

## **Synopsis for EU-GEI publication**

**Synopsis no: S2.56**

**Preliminary title: Psychosis risks for minority ethnic groups and cannabis use.**

**Proposal for an analysis of EU-GEI data.**

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### **Introduction**

The aetiology of the increased psychosis risk for certain minority ethnic groups in Europe is uncertain. While most researchers assume an important role for social stressors, few studies examined the possible role of drug abuse. The use of illicit drugs, in particular cannabis, is an important causal risk factor for psychosis (DiForti et al., 2019). Thus, the association between ethnic minority status and psychosis risk may be confounded by illicit drug use. Further, since many individuals use these drugs to diminish their stress levels, a social stress hypothesis and an illicit drug hypothesis are not incompatible. On the contrary, the use of illicit drugs might act a mediator between social stressors and psychosis.

Two first-contact incidence studies compared the proportions of drug users among first episode patients with and without an ethnic minority status and found no significant differences (Cantwell et al., 1999; Veen et al., 2002). However, these studies did not include control groups from the general population and, thus, may give a distorted impression of the association between cannabis use and risk of psychosis among minority ethnic groups due to collider stratification bias (Greenland, 1999).

The EU-GEI case-control study provides a good opportunity to examine this issue in more depth (Gayer-Anderson et al., 2020). We propose to examine to what extent the association between minority status and psychosis risk is confounded or mediated by cannabis use. We also will examine whether the heterogeneity in the RR across the European regions is explained by local differences in cannabis use between migrants and the reference population (Termorshuizen et al., 2020).

#### **We propose to test the following hypotheses:**

1. The contribution of cannabis use to the association between minority status and psychosis risk is significant, but amounts to less than 50%.
2. The contribution of cannabis use to the variance in Relative Risks for minorities between sites is significant, but amounts to less than 50%.

## Methods

### Study population

We will use the case-control data of Work Package 2 of the EU-GEI study including 17 clearly defined catchment areas across 5 countries (UK, The Netherlands, France, Spain, Italy) (Table 1). A subset of incident cases participated in the questionnaire part of the EU-GEI study. Controls were volunteers selected from the same catchment areas to create a representative sample of the source population. Some sites oversampled minority ethnic groups among the controls to enable subsequent sub-group analyses. In sites where oversampling was used, sampling weights were created to account for this in the analysis. A number of sites will probably be excluded because of missing information (Table 1).

**Table 1 EU-GEI Catchment areas**

Area	N controls	N cases	Inclusion
<b>England</b>			
Southeast London	<b>230</b>	<b>201</b>	<b>Yes</b>
Cambridgeshire	<b>108</b>	<b>45</b>	<b>Yes</b>
<b>The Netherlands</b>			
Amsterdam	<b>101</b>	<b>96</b>	<b>Yes</b>
Gouda & Voorhout	<b>109</b>	<b>100</b>	<b>Yes</b>
<b>Spain</b>			
Madrid	<b>38</b>	<b>39</b>	<b>? if classification of ethnic origin possible</b>
Barcelona	<b>37</b>	<b>31</b>	<b>Yes</b>
Valencia	<b>32</b>	<b>49</b>	<b>? missing information</b>
Oviedo	<b>39</b>	<b>39</b>	<b>? missing information</b>
Santiago	<b>38</b>	<b>28</b>	<b>No, no migrants among the cases</b>
Cuenca	<b>38</b>	<b>18</b>	<b>? missing information</b>
<b>France</b>			
Paris (Maison Blanche)	<b>0</b>	<b>36</b>	<b>No, no controls recruited</b>
Val-de-Marne	<b>100</b>	<b>54</b>	<b>Yes</b>
Puy-de-Dome	<b>47</b>	<b>15</b>	<b>? if classification of ethnic origin possible</b>
<b>Italy</b>			
Bologna	<b>65</b>	<b>70</b>	<b>Yes</b>
Verona	<b>115</b>	<b>59</b>	<b>? missing information</b>
Palermo	<b>100</b>	<b>58</b>	<b>Yes</b>
<b>Brazil</b>			
Ribeirao Preto	<b>302</b>	<b>192</b>	<b>No, situation Brazil different from Europe</b>
<b>Total all</b>	<b>1499</b>	<b>1130</b>	
<b>Total Included (including '?')</b>	<b>1159</b>	<b>874</b>	
<b>Total Included (excluded '?')</b>	<b>850</b>	<b>655</b>	

## **Variables**

### *Outcome: case-control status*

The participant's status as case or control is the outcome variable in the analysis. In this case-control design cases will be compared with controls with respect to two important variables: ethnic minority status and cannabis use.

### *Independent variable of primary interest: ethnic minority status*

Members of minority ethnic groups in France, Italy and Spain and the Netherlands will be divided according to their birth country and the birth country of their parents into subjects from Western and non-Western countries. The definitions are in accordance with our earlier analysis of the EU-GEI data: "Western" embraces Europe, the USA, Canada, Australia, New Zealand and countries of the former Soviet Union with a predominantly Christian religion, "Non-Western" indicates all other countries (Termorshuizen et al. 2020). Second-generation migrants will be considered subjects with an ethnic minority status and categorized in the same way.

With reference to the UK, participants who do not assign themselves a White British ethnicity will be considered subjects with an ethnic minority status. Subjects who classify themselves as White Irish, Other White, White traveller or Gypsy will be considered subjects from Western countries. Others as Non-Western. This classification is far from perfect, but feasible.

Native-born participants in France, Italy, Spain and the Netherlands, whose parents are also without a migration history are put in the reference category. As for the UK: subjects who consider themselves White British.

Given the high rates of both psychosis and cannabis consumption among African-Caribbeans in the UK, we will compute separate results for this group. If possible, we will enlarge the group with African-Caribbeans in France and the Netherlands.

If the numbers of cases and controls make that possible, the group of non-Western migrants may be further broken down by region of origin: Middle East, Maghreb, sub-Saharan Africa, Caribbean and French overseas departments, Asia, Latin America.

### *Confounding variable of primary interest: cannabis use*

Six measures of cannabis use will be included in the analysis: 1. lifetime cannabis use (yes/ no), 2. currently using cannabis (yes/ no), 3. age at first use of cannabis, 4. lifetime frequency of use (that is, the frequency that characterized the individual's most consistent pattern of use), 5. money spent weekly on cannabis use during their most consistent pattern of use, and 6. a measure of cannabis potency. These 6 indicators will be defined according to an earlier analysis of the EU-GEI data (Di Forti, 2019). Next, frequency of use will be combined with type of cannabis used (that is the potency) in one measure ('measure 7. '), because these two variables showed the highest ORs of psychosis and their combination showed a nice dose-response relationship in the earlier EU-GEI analysis (Di Forti, 2019).

### *Modifying variable of secondary interest: EU region of recruitment*

The ORs of psychosis for members of minority ethnic groups compared to natives will also be estimated by host region: London, Cambridge, Amsterdam, Gouda & Voorhout, Barcelona, Valencia, Oviedo, Santiago, Cuenca (last 3 towns collapsed in one category because of small numbers), Paris, Val-de-Marne, Bologna, Verona, Palermo (see Table 1).

## Covariables

The following variables will be included as co-factors and possible confounders of the region of origin- cannabis-psychosis association: age at interview, gender, education, employment status 1 year before assessment, parental social class, parent with psychosis (yes/ no). We will also adjust the analysis for: use of tobacco (smoked < 10 cigarettes per day vs  $\geq$  10 cigarettes per day), alcohol (mean number of drinks on average week), stimulants, hallucinogens, ketamine, legal highs (never vs. ever tried).

## Statistical Analysis

At first, the three groups (natives, subjects with a Western and non-Western background) will be described by case-control status with respect to the frequency distribution of the different measures of cannabis use (1.-7.) and above mentioned covariables. This will be done for all recruitment regions collapsed in one category, and –for a Supplemental Table- for the different recruitment regions separately.

Secondly, in part I. of the multivariable analysis, logistic regression models are used to assess the association between ethnic minority group and psychosis, with and without adjustment for the different measures of cannabis use separately (1.-7.). The difference in the two ORs for ethnic minority group (Western vs reference, non-Western vs reference) between the model without and the model with adjustment for cannabis use indicates the influence of cannabis use as confounder or mediator variable in the association between ethnic minority group and psychosis. By calculating the percent change in ORs following inclusion of cannabis use as cofactor, this influence is quantified. The results with the measure for cannabis use with the greatest influence on this association will be presented in the main document, the results for the other measures will be shown in a Supplemental Table. In part I. of the analysis, region of recruitment is included as random intercept to take the cluster structure of data collection by EU region into account.

In the second part of the analysis (part II.), the two ORs for ethnic minority group (Western vs reference, non-Western vs reference) are estimated for each EU region separately. This is done in a model with ethnic minority group, region as fixed effect, and with terms for the interaction between these two independent variables. At first, this model is run without adjustment for cannabis use to make visible the heterogeneity in ORs across sites, as was done in the earlier incidence study of the EU-GEI (Termorshuizen, 2020). Then, the two ORs estimated by site with the terms for interaction are adjusted for that measure of cannabis use with the greatest influence on the association between ethnic minority group and psychosis risk as assessed in part I. This is done to find out if differences in cannabis use between host regions may explain the heterogeneity in the ORs of psychosis for ethnic minority group across the EU host regions.

If the numbers of cases and controls for a specific ethnic non-Western groups make it possible, part I of the logistic regression analysis will be performed restricted to that specific group (eg migrants from sub-Saharan Africa vs native-born participants). In this way, we may assess whether the increased OR in specific ethnic groups may be explained by use of cannabis, but possibly not in another ethnic groups.

## Collaboration

All coworkers of the EU-GEI study will be invited to become a co-author of the report. We would like to collaborate with Marti Di Forti for statistical advice and for sharing examples of the STATA

syntaxes that were used for the report in *Lancet Psychiatry* 2019. In this way, we will get a consistent continuation of the earlier case-control analysis of the EU-GEI concerning cannabis use. We would like to invite her to become the second co-author. Jean-Paul Selten and Fabian Termorshuizen will become the first and last author of the manuscript.

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