained.

RESULTS

Figure 3 shows our calculations of the median number of light or heavy/dependent cannabis users who would need to be prevented (NNP) in order to prevent one case of schizophrenia or psychosis per year in 1997–99. For men aged 15–19 to 35–39 the mean (and median) NNP for heavy cannabis use and schizophrenia ranges from 2800 (2900 90% CI 2018–4530) in those aged 20–24 to 4700 (4950 90% CI 3114–8416) in those aged 35–39. For women the mean (and median) NNP for heavy cannabis use and schizophrenia is from 5470 (5750 90% CI 3640–9839) in those aged 25–29 to 10 870 (11 680 90% CI 6786–22 732).

Among men the mean (and median) NNP for heavy cannabis use and psychosis ranges from 1360 (1410 90% CI 1007–2124) in those aged 20–24 to 2900 (3026 90% CI 1995–4898) in those aged 35–39; and among women the median (and mean) NNP for heavy cannabis use and psychosis ranges from 2480 (2150 90% CI 1408–3518) in those aged 16–19 and 3260 (3420 90% CI 2217–5646).

Figure 3 shows that the median number of light cannabis users who would need to be prevented in order to prevent one case of schizophrenia or psychosis per year are four to five times greater than among heavy users. For example, the mean (and median) NNP for men aged 15–24 who were light cannabis users was 10 500 (10 790 90% CI 5877–27 927) and 5150 (5240 90% CI 2901–13 390) for schizophrenia and psychosis, respectively; and for women aged 15–24 who were light cannabis users the mean (and median) NNP was 29 000 (30 800 90% CI 15 606–83 646) and 9950 (10 190 90% CI 5609–26 067) for schizophrenia and psychosis, respectively.

Following the calculations above, if cannabis is related causally then the risk of schizophrenia in 1997–99 for men aged 20–24 was approximately 1 in 1500 for heavy cannabis users and 1 in 2400 for light/heavy users. For women aged 20–24 the risk of schizophrenia was 1 in 4000 for heavy cannabis users and 1 in 6600 for light cannabis users.

DISCUSSION

We calculated how many heavy or light cannabis users would need to be prevented (NNP) in order to prevent one

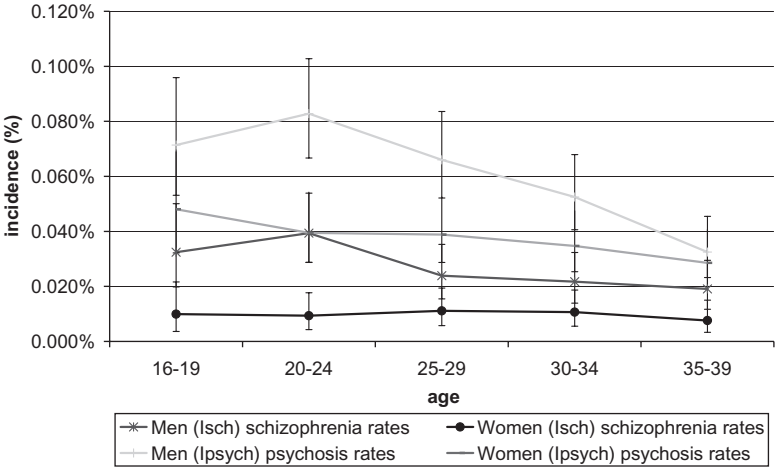

Figure 2 Estimated annual rates of schizophrenia and psychosis for men and women aged 16–39 years

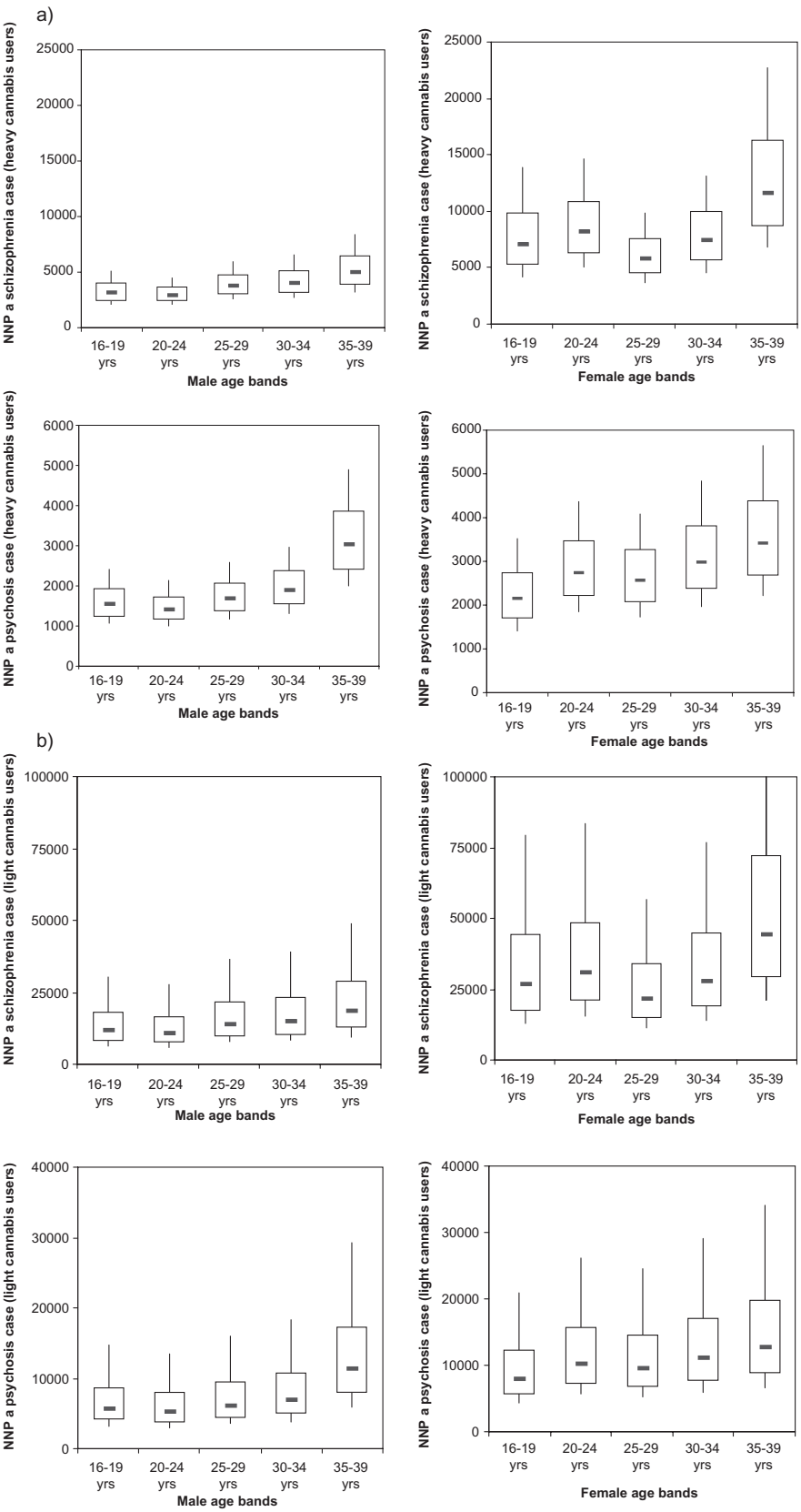

Figure 3 (a) Number needed to prevent (NNP) calculations showing median, 10th, 25th, 75th and 90th percentiles of how many heavy/dependent cannabis users need to be prevented in order to prevent one case of schizophrenia or psychosis in men and women aged 16–39 years. (b) NNP calculations showing median, 10th, 25th, 75th and 90th percentiles of how many light cannabis users need to be prevented in order to prevent one case of schizophrenia or psychosis in men and women aged 16–39 years

case of schizophrenia or psychosis in men and women under 40. These estimates were considerably high, even for young people who have the highest rates of schizophrenia, ranging for men aged 20–24 from 2800 for heavy cannabis users to more than 10 000 for light cannabis users; and for women aged 20–24 from 7700 for heavy cannabis users to 29 000 for light cannabis users. None the less, they suggest that strategies to prevent progression to cannabis dependence may be more effective than those that target cannabis onset.

Despite the uncertainty and limitations explored below, these calculations are based on the best available evidence. The key strength of our study is that our estimates are transparent, but they also serve to illustrate several important factors and limitations that need to be considered by policy-makers. First, questions must remain over whether cannabis is directly related causally to schizophrenia and psychosis if it is based solely on observational longitudinal studies and in the absence of corroborating evidence from trends in schizophrenia and psychosis diagnoses in the population [14]. Equally, our estimates of NNP might be considered a minimum, as we are assuming that the RR for schizophrenia associated with heavy or light cannabis is entirely explained, and due to cannabis exposure and not to any other factor (such as confounding or reverse causation).

Secondly, if cannabis is related causally, for how long does the risk persist after exposure? Here we assumed that the risk occurred only during and a short time after heavy cannabis use and estimated an annual risk and NNP. Further, our information on psychotic outcomes was based on an annual incidence [13]. If the elevated risk of schizophrenia following cannabis use did persist over time, then the cumulative NNP may be lower but the number of person-years that would need to be prevented would remain the same. For example, if the risk of schizophrenia persisted for 10 years after heavy cannabis exposure, then the NNP for men and women aged 20–24 who have used cannabis heavily would be 280 and 780, respectively, in order to prevent one case of schizophrenia over a 10-year period, i.e. in order to prevent one schizophrenia case per year among men and women aged 20–24 would still require 2800 and 7800 heavy users prevented, respectively, as shown in Fig. 3.

Thirdly, in the United Kingdom recent attention has been given to whether cannabis with higher Δ-9tetrahydrocannabinol (THC) content is more likely to cause psychosis and schizophrenia [15]. This is an important area of concern, but there are no epidemiological data on the size of any risk of psychosis or schizophrenia following exposure to more potent forms of cannabis, and it is too early to tell whether there has been any impact on psychosis and schizophrenia incidence in the population. Clearly, if cannabis was related causally, and we could characterize who may be at greatest risk of psychosis outcomes following exposure to cannabis use (in relation either to a genetic, psychological or behavioural vulnerability), then the number needed to prevent may be lower than our current estimates—but such information remains elusive and unproven [7].

Fourthly, a key policy question should be what is the NNT, i.e. the number of people exposed to population or individual-based intervention that could generate the NNP estimates required to prevent one case of schizophrenia? Clearly, NNT estimates will be substantially larger, but remain uncertain because evidence on an intervention effect is missing. Primary prevention of cannabis onset and treatment of cannabis dependence is an evolving area [16] and, typically, effective primary and secondary interventions targeting drug use have modest intervention effects [17,18]. For example, if the intervention effect was 20% then the NNT to prevent one case of schizophrenia by preventing either the onset of cannabis (light cannabis) or progression to heavy cannabis use would be five times the number needed to prevent. That is, the NNT could be 14 000 for preventing heavy cannabis use and 44 000 for preventing cannabis onset among men aged 20–24; and would be even higher for women and other age groups. In contrast, the NNT has been estimated as: 108 for appropriate statin treatment to prevent heart disease deaths [19]; 1224 for breast cancer screening to prevent one death after 14 years [20]; and 8.5 for web-based self-help to reduce drinking among problem drinkers [21].

Finally, we acknowledge of course that preventing onset of cannabis use and progression to dependence is important for many other reasons—including tobacco dependence, school performance and drug dependence itself [1,22,23]. Policy makers and the public face a number of uncertainties and 'what if' questions in relation to the potential number of cannabis users who need to be prevented in order to reduce schizophrenia and psychosis. The probable impact of re-classifying cannabis in the United Kingdom on schizophrenia or psychosis incidence is even more uncertain and doubtful. Instead, more attention needs to be given to elaborating on and testing the hypothesis that cannabis is related causally to psychosis outcomes, focusing attention on more immediate and common health and social problems associated with cannabis use, and to considering what strategies will be the most effective in reducing heavy cannabis use [24].

Declarations of interest

None.

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