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Title: Differences in patterns of stimulant use and their impact on first-episode psychosis incidence: An analysis of the EUGEI study

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ABSTRACT:

Background: Use of illegal stimulants is associated with increased risk of psychotic disorder. However, the impact of stimulant use on odds of first-episode psychosis (FEP) remains unclear. Here, we aimed to describe patterns of stimulant use and examine their impact on odds of FEP.

Methods: We included patients with FEP aged 18-64 years who attended psychiatric services at 17 sites across 5 European countries and Brazil, and recruited controls representative of each local population (FEP=1,130; controls=1,497). Patterns of stimulant use were described. We computed fully adjusted logistic regression models (controlling for age, sex, ethnicity, cannabis use, and education level) to estimate their association with odds of FEP. Assuming causality, we calculated the population attributable fractions (PAFs) for stimulant use associated with the odds for FEP.

Findings: Prevalence of lifetime and recent stimulant use in the FEP sample were 14.50% and 7.88%, and in controls 10.80% and 3.8%, respectively. Recent and lifetime stimulant use was associated with increased odds of FEP compared with abstainers (fully adjusted odds ratio (OR) 1.74,95% confidence interval (CI)1.20–2.54,p=0.004 and 1.62, 95%CI 1.25–2.09,p<0.001, respectively). According to PAFs, a substantial number of FEP cases (3.35% (95%CI 1.31–4.78) for recent use and 7.61% (95%CI 3.68–10.54) for lifetime use) could have been prevented if stimulants were no longer available and the odds of FEP and PAFs for lifetime and recent stimulant use varied across countries.

Interpretation: Illegal stimulant use has a significant and clinically relevant influence on FEP incidence, with varying impact across countries.

1. INTRODUCTION

Illegal amphetamine-type stimulants (hereafter illicit stimulants) are the second most widely used of illegal drugs in the world after cannabis [1,2]. According to the last European Drug Report 2021 from the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), the prevalence of last year stimulant consumption in adults (15-64 years) is around 1.7 million (0.5% of the total population) with 4.5% of European adults having used stimulants in their lifetime [3]. Patients with first episode psychosis (FEP) have higher rates of co-occurring substance use disorders (SUD) compared to the general population [4], with alcohol, tobacco, cannabis, and stimulants the most frequently used substances [5,6]. SUD in patients is associated with male sex and with an earlier age at onset of psychosis [4–6]. The prevalence of stimulant use has been reported to be 8.9% in psychosis[7] and 6.9% in FEP [8]. The relationship between stimulant use and both psychotic symptoms and the presence of a diagnosis of psychotic disorder has been previously studied [9]. Stimulants enhance dopamine neurotransmission in the brain [10] and the use of illicit stimulants is associated with higher odds of developing psychotic symptoms in recreational drug users [11,12], and people with psychotic disorders [13]. A prospective longitudinal study of chronic amphetamine users, found a 5-fold dose-dependent increase in the likelihood of developing psychotic symptoms [14]. In addition, illicit stimulant use has been associated with roughly 2 to 3-fold increases in the odds for schizophrenia and other psychotic disorders [9,15]**.** However, it is still uncertain whether the prevalence of illicit stimulant consumption varies across geographical regions and to what extent the incidence of psychosis can be attributed to illicit stimulant use, a concept known as population attributable fraction (PAF).

Using data from the EUropean Network of National Schizophrenia Networks Studying Gene-Environment Interactions (EU-GEI) study [17] we sought to: i) describe patterns of illicit stimulant use in a large and representative sample of FEP and controls; ii) examine the impact of illicit stimulant use on the odds of FEP in the whole sample and across countries; iii) compute the PAF for illicit stimulant use in the whole sample and across countries; iv) investigate the relationship between stimulant prevalence use and psychosis incidence rates across countries; and v) investigate these

issues in a subsample of patients with a less heterogeneous psychotic condition, such as first episode schizophrenia (FES).

2.- METHODS

2.1. EU-GEI study design and participants

The EU-GEI project set out to estimate the incidence of psychosis and to investigate risk factors for psychotic disorders by recruiting a sample of FEP cases and controls [17]. The study was conducted between May 1, 2010, and April 1, 2015 across 17 catchment areas in 6 countries including urban and non-urban populations: United Kingdom, the Netherlands, Italy, France, Spain and Brazil.

Patients were eligible if they met the following criteria during the recruitment period: ages between 18 and 64; first presentation with a diagnosis of psychosis per the International Statistical Classification of Diseases, Tenth Revision (ICD-10) (codes F20–33); and residing within the catchment area. Trained researchers identified cases and clinical teams invited patients to participate. Using the Operational Criteria Checklist algorithm, all patients interviewed received a research-based diagnosis [18]. Exclusion criteria included: prior contact with psychiatric services for psychosis; any evidence of an organic cause of psychotic symptoms; transient psychological symptoms resulting from acute intoxication (ICD-10: F1x.0); and, for the case–control study only, insufficient fluency in the primary language. The incidence study included 2774 individuals by identifying all individuals with FEP seen in mental health services in each catchment area [19]. Of those, 1519 were approached when considered appropriate by clinical staff, and 1130 (41% of the total incidence sample) consented to be assessed. The main reasons for non-inclusion in the case-control study were refusal to participate, language barriers, or not meeting the age inclusion criterion. A sample of 1497 of controls was also recruited. The groups of patients included and not included did not differ with respect to the proportion of minority ethnic groups, but the proportion of men and younger individuals was greater among patients included versus not included. Further details can be found elsewhere [17]. All sites contributed to the recruitment of control populations except for Maison Blanche. The recruitment of controls followed a mixture of random and quota sampling strategy. Local demographic data were used to set quotas for

controls to ensure the best possible representativeness in age, sex, ethnicity and catchment areas. The identification of controls was based on locally available sampling frames, including lists of postal addresses and general practice lists from randomly selected surgeries. Additionally, we used internet and newspaper advertisements, leaflets at local stations, and job centers. All participants who agreed to participate provided written informed consent. Local research ethics committees gave ethical approval each site. More details are provided in previous studies [18,20].

2.3. Measures

The network obtained sociodemographic data using a modified version of the Sociodemographic Program of the Medical Research Council [21]. Ethnicity was self-reported and classified by researchers as: Asian, Black, Mixed, North African, White and Other. Data related to recreational use of stimulants, cannabis, and cocaine use were obtained through the Updated version of the modified Cannabis use Experience Questionnaire (CEQ) for EU-GEI [20]. This questionnaire includes the registration of a detailed history of use of several substances in both FEP patients and controls. Researchers asked participants whether they had used illicit stimulants in their lifetime and in the year preceding the study (hereafter, recent use) and participants spontaneously provided information about the type. We defined illicit stimulant use as use of amphetamine-type stimulants or amphetamines not prescribed by a health professional. In EU-GEI study participants reported use of khat or amphetamines, including methamphetamine and MDMA (Ecstasy/Molly). In affirmative cases, participants were requested to provide additional details on their pattern of use including the age at first use and the age at stop for lifetime use and the number of weeks and frequency of use (daily, weekly or occasional use (less than once a week)) for participants with recent stimulant use. Cannabis use was recorded as (1) current and lifetime history of cannabis; (2) frequency of cannabis use, ie, the frequency that characterized the participant's most consistent pattern of use; and (3) type of cannabis used, ie, the type preferentially used by the participant. The frequency variable was grouped as "low frequency" when subjects did not use cannabis, or used on weekends or less frequently and "high frequency" if participants used cannabis every day. Type of cannabis was classified as "low potency" if participants used "hash-type" and "high potency" when they reported use of skunk-type [20]**.** All the

researchers undertook training on the assessment instruments before and throughout the study. To ensure the comparability of procedures and methods across sites, inter-rater reliability was assessed annually, with acceptable scores for all the scales (i.e., $\kappa>0.7$ in OPCRIT).

2.4. Statistical analysis

All analyses were performed using R version 4.0.3.

We used adjusted logistic regression models to estimate the effect of each of the nine measures of stimulant use on the odds of a diagnosis of FEP for the whole sample. We computed clustered standard errors to account for the fact that cases and controls are nested within sites using the command "summ" from the R package "jtools". In addition, we computed adjusted logistic regression models of recent or lifetime use for each country and site separately using never used or not used and either lifetime or recent use as the reference group in each statistical model.

A previous study found age, sex, ethnicity, cannabis use and education level to be significant contributors to psychosis incidence in this sample [20] and cannabis use often precedes or accompanies stimulant use[22]. Therefore, we adjusted raw models for age, sex, and ethnicity, and fully adjusted models additionally controlled for current use or lifetime use of cannabis and education level. Three sets of sensitivity analyses were run: controlling for i) potency (high vs. low) of cannabis and ii) frequency (daily vs. other) of cannabis use, instead of current use or lifetime use of cannabis, and iii) adding first-degree family history of mental illness covariate to the fully adjusted models. Propensity score matching to estimate the effect of stimulant use on FEP. First, we attempted 1:1 nearest neighbor propensity score matching with a propensity score estimated using logistic regression of the diagnosis on age and sex. This matching specification yielded poor balance, so Coarsened Exact Matching (CEM) on the propensity score was used. After matching, all standardized mean differences for the covariates were below 0.001, indicating good balance. All missing values were removed for these analyses. To estimate the effect of stimulant use and its confidence intervals, we fit a generalized linear regression model with diagnosis as the outcome and stimulant use and covariates, and included the CEM matching weights in the estimation using the MatchIt package [23].

Based on the prevalence of recent and lifetime stimulant use in FEP and controls and the corresponding fully adjusted ORs' upper and lower confidence intervals, we estimated the PAFs with 95% confidence intervals (CI) for recent and lifetime stimulant use, for the whole sample and for each country. PAF measures were calculated using Miettinen's equation [24] with fully adjusted OR: PAF = prevalence of exposure in cases *((fully adjusted OR - 1)/fully adjusted OR). The PAF measures the population effect of an exposure by providing an estimate of the proportion of new FEP cases that would be prevented if the exposure were removed, assuming causality.

Cocaine shares some mechanisms of action with illicit stimulants at both behavioral and cellular levels [25], so we investigated its prevalence by calculating ORs and PAF to estimate the effect of the use of cocaine and/or stimulants on FEP (considering stimulants users if the subjects used cocaine, stimulants or both).

We used Pearson's correlation to test for an association between the incidence rates for psychotic disorder in each country and recent and lifetime use in controls (as representing the general population for each country).

Finally, as FEP is a heterogeneous group, including different syndromes and disorders with indeterminate neurobiological mechanisms, we repeated all analyses in the subsample of participants with FES, which represents a less heterogeneous group.

3. RESULTS

3.1. Sample description

This analysis included 1,130 people with FEP (mean age=31.25 years old, standard deviation (SD)= 10.61; 38.3% female, 61.7% male) and 1,497 controls (mean age = 36.06 years old, SD = 12.90; 52.8% female, 47.2% male). Compared with controls, the FEP group was younger and included a higher percentage of males and ethnic minorities. Controls were likelier to have pursued higher education. Controls reported lower rates of recent and lifetime cannabis use. Demographic data are shown in Table 1.

INSERT TABLE 1

3.2. Patterns of illicit stimulant use and the impact of stimulant use on odds of FEP

More FEP subjects than controls reported having ever used illicit stimulants both recently (7.9% (n=89) in FEP and 3.8% (n=57) in controls, $p<0.001$) and lifetime (14.5% (n=217) in FEP and 10.8% (n=162) in controls, $p<0.001$). We found no significant differences between FEP and controls at the age of first illicit stimulant use and age at stopping. Among FEP and controls, the most common pattern of illicit stimulant use was less than weekly. There were no significant differences in the odds of FEP based on frequency of illicit stimulant use (see Table 2).

Fully adjusted logistic regression models showed that those with recent ($OR_{\text{fully adjusted}} = 1.74$, 95%CI 1.20–2.54, $p=0.004$) or lifetime illicit stimulant use ($OR_{\text{fully adjusted}} = 1.62$, 95%CI 1.25–2.09, $p<0.001$) had greater odds of FEP than abstainers. These findings were consistent in both raw and fully adjusted models (see Table 2). Figure 1 shows raw and fully adjusted ORs values according to lifetime patterns of illicit stimulant use. Sensitivity analyses showed comparable results overall in terms of the direction and magnitude of the effects for lifetime and recent stimulant use after adjusting for type (high vs. low potency) and frequency (daily vs. other) of cannabis use and after adding first-degree family history mental illness covariate to the fully adjusted model, although recent stimulant use no longer reached statistical significance after controlling for frequency of cannabis use (p=0.086) (Supplementary eTable1). Also, comparable results were obtained after running analyses using an age-and sex-matched control sample (Supplementary eTable 2).

We also estimated the odds ratios for recent and lifetime cocaine and/or stimulant use for the whole sample, by country and by site (results can be found in Table 2 and Supplementary Results1).

INSERT TABLE 2 AND INSERT FIGURE 1

When considering the prevalence of exposure to stimulants by country, both prevalence and ORs of FEP for recent or lifetime illicit stimulant use varied across countries. Fully adjusted ORs of FEP for

last year use ranged from 1.04 (95% CI 0.28–3.84) in Spain to 8.89 (95% CI 0.95–83.47) in Brazil. Fully adjusted ORs of FEP for lifetime illicit stimulant use ranged from 1.01 (95% CI 0.60–1.68) in the United Kingdom to 6.07 (95% CI 2.16–17.07) in Italy. All results are presented in Supplementary eTable 3.

Analyses for recent and lifetime illicit stimulant use by site can be found in Supplementary Results 2 and Supplementary eTable 4. Results for cocaine and/or stimulant use for the whole sample, by country and site identified differences in the ORs and can be found in Supplementary eTables 5 and 6 and Supplementary Results 3.

3.3. Population attributable fractions of FEP associated with stimulant use

Assuming causality, for fully adjusted models, the proportion of new cases of psychotic disorder in the whole sample attributable to recent use was 3.35 % (95% CI 1.31–4.78) and 7.61% (95% CI 3.68–10.54) for lifetime use. Supplementary eTable 3 shows raw and fully adjusted models of PAF.

In addition, the PAF analysis revealed variations by countries (see Figure 2 and Table 3). PAFs in fully adjusted models ranged from 4.95% (95% CI -8.96–12.37) of new cases of FEP in the Netherlands being attributable to recent use to just 0.13% (95%CI -1.91–2.43) of cases in Spain. Furthermore, the PAF for lifetime stimulant use ranged from 19.61% (95% CI 3.70–28.59) of cases in the Netherlands to 0.25% (95% CI -16.67–10.12) estimated in the United Kingdom (see Supplementary eTable 3).

In addition, PAFs were also estimated for each of the 17 sites for recent and lifetime illicit stimulant use. Also, PAFs were calculated for the whole sample, for each country and for each site for recent and lifetime cocaine and/or stimulant use (results can be found in Supplementary Results 1, 2 and 3, and Supplementary eTables 4, 5 and 6).

INSERT FIGURE 2

We did not find any significant association between raw incidence rates of FEP and prevalence of illicit stimulant use in controls across countries (r_{recent}= 0.399, *p*=0.433; $r_{lifetime}$= 0.303, *p*= 0.559, see Supplementary Figure).

3.4. Analyses in the subsample of participants with FES

Analyses of the subsample of participants with FES (N_{FES}=573, see Supplementary eTable 7) showed that those who had used illicit stimulants at least once in their lifetimes ($OR_{fully\ adjusted}$ = 1.70, 95%CI 1.24 - 2.32, p<0.001) had greater odds of FES than abstainers. Recent use was not statistically significantly related to odds of FES ($OR_{fully\ adjusted}$ = 1.57, 95% CI 0.99 - 2.50, p=0.054). These findings were consistent using both raw and fully adjusted models (see Supplementary eTable 8). PAFs in fully adjusted models was 2.85% (95%CI -0.08 - 4.71) for recent use and 8.56 % (95% CI 4.02 - 11.83) for lifetime use for the whole sample. See Supplementary eTable 9 for all details.

4. DISCUSSION

This study suggests that less illicit stimulant use could reduce psychosis incidence. Assuming causality, stopping illicit stimulant use could prevent 3.4% of new cases of psychosis. An additional finding is that rates and patterns of stimulant use, the strength of their association with odds of FEP, and the population attributable fraction varied notably across geographical areas.

Prevalence of recent illicit stimulant use in people with FEP was about 3% while prevalence of lifetime illicit stimulant use was about 20%. These figures are greater than those previously reported. A meta-analysis of sixty-four studies of stimulant use in more than 22,000 people with psychosis found a lifetime prevalence of stimulant use in people with psychosis of about 9%, with significant differences across regions [7]. Our study also showed that the prevalence of recent and lifetime stimulant use in controls was around 4% and 10%, respectively. These figures are higher than those found in adults in the European Drug Report 2021 from the EMCDDA (around 0.5% for recent use

and around 4.5% for lifetime use) [3]. In addition, our reported prevalence rates in the control group were also higher than those found by a study conducted during 2015–2016 in the adult (≥18 years) general population of the U.S. (which had a prevalence of 1.9% misused without use disorders, and 0.2% use disorders for recent use) [26].

The high prevalence rates found in our study in both FEP cases and controls could possibly imply that our data represents a more realistic approach to the measurement of illicit stimulant use or that we overestimated of stimulant use by using self-reported questionnaires.

Our results also highlight substantial between-study and between-country heterogeneity. This finding is supported by previous studies reporting significant between-country differences in illicit stimulant use in both the general population [3] and in the population with psychosis, ranging in the latter from 0.5% to 37% [7]. Further, we found heterogeneity by site within each country (see Supplementary eTable4), so an important caveat to these national numbers is the degree to which they mask regional variability. Geographical heterogeneity may be related to stimulant availability in the illegal market or to legal issues such as different social policies or legal penalties by country [3,26].

Importantly, our results showed that recent and lifetime use prevalence were greater in people with FEP than in controls. Both were associated with increased odds of FEP, with excess risk of 74% and 62% (OR 1.74 and 1.62), respectively, compared to abstainers. These results were similar even after controlling for cannabis use. Our results are in accordance with the European Drug Emergencies Network, which reported in 2016 (using data collected in 2013 and 2014) an OR of psychosis of 3.0 for lifetime illicit stimulant use (including both FEP and chronic psychosis) [15]. The results of the 95% CI, with overlap between groups, showed that there were no significant differences in the odds of FEP related to the frequency of illicit stimulant use. This may be due, at least in part, to the fact that the dominant frequency of illicit stimulant use was less than weekly. We found comparable results in a less heterogeneous subsample of participants with FES, suggesting that the impact of illicit stimulant use on the risk of psychosis is similar across the psychosis spectrum.

In this study, we report for the first time the extent to which a lack of illicit stimulants may affect the incidence of psychosis. We found that such a lack could prevent a substantial number of FEP cases

(3.35% recent and 7.61% lifetime use) (see Table2). As mentioned before, these numbers are higher than those previously reported in the EMCDDA [3]. This could be due to reasons associated with differences in methodology and sampling procedures. In comparison with the EU-GEI interview and questionnaire, EMCDDA conducted general population surveys at a national level. Surveys could present limitations in estimating prevalence of intensive forms of drug due to low prevalence figures and to non-probabilistic errors (exclusion from the sampling frame, non-response). Moreover, in EU-GEI project, although recruitment followed a mixture random and quota sampling strategy, the participating sample could have traits different from the general population, which could mask or strengthen effects. Finally, in EMCDDA, most countries included 15–64 age range, but occasionally countries used wider age ranges. As EU-GEI project included subjects 18-64 years old, and substance use is less common at very young and very old ages, this could also be influencing results.

Although there is evidence supporting the relationship between illicit stimulant use and psychotic symptoms, we cannot confirm causality. Therefore, PAF indexes derived from this study should be interpreted with caution. The high PAF in the Netherlands (4.95% for recent and 19.61% for lifetime use) are a consequence of the high prevalence of exposure to stimulants in FEP (20.9% for last year use and 40.7% for lifetime use). The 2015 Dutch National Drug Report also reported greater prevalence of ecstasy and amphetamine use in the Netherlands as compared with the general population in the European Union member states and Norway [27].

Contrary to the correlation found between incidence rates for psychotic disorder and prevalence of cannabis use in controls across sites [20], we did not find a significant correlation between recent and lifetime stimulant use in controls and variation in the raw incidence rates for FEP across countries. However, this could be influenced by the low number of countries (6 countries were included in this study) and the large heterogeneity among rates by country (see Supplementary Figure).

Our findings need to be appraised in the context of some limitations. First, data on illicit stimulant use are self-reported and not validated by biological measures, such as urine, blood, or hair samples. However, other studies with laboratory and self-reported information have shown that substance users report frequency and type of substance used with enough accuracy to be useful [28,29]. Second, we were

not able to report stimulant dose. Moreover, the study included subjects with substance-induced psychosis and we did not differentiated them from stimulant users with FEP. These two groups may have different biological and clinical characteristics [30]. Stimulant-induced psychosis develops more frequently in stimulant users with higher doses and a family history of psychosis [31]. Nevertheless, we found comparable effect sizes in the subsample with FES to those found in the FEP sample, suggesting that the association may not be attributable only to the presence of substance-induced psychosis in the group of FEP. Also, although the present study analyzed a large sample of 1130 FEP patients, it cannot be guaranteed that the results are representative of the whole FEP population. Additionally, in the case-control comparison, we should consider possible sources of unmeasured or residual confounding. Substantial evidence supports an association between stimulant use and prior risk factors including use of alcohol, cannabis, or other drugs, family history of mental illness and comorbidity, or developmental issues, as reflected in higher rates of learning disorders [32]. A recent systematic review reported cannabis use and family history of mental illness but not sociodemographic variables as risk factors for methamphetamine-related psychosis [33]. In the present study, we tried to account for some of these confounding variables by adjusting for age, sex, and ethnicity, education level, use of cannabis (recent use, lifetime use, use of high potency, and daily use) and first-degree family history of mental illness. We also conducted supplementary analyses using an age- and sex-matched control sample. The greater odds of FEP found in stimulant users versus abstainers remained significant after controlling for the additional covariates (Supplementary eTable 1) and after repeating the analysis in an age- and sex-matched sample of patients and controls (Supplementary eTable2). However, the effects of recent stimulant use no longer reached statistical significance after controlling for frequency of cannabis use. Furthermore, 192 cases (17%) reported a duration of psychosis longer that 52 weeks at the date of first contact with a healthcare professional. Although we found comparable effects for recent stimulant use after excluding these participants (see Supplementary eTable 1), long duration of psychosis in some of the participants could have affected our results. Finally, we do not have information on the use of stimulants with a medical prescription, which may be a confounding variable. Methylphenidate, the most common medication for children with Attention Deficit/Hyperactivity Disorder (ADHD) in many countries, is often prescribed for long

periods of time. An estimated 16 million (6.6%) U.S. adults [26] and 2.8 million (3.5 %) children [34] use stimulants annually. Any long-term psychotropic treatment in childhood raises concerns about possible adverse neurological and psychiatric outcomes. An association between a history of childhood ADHD and schizophrenia-spectrum disorders later in life has been described [35], and therefore FEP group is more likely to have received stimulants for this condition. Although a recent systematic review of observational studies of prescribed stimulants and psychosis risk concluded that observational studies do not support a clear-cut effect of prescribed methylphenidate on psychosis risk[36], we cannot rule out a potential effect of prescribed stimulants on our results.

In conclusion, our findings confirm previous evidence of the harmful effect of illicit stimulant use on mental health, increasing the odds of a first episode of psychosis by 74% (for recent use) and 62% (for lifetime use). For the first time, this study shows that if illegal stimulants were no longer available, the number of new cases of psychosis could be reduced. It is important for public health to acknowledge the adverse effects associated with stimulant use and promote early intervention and prevention programs.

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Figure 1 legend: **Figure 1. Raw and fully adjusted ORs of first-episode psychosis for lifetime patterns of stimulant use and the combined measure of cocaine and/or stimulant use for the whole sample.** Raw ORs are adjusted for age, sex, and ethnicity, whereas fully adjusted ORs were additionally adjusted for recent and lifetime cannabis use and education level. Error bars represent 95% CIs. The reference group for both raw and fully adjusted ORs is abstainers (recent or lifetime, accordingly). Asterisks represent significant ORs (p<0.05). CI=confidence interval, OR=odds ratio.

Figure 2 legend: **Figure 2. Fully adjusted ORs and PAFs of psychotic disorder for recent or lifetime use for the whole sample and across countries.** In bold, PAFs are shown in percentages. Error bars represent 95% CIs. CI=confidence interval, OR=odds ratio, PAF=population attributable fraction. * $p < 0.05$.