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Perceived major experiences of discrimination, ethnic group, and risk of psychosis in a six-country case-control study

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Abstract:	Background Perceived discrimination is associated with worse mental health. Few studies have assessed whether perceived discrimination (i) is associated with risk of psychotic disorders, and (ii) contributes to an increased risk among minority ethnic groups relative to the ethnic majority. Methods We used data from the European Network of National Schizophrenia Networks Studying Gene-Environment Interactions Work Package 2, a population-based case-control study of incident psychotic disorders in 17 catchment sites across six countries. We calculated odds ratios (OR) and 95% confidence intervals (95% CI) for the associations between perceived discrimination and psychosis using mixed-effects logistic regression models. We used stratified and mediation analyses to explore differences for minority ethnic groups. Results Reporting any perceived experience of major discrimination (e.g., unfair treatment by police, not getting hired) was higher in cases than controls (41.8% vs. 34.2%). Pervasive experiences of discrimination (≥3 types) were also higher in cases than controls (11.3% vs. 5.5%). In fully adjusted models, the odds of psychosis were 1.20 (95% CI: 0.91-1.59) for any discrimination and 1.79 (95% CI: 1.19-1.59) for pervasive discrimination compared with no discrimination. In stratified analyses, the magnitude of association for pervasive experiences of discrimination appeared stronger for minority ethnic groups (OR=1.73, 95% CI: 1.12-2.68) than the ethnic majority (OR=1.42, 95% CI: 0.65-3.10). In exploratory mediation analysis, pervasive discrimination minimally explained excess risk among minority ethnic groups (5.1%). Conclusions Pervasive experiences of discrimination are associated with slightly increased odds of psychotic disorders, and may minimally help explain excess risk for minority ethnic groups.

Abstract

Background: Perceived discrimination is associated with worse mental health. Few studies have assessed whether perceived discrimination (i) is associated with risk of psychotic disorders, and (ii) contributes to an increased risk among minority ethnic groups relative to the ethnic majority.

Methods: We used data from the European Network of National Schizophrenia Networks Studying Gene-Environment Interactions Work Package 2, a population-based case-control study of incident psychotic disorders in 17 catchment sites across six countries. We calculated odds ratios (OR) and 95% confidence intervals (95% CI) for the associations between perceived discrimination and psychosis using mixed-effects logistic regression models. We used stratified and mediation analyses to explore differences for minority ethnic groups.

Results: Reporting any perceived experience of major discrimination (e.g., unfair treatment by police, not getting hired) was higher in cases than controls (41.8% vs. 34.2%). Pervasive experiences of discrimination (≥3 types) were also higher in cases than controls (11.3% vs. 5.5%). In fully adjusted models, the odds of psychosis were 1.20 (95% CI: 0.91-1.59) for any discrimination and 1.79 (95% CI: 1.19-1.59) for pervasive discrimination compared with no discrimination. In stratified analyses, the magnitude of association for pervasive experiences of discrimination appeared stronger for minority ethnic groups (OR=1.73, 95% CI: 1.12-2.68) than the ethnic majority (OR=1.42, 95% CI: 0.65-3.10). In exploratory mediation analysis, pervasive discrimination minimally explained excess risk among minority ethnic groups (5.1%).

Conclusions: Pervasive experiences of discrimination are associated with slightly increased odds of psychotic disorders, and may minimally help explain excess risk for minority ethnic groups.

Key words: discrimination, minority ethnic group, psychotic disorder, psychosis, first-episode, case-control, multi-country

Introduction

Perceived discrimination, the perception of unfair treatment of members of a social group, is associated with worse mental and physical health outcomes (Williams & Mohammed 2009; Krieger 2014; Schmitt et al., 2014; Lewis et al., 2015; Paradies et al., 2015). It is posited that minority ethnic groups have more pervasive and more severe experiences of discrimination (Schmitt et al., 2014; Paradies et al., 2015), regardless of whether or not they explicitly attribute this unfair treatment to their race or ethnicity (Williams & Mohammed 2009; Lewis et al., 2015). Discrimination is considered a key factor in driving mental health inequities among minority ethnic groups (Williams & Mohammed 2009; Krieger 2014; Schmitt et al., 2014; Lewis et al., 2015; Paradies et al., 2015). A meta-analysis confirmed that perceived ethnic discrimination is associated with worse mental health for minority ethnic groups in Europe, although this only included four studies on psychotic symptoms (de Freitas et al., 2018).

A recent systematic review identified 24 studies on the relationship between perceived discrimination and psychosis, which produced suggestive findings that discrimination may be associated with increased risk of psychosis and tentatively indicated a dose-response relationship (Pearce et al., 2019). While these studies provide preliminary support for a link between discrimination and psychosis, the current body of evidence is limited in at least three ways. First, the majority of studies were of subthreshold psychotic experiences or clinical high-risk status, not psychotic disorders. While this information is important, subthreshold experiences are not sufficient to predict who goes on to develop psychotic disorders (Fusar-Poli et al., 2013). Second, measures of discrimination included in previous studies have often only used one or a few items, restricted these experiences to the past year, and/or required attribution to race. Such measurement is unlikely to capture the full experience of discrimination or allow for testing of

dose-response relationships; requiring attribution to race also underestimates experiences of unfair treatment among minority ethnic groups (Williams & Mohammed 2009). Third, most previous study samples have typically lacked an ethnic majority comparison group, preventing investigation of how discrimination may uniquely affect psychosis risk in minority ethnic groups relative to the ethnic majority.

In this study, we analyzed data from Work Package 2 of the European Network of National Schizophrenia Networks Studying Gene-Environment Interactions (EU-GEI) study, a population-based incidence and case-control study of psychotic disorders and the largest international investigation of psychotic disorders in the last 40 years, to examine the relationship between perceived discrimination and psychotic disorders. We sought to test three hypotheses: (1) There will be an association between *any* experience of major discrimination and odds of psychotic disorders; (2) There will be a dose-response association between *more types* of major discrimination and increasing odds of psychotic disorders; (3) Experiencing more types of major discrimination will *partially explain* the association between minority ethnic groups and excess odds of psychotic disorders.

Methods

Study Population

Work Package 2 of the EU-GEI study ran from May 2010 to April 2015 and the incidence and first-episode case-control program included 17 clearly defined catchment areas across six countries (Brazil, France, Italy, Netherlands, Spain, United Kingdom) (Gayer-Anderson et al., 2020). The primary goal was to study genetic and socio-environmental interactions in the onset of psychosis. Catchment sites were selected for large migrant and minority ethnic populations and to represent a mix of urban and rural regions. Incidence data

included anyone who came into contact with specialist mental health services with a first-episode psychotic disorder. A subset of these incident cases was approached for participation in the concurrent case-control study to collect and analyze data on putative risk factors (41% of incidence sample). In analyses for this paper, we excluded 36 cases from the site in Paris (where no control participants were recruited) and 84 participants missing all discrimination data. Participants who were excluded from analyses had similar characteristics (e.g., age, sex, parent social class) to those included. Ethical approval was provided by research ethics committees in each site. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Written informed consent was obtained from all participants.

Variables

Case/Control Status. Cases were individuals aged 18 to 64 years residing in the specified catchment areas who made contact with specialist mental health services with a first-episode psychotic disorder (e.g., schizophrenia, schizoaffective disorder, bipolar disorder) based on the International Classification of Diseases, Tenth Edition (ICD-10) research diagnoses (codes F20-F33) during the time frame of the study (median 25 months, range 12 to 48 months depending on site). Individuals were excluded if they had previous contact with mental health services for psychosis, or if there was evidence that their psychotic symptoms were precipitated by an organic cause or due to acute intoxication. Controls were volunteers selected from the same catchment areas using a mixture of random and quota sampling to maximize representativeness, including randomly selecting from general practitioner lists and housing lists in some sites and more ad hoc approaches (e.g., leaflets at local stations, shops and job centers, Internet and

newspaper advertisements) in others. Controls were excluded if they reported a prior diagnosis of or treatment for any psychotic disorder (Gayer-Anderson et al., 2020). Some sites also 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.

Ethnic Group. Respondents provided self-reported ethnic categorizations relevant to each country's context, which were then collapsed into six categories for standardization across sites: Asian, Black, Mixed, North African, White, and Another. White is the majority ethnic group in all six countries included in this dataset. A binary variable was created to distinguish the ethnic majority (White) and minority ethnic groups (Asian, Black, Mixed, North African, Another) based on these classifications, as we were most interested in assessing whether there was a difference in the association across all minority ethnic groups compared with the ethnic majority.

Perceived Discrimination. Perceived discrimination refers to perceptions of unfair treatment. This study specifically addressed perceived lifetime experiences of discrimination that might have major interference with advancing socioeconomic position (referred to as "major discrimination"), rather than day-to-day, routine, and relatively minor experiences of unfair treatment. These experiences of major discrimination were assessed using a modified version of the Major Experiences of Discrimination Scale originally developed by Williams and colleagues (1997) for the Detroit Area Study in Michigan, USA. The scale has demonstrated good reliability and validity (Williams et al., 1997) and has been widely used in the literature (Kessler et al., 1999; Taylor et al., 2004). Respondents were asked whether they have ever *unfairly* experienced any of the following twelve events: being fired; not being hired; being denied a promotion; being stopped, questioned, or threatened by the police; being treated unfairly by the court system; being

discouraged in education; being prevented from renting or buying housing; experiencing poor treatment by neighbors or family; being denied a loan or preferable mortgage rate; receiving worse service than others; experiencing unfair treatment when getting medical care; and experiencing unfair treatment when using public transport. For each affirmative response, participants were then asked to select one reason why they believe they had been treated unfairly (gender, race or ethnicity, religion, mental illness, sexuality, age, other; a binary variable was created for each reason ever endorsed). For analysis, two aggregate variables of perceived lifetime experiences of major discrimination were created: 1) A binary variable for endorsement of any experience of major discrimination across the 12 items, and 2) a categorical variable for the number of different types of experiences of major discrimination grouped into 0, 1, 2, and ≥3 types consistent with prior studies (Oh et al., 2016). For this paper, perceived experiences of ≥3 types of major discrimination will be described as "pervasive experiences of discrimination" to distinguish it from a single isolated experience of discrimination (Schmitt et al., 2014).

Other Variables. Information on potential confounders was collected at the time of assessment and selected a priori based on their established relationships with perceived discrimination and psychosis: age (continuous), sex (male/female), parent social class (professional, intermediate, working-class, long-term unemployed), parent history of psychosis (yes/no), and cannabis use (never, past, current).

Statistical Analysis

All analyses were conducted in Stata 15 (StataCorp 2017). Frequency distributions of sociodemographic and lifestyle characteristics of participants were explored. Continuous variables were expressed as mean ± standard deviation (SD). Categorical variables were expressed as number (percent, %). Chi-square and t-tests were used to compare

sociodemographic characteristics, types of major discrimination, and reasons for major discrimination among cases versus controls and minority ethnic groups versus the ethnic majority (all comparisons between ethnic groups were restricted to controls to provide population-representative estimates since the cases would over-represent ethnic minorities).

To test the hypothesis of an association between *any* experience of major discrimination and case-control status, we used mixed-effects logistic regression models while accounting for clustering by catchment site. Inverse probability weights were used to account for oversampling of minority ethnic groups among the controls relative to the populations at risk. First, a parsimonious model adjusting for age and sex was constructed. Next, a fully adjusted model taking measured confounding variables into account was fitted (i.e., age, sex, parent social class, parent history of psychosis, cannabis use). These confounders were chosen *a priori* based on our literature review. A sensitivity analysis was conducted to substitute parent social class with participant social class.

To test the hypothesis of a dose-response association for number of types of discrimination and case-control status, we constructed the next model by treating the number of types of major discrimination (0, 1, 2, 3+) as an ordinal variable to test the linear trend and then as indicator variables to assess the odds ratio for each number of types.

To test the hypothesis that the binary and dose-response associations between perceived discrimination and case-control status were stronger among minority ethnic groups compared with the ethnic majority, each association was tested for modification by ethnic group by (i) running the analyses separately among minority ethnic groups and the ethnic majority (stratification) and (ii) assessing whether addition of cross-products between ethnic group and case status improved the fit of the model (likelihood ratio test).

Finally, to test the hypothesis that more types of discrimination partially explained the association between minority ethnic status and case-control status, exploratory mediation analysis was conducted by specifying ethnic group as the independent variable, case status as the dependent variable, and a binary variable of three or more versus two or fewer types of major discrimination as the mediating variable. We consider these analyses as exploratory since we are using data collected at a single moment of time that limit inferences about temporal ordering and also cannot adjust for exposure-mediator, exposure-outcome, and mediator-outcome confounding. This mediation model did not allow for adjustment for clustering by catchment site or sampling weights for the oversampling of minority ethnic groups among the controls. Bootstrapping was used to generate bias-corrected confidence intervals (1000 repetitions, seed specified as 1234) (Valeri & VanderWeele 2014; VanderWeele & Vansteelandt 2010). The odds ratios reflecting total effect (OR^{MTE}), natural direct effect (OR^{NDE}) and natural indirect effect (OR^{NIE}) are used to be consistent with the terminology of mediation analysis, not to imply causality. The proportion mediated was calculated by using the formula $(OR^{NDE}*(OR^{NIE} - 1)) / (OR^{NDE}*OR^{NIE} - 1)$ (VanderWeele & Vansteelandt 2010).

Results

The final analytic sample was 2,507 participants, of which 41.5% were cases (69.7% non-affective psychosis, 28.3% affective psychosis, 2.0% unspecified psychotic diagnoses) and 27.3% were classified as members of minority ethnic groups. Cases and controls differed on all measured sociodemographic characteristics. Cases were more likely to be younger ($t(2503)=10.2$, $p<0.001$), men ($\chi^2(1)=50.2$, $p<0.001$), from a minority ethnic group ($\chi^2(1)=66.5$, $p<0.001$), have parents who had psychosis ($\chi^2(1)=42.6$, $p<0.001$), have parents who were

working-class or long-term unemployed ($\chi^2(3)=23.9$, $p<0.001$), and have ever used cannabis ($\chi^2(2)=94.2$, $p<0.001$) (Table 1).

[Insert Table 1 here]

Lifetime Prevalence of Perceived Experiences of Major Discrimination

Over a third (37.3%) of participants reported any perceived experience of major discrimination, and this was higher in cases than in controls (41.8% vs. 34.2%, $\chi^2(1)=15.3$, $p<0.001$) and in minority ethnic groups than the ethnic majority (45.8% vs. 31.0%, $\chi^2(1)=23.9$, $p<0.001$, restricted to controls). Only 7.9% of participants reported pervasive experiences of discrimination (i.e. ≥3 different types of major discrimination), and this was higher in cases (11.3% vs. 5.5% in controls, $\chi^2(3)=33.7$, $p<0.001$) and minority ethnic groups (9.4% vs. 4.4% in ethnic majority, $\chi^2(3)=36.9$, $p<0.001$, restricted to controls). See Supplemental Table 1 for prevalence of the 12 individual types of major discrimination in the total sample, by case/control status, and by ethnic group status. See Supplemental Figure 1 for prevalence of the perceived reason for experiences of major discrimination (i.e. ethnicity, age, gender, mental illness, religion, sexuality, other) in the total sample, by case/control status, and by ethnic group status.

Association Between Any Experience of Major Discrimination and Psychosis

The unadjusted, age- and sex-adjusted, and fully adjusted models for the associations between major discrimination and psychosis are presented in Table 2. After adjusting for age, sex, parent social class, parent history of psychosis, and cannabis use, there was no evidence of a difference in odds of psychosis after experiencing any major discrimination compared with no discrimination (OR=1.20, 95% CI: 0.91-1.59).

Dose-Response Association of More Types of Major Discrimination and Psychosis

In fully adjusted models, there was a dose-response association between more types of major discrimination and increasing odds of psychosis (OR: 1.16, 95% CI: 1.02-1.31). Participants reporting pervasive experiences of major discrimination (i.e. ≥ 3 types) had 1.79-fold greater odds of psychosis than those who experienced no discrimination (95% CI: 1.19-2.71).

Differences in Associations for Discrimination and Psychosis by Ethnic Group

In fully adjusted models, minority ethnic groups had 1.42-fold greater odds of psychosis (95% CI: 1.08-1.85) compared with the ethnic majority (Table 2). In analyses stratified by minority ethnic groups and ethnic majority group, the association between pervasive experiences of major discrimination (i.e. ≥3 types) and odds of psychosis was OR=1.73 (95% CI: 1.12-2.68) for minority ethnic groups and OR=1.42 (95% CI: 0.65-3.10) for the ethnic majority. To test for interaction, we compared results from this model with those from a model with the interaction terms (cross-product with ethnic group) using a likelihood ratio test. We found no strong evidence of interaction for pervasive experiences of major discrimination (χ^2 = 5.96, p=0.11).

[Insert Table 2 here]

In exploratory mediation analysis, pervasive experiences of major discrimination (i.e. ≥ 3 types) minimally explained the association between ethnic group and risk of psychosis. Pervasive experiences of major discrimination only accounted for a small proportion (5.1%) of the total effect of being a member of a minority ethnic group on odds of psychosis (OR^{MTE}=1.90, 95% CI: 1.55- 2.34; OR^{NDE}=1.85, 95% CI: 1.50-2.30; OR^{NIE}=1.02, 95% CI: 1.00-1.07).

All results were similar in direction, magnitude, and significance in sensitivity analyses.

Discussion

This study is the largest to date to investigate the relationship between perceived discrimination and psychosis. We extend previous investigations by including participants with a diagnosis of a psychotic disorder; an established scale that measures lifetime experiences of major discrimination that does not require attribution to race; and an ethnic majority comparison group. While over a third of participants reported ever experiencing major discrimination, a much smaller proportion (7.9%) reported pervasive experiences of major discrimination (i.e. ≥3 different types). Reporting pervasive experiences of major discrimination was associated with increased odds of psychosis of around two-fold after adjusting for measured confounders (age, sex, parent social class, parent history of psychosis, cannabis use). This is one of the first studies to show that perceived discrimination is also associated with increased risk of psychosis among the ethnic majority. Among controls, who are expected to represent the underlying source population, reporting pervasive experiences of major discrimination was twice as common among minority ethnic groups compared with those among the ethnic majority. Exploratory mediation analyses suggested that these higher levels of pervasive experiences of major discrimination might help explain a small part of the excess risk for psychosis among minority ethnic groups, and also suggest that perceived discrimination is relatively rare and only a small part of what is likely a larger constellation of social adversities that cumulatively contribute to excess risk among minority ethnic groups.

Study Limitations

The case-control design limits any inferences about causality since it is collected at a single moment of time; however, embedding the case-control study within a population-based incidence study is a powerful and efficient approach to measure exposures at the presumed onset of the outcome. Case-control studies are typically the most feasible study designs for rare

outcomes such as psychosis but are subject to recall bias. It is well established that mood-dependent recall, including due to current symptoms, influences recollection of prior life events. This is particularly a consideration in a first-episode study, where cases are identified based on current symptoms and may not yet have fully recovered. Within psychotic disorders, symptoms of paranoia in particular may influence retrospective perceptions of unfair treatment. This could lead to an overestimation of the association, including for dose-response relationships (Dohrenwend 2006). However, it would not be appropriate to adjust for paranoia as discrimination also leads to paranoia symptoms (Pearce et al., 2019) and so it is likely to be on the causal pathway between discrimination and psychosis. Some research suggests that severe events tend to be recalled better than less severe ones, as might be the case for the major experiences of discrimination reported here (Williams & Mohammed 2009). Nevertheless, current paranoia remains a major limitation as it may influence reporting of perceived lifetime experiences of major discrimination.

Ethnic group is a crude proxy of the social status of groups of people classified as members of minority ethnic groups (Bhopal 1997) and misses variability in socioeconomic status, health status, exposure to adversity, timing and context of migration and reception. This applies both across ethnic groups and across national boundaries. Nonetheless, it provides important preliminary evidence about the potential consequences of relatively lower social status and is strengthened by comparison to the ethnic majority. Clinical diagnosis of psychotic disorder required contact with specialist mental health services, which does not capture all individuals with psychosis. However, it is considered to be fairly comprehensive at measuring the treated incidence of psychosis in these countries (Jongsma et al., 2018). Importantly, using research diagnoses expands upon prior research that predominantly relied on subthreshold

psychotic experiences, which have an indeterminate relationship with subsequent psychotic disorder diagnoses. Like most research, the measure of discrimination relied on self-report. However, many of the proposed mechanisms emphasize the importance of *perceiving* treatment by society as unfair, and pervasively so. This measure has not yet been cross-culturally validated in all the countries included in this dataset. The measure also did not capture all dimensions of discrimination (e.g., structural discrimination, other forms of major discrimination, any measures of chronic, everyday discrimination, and experiences not perceived as discriminatory by the individual) and therefore likely underestimates experiences of discrimination, yet it is a more comprehensive measure than most prior studies investigating discrimination and psychosis.

Perceived Discrimination and Psychosis

These limitations noted, our finding that broadly reporting any experience of major discrimination was not associated with increased odds of psychotic disorders aligns with the one prior case-control study that also used clinical diagnoses (Veling et al., 2008; Pearce et al., 2019) and suggests this may not be a sufficient risk factor on its own. The finding that experiencing multiple types of major discrimination (i.e. pervasive experiences of discrimination) was associated with increased risk of psychotic disorders aligns with the recent systematic review that identified multiple studies that also found dose-response relationships using subthreshold psychotic experiences (Pearce et al., 2019). One of these prior studies also used the Major Experiences of Discrimination Scale, albeit a nine-item version restricted to items attributed to race or ethnicity, and also found ≥3 types of major discrimination was associated with the highest risk for psychotic symptoms (Oh et al., 2016). Social adversities such as perceived discrimination are postulated to influence risk of psychosis via both biological processes (e.g., stress dysregulation, abnormal dopaminergic functioning) (Van Winkel et al., 2013; Berger &

Sarnyai 2015; Morgan & Gayer-Anderson 2016; Misiak et al., 2017; Murray et al., 2017) and psychological mechanisms (e.g., affective dysfunction, maladaptive cognitive schema) (Bentall et al., 2014; Collip et al., 2008; Howes & Murray 2014; Morgan & Gayer-Anderson 2016; Misiak et al., 2017; Williams et al., 2018).

Study Implications

While advances in genetics and neurobiology offer critical insights into the onset and progression of psychosis, there is now growing evidence for the additional role of social adversities (Murray et al., 2017). Social adversities affect risk across groups, including the ethnic majority as demonstrated by inclusion in this study, although the relative importance of social adversities appears to be greater for minority ethnic groups. Current findings support this idea that greater experiences of social adversities such as perceived discrimination may contribute to the excess risk of psychosis among minority ethnic groups (Morgan et al., 2010; Dykxhoorn & Kirkbride 2018; Morgan et al., 2019). Recent global meta-analyses have found being a migrant and/or member of a minority ethnic group are consistently associated with increased risk of psychotic symptoms (Leaune et al., 2019) and psychotic disorders (McGrath et al., 2004; Selten et al., 2019), as confirmed in the recent EU-GEI incidence study (Jongsma et al., 2018) from which this case-control study is drawn. These rates vary both by region of ethnic origin and the specific catchment region, further supporting differences due to the social context (Termorshuizen et al. 2020). Self-reported experiences of major discrimination operationalize one aspect of potential unfair treatment for individuals perceived as members of minority ethnic groups within these contexts. Further, even when the prevalence of these types of major experiences are similar across ethnic groups with psychotic disorders, minority ethnic groups are more likely to attribute them to discrimination based on race or ethnicity (Gilvarry et al., 1999).

It is important to note that the higher prevalence of social adversities among minority ethnic groups are part of the broader fabric of racism that leads to systemic, avoidable, and unfair inequalities in power, resources, capacities and opportunities across racial or ethnic categorizations perceived as inferior (Paradies et al., 2015; Williams et al., 2019). Racism occurs simultaneously across multiple levels including structural (e.g., institutions, policies), interpersonal (between individuals), and internalized (negative beliefs and stereotypes applied to self) levels. For example, it is postulated that minority ethnic groups experience greater economic disadvantage, a sense of being a member of a devalued, low-status group, and the personal experiences of racial discrimination (Nazroo 2003). But studies including our own typically rely only on self-reported perceptions of interpersonal discrimination and therefore underestimate the full consequences of structural racism on health. The types of perceived major discrimination measured in this study hint at a further social disadvantage, as each domain can have a cascade of consequences of their own (e.g., being unfairly targeted by the police affecting employment opportunities, being unfairly fired preventing the purchase of basic needs). This may help contextualize why the exploratory mediation analysis found that discrimination only explained a small proportion of excess risk for psychosis among minority ethnic groups. It is worth considering the role of discrimination as a risk factor for psychosis among minority ethnic groups within the constellation of other social adversities (e.g., Jongsma e al. 2020).

In this context, the higher prevalence of multiple different types of discrimination among minority ethnic groups could contribute to stronger feelings of distrust and hostility, as these experiences of unfair treatment start to feel pervasive rather than isolated events (Schmitt et al., 2014). It has been posited that greater exposure to systemic social adversities over time, particularly those involving high levels of interpersonal threat, hostility, and violence, could help

explain the excess rates of psychotic disorders in some minority ethnic groups (Morgan et al., 2019). This could also be exacerbated by additional unfair treatment of members of minority ethnic groups *with psychosis*, such as more harmful entries into care (e.g., compulsory admission, police and criminal justice contact) (Halvorsrud et al., 2018). This becomes complex given the symptoms of psychosis such as paranoia, in which individuals have persistent concerns that others intend to cause them harm. It will be crucial to parse symptoms of psychosis such as paranoia and delusions from a reasonable response to prior experiences of discrimination or else risk additional harms by the very institutes that are supposed to support these individuals.

Future studies should consider how perceived discrimination fits into the broader constellation of social adversities that may interactively increase the risk of psychosis. Much of the evidence to date for the role of social adversities on risk of psychosis points to the role of early life adversities, the influence of early life adversities on later life adversities, and the cumulative experience of adversities across the life course (e.g., Varese et al., 2012; Morgan et al., 2014; Stilo et al., 2017), so it will be valuable to assess multiple social adversities simultaneously. Future studies should expand their measures of discrimination to include structural discrimination, additional domains of major discrimination, and chronic, everyday experiences of discrimination. They should also consider related consequences of perceived experiences of major discrimination, such as changes in employment, housing, and social relationships, which could lead to further social disadvantage and also increase the risk of psychosis. These future studies should consider protective factors that may attenuate the risk of psychosis among members of minority ethnic groups even after experiences of discrimination.

Conclusions

In this international investigation of psychotic disorders, pervasive experiences of major discrimination were associated with almost two-fold increased odds of a psychotic disorder. This appears to be driven in part by the much higher prevalence of pervasive experiences of discrimination among minority ethnic groups. This study bolsters prior ones by including psychotic disorder diagnoses, a more robust measure of discrimination, and an ethnic majority comparison group. Future studies should continue to investigate how additional aspects of discrimination, in combination with other social adversities, might help explain the excess risk of psychosis among minority ethnic groups.

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Table 1. Sociodemographic characteristics of the EU-GEI case-control sample by case status and by minority ethnic group status

	All (N = 2507)		**Case vs. control (N = 1040 cases)**		**Minority vs. majority (N = 683 minorities)**	
	n	**Total %**	**Case %**	**Control %**	**Minority %**	**Majority %**
Age in years*	34.1 (12.3)		31.2 (10.6)	36.2 (12.9)	31.5 (11.0)	35.1 (12.6)
Catchment site						
London	395	15.8	18.1	14.1	29.4	10.6
Cambridge	146	5.8	3.9	7.2	2.2	7.2
Amsterdam	197	7.9	9.2	6.9	13.8	5.6
Gouda/Voorhout	207	8.3	9.4	7.4	2.8	10.3
Madrid	75	3.0	3.6	2.6	1.5	3.6
Barcelona	65	2.6	2.7	2.5	0.6	3.3
Oviedo	76	3.0	2.6	2.7	1.8	3.5
Valencia	80	3.2	4.6	2.2	1.2	3.9
Créteil	154	6.1	5.2	6.8	11.4	4.2
Puy de Dôme	62	2.5	1.4	3.2	0.7	3.1
Bologna	129	5.2	6.3	4.4	2.6	6.1
Palermo	151	6.0	5.0	6.7	1.3	2.8
Ribeirão Preto	493	19.7	18.3	20.6	29.1	16.1
Santiago	65	2.6	2.6	2.6	0.1	3.5
Verona	156	6.2	4.3	7.6	0.6	8.3
Cuenca	56	2.2	1.7	2.6	0.9	2.7
Ethnic group						
White	1823	72.8	64.1	78.9	0	100
Black	279	11.1	15.8	7.8	40.8	0
Mixed	219	8.7	10.0	7.8	32.1	0
Asian	63	2.5	3.0	2.2	9.2	0
North African	67	2.7	4.1	1.6	9.8	0
Another	55	2.2	3.0	1.6	8.1	0
Sex						
Female	1177	46.9	38.6	52.9	45.8	47.4
Male	1330	53.1	61.4	47.1	54.2	52.6

	All (N = 2507)		Case vs. control (N = 1040 cases)		Minority vs. majority (N = 683 minorities)	
	n	Total %	Case %	Control %	Minority %	Majority %
Parent social class						
Professional	657	29.3	25.9	31.5	24.2	31.1
Intermediate	611	27.2	26.1	28.0	25.7	27.8
Working class	958	42.7	46.4	40.3	48.8	40.5
Unemployed	17	0.8	1.6	0.2	1.3	0.6
Parent with psychosis						
No	2145	96.1	92.9	98.3	95.5	96.3
Yes	88	3.9	7.1	1.7	4.5	3.7
Cannabis use						
Never	1128	45.7	35.6	52.8	50.2	44.1
Past use	963	39.0	42.6	36.6	32.8	41.4
Current use	376	15.2	21.9	10.6	16.9	14.6
Major discrimination						
None	1571	62.7	58.2	65.8	50.2	67.4
1 type	504	20.1	20.2	20.0	22.3	19.3
2 types	235	9.4	10.4	8.7	12.9	8.1
3+ types	197	7.9	11.3	5.5	14.6	5.3

**Mean (SD); due to missing data, n may not add to the sample totals*

Table 2. Associations between major discrimination and psychosis in the EU-GEI case-control sample

	Sample		Unadjusted		Age- & Sex-Adjusted		Fully Adjusted*	
	N	**%**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Minority ethnic group								
No	1823	72.8	*Reference*		*Reference*		*Reference*	
Yes	683	27.2	1.58	1.21, 2.07	1.41	1.06, 1.87	1.42	1.08, 1.85
Any discrimination								
No	1571	62.7	*Reference*		*Reference*		*Reference*	
Yes	936	37.3	1.27	0.91, 1.78	1.36	0.99, 1.88	1.20	0.91, 1.59
Discrimination types**								
None	1571	62.7	*Reference*		*Reference*		*Reference*	
1 type	504	20.1	1.11	0.79, 1.57	1.16	0.83, 1.62	1.08	0.77, 1.51
2 types	235	9.4	1.19	0.72, 1.96	1.30	0.78, 2.19	1.14	0.69, 1.87
3+ types	197	7.9	2.02	1.25, 3.24	2.26	1.46, 3.50	1.79	1.19, 2.71
Age	2505	99.9			0.94	0.93, 0.96	0.94	0.93, 0.96
Sex								
Female	1177	46.9			*Reference*		*Reference*	
Male	1330	53.1			1.52	1.33, 1.75	1.42	1.15, 1.76
Parent social class								
Professional	657	29.3					*Reference*	
Intermediate	611	27.2					1.18	0.91, 1.53
Working class	958	42.7					1.56	1.15, 2.12
Long-term unemployed	17	0.8					7.02	2.20, 22.44
Parent with psychosis								
No	2145	96.1					*Reference*	
Yes	88	3.9					3.52	2.39, 5.19
Cannabis use								
Never	1128	45.7					*Reference*	
Past	963	39.0					1.54	0.99, 2.37
Current	376	15.2					1.89	1.10, 3.24

**Separate models were fit for minority ethnic group, any discrimination, and types of discrimination; each model adjusted for age, sex, parent social class, parent history of psychosis, cannabis use; ORs for covariates are from the models for types of discrimination*

Perceived major experiences of discrimination, ethnic group, and risk of psychosis in a six-country case-control study

Individual Types Of Major Discrimination

The most common types of major discrimination were unfair treatment by the police (11.2%), not getting hired (10.4%), being fired (9.7%), and from neighbors and family (9.1%). These four types of discrimination were also the most common ones among cases and minority ethnic groups, and all were more common in cases except not getting hired, and more common in minority ethnic groups except being fired. For minority ethnic groups, the most frequent types of major discrimination were receiving worse services (10.4%) and negative treatment on public transport (6.8%), whereas the least frequent types were for getting a loan (1.8%), securing housing (2.6%) and in the court system (3.2%).

Supplemental Table 1. Twelve types of major discrimination in the EU-GEI case-control sample by case status and minority status

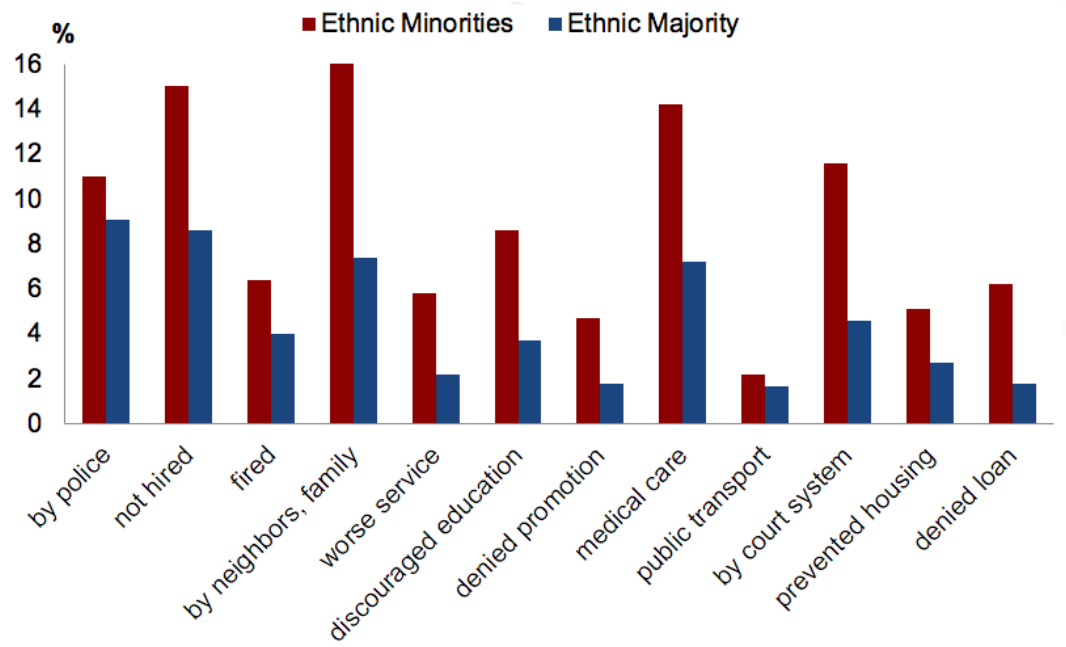
	All (N = 2507)		**Case vs. control (N = 1040 cases)**			**Minority vs. majority (N =310 minorities)**		
	Total n	**Total %**	**Case %**	**Control %**	***p*-value**	**Min-ority %**	**Maj-ority %**	***p*-value**
Fired	241	9.7	12.1	7.9	.001	6.8	8.3	.402
Not hired	257	10.4	10.1	10.6	.692	16.2	9.0	<.001
Promotion	116	4.7	4.8	4.6	.874	5.5	4.4	399
Police	279	11.2	15.2	8.4	<.001	17.8	5.8	<.001
Court system	79	3.2	4.8	2.1	<.001	4.2	1.5	.003
Education	125	5.0	6.3	4.1	.015	6.8	3.4	.008
Housing	64	2.6	2.5	2.6	.881	4.5	2.1	.018
Neighbors, family	226	9.1	13.9	5.7	<.001	8.4	5.0	.022
Loan	45	1.8	2.1	1.6	.312	1.3	1.7	.642
Service	160	6.5	7.4	5.8	.109	10.4	4.6	<.001
Medical care	86	3.5	5.2	2.3	<.001	1.9	2.4	.656
Public transport	83	3.4	4.2	2.8	.054	6.8	1.7	<.001

Comparison by minority status restricted to controls; due to missing data, n may not add up to sample totals; p-value was calculated using Pearson's chi-square test

Perceived Reason for Experiences of Major Discrimination

In the total sample, 10.5% of participants reported experiences of major discrimination that they attributed to race or ethnicity, while 26.8% had experienced major discrimination that they attributed to factors not related to race or ethnicity (age, gender, mental illness, religion, sexuality, other). Discrimination attributed to race or ethnicity was higher among cases (12.5% vs. 9.1% in controls, $\chi^2(2)=16.6$, $p<0.001$) and minority ethnic groups (32.3% vs. 2.9% in ethnic majority, $\chi^2(2)=261.8$, $p<0.001$, restricted to controls). Discrimination attributed to the category of "other" (i.e. self-reported reasons such as nationality, immigration status, language ability, education level, social class, physical appearance, physical illness, disability, ideology), was also higher among cases (29.3% vs. 25.1% in controls, $\chi^2(2)=16.6$, $p<0.001$), but lower among minority ethnic groups (13.6% vs. 28.1% in ethnic majority, $\chi^2(2)=261.8$, $p<0.001$, restricted to controls). Among controls who experienced any major discrimination (N=936), most attributions for discrimination differed between minority ethnic groups and the ethnic majority.

Supplemental Figure 1. Reasons for major discrimination among N=936 who experienced discrimination by minority status restricted to the EU-GEI control sample



Dear Editor,

Thank you for the opportunity to revise and resubmit our manuscript, "**Perceived major experiences of discrimination, ethnic group, and risk of psychosis in a six-country case-control study**" for consideration at *Psychological Medicine.* We appreciate the reviewers' positive endorsements about the contributions of the paper and their thoughtful suggestions for minor revisions. We have responded to their feedback below, and include two copies of the updated manuscript: one a clean copy and one highlighting all changes discussed below.

On an administrative note, I'm transitioning between academic positions right now, so I have updated my information on the title page and in the online system to reflect my new affiliation.

REVIEWER #1

This is a very important study, as it is well identified that migrants and ethnic minorities have an increased risk for developing a psychotic disorder, however it is not yet known why this is the case. One of the leading theories is that these groups experience high levels of discrimination. It is a very large cohort and it has been conducted as part of the large collaboration study across six countries. Overall, it is a well written article and the authors have addressed a lot of my concerns in their limitations section, so I think they have been up front about the limitations of their study. I think the findings of this study could help progress our understanding of the excess risk of psychotic disorders in ethnic minorities.
Thank you for your kind comments on the contributions and considered limitations of this paper.

There are some issues that need to be addressed:
1. The cases and controls differ on a large number of significant factors - age, sex, family history of psychosis, parental unemployment or social class and cannabis use. However it would appear that they have not controlled for all these potential confounders in the analysis (they did for age & sex, but not the others - from my reading anyway), these could all influence the perception of discrimination. Could they confirm whether these factors were controlled for.
Thank you for pointing out these important confounders, which we did control for in our models. We present three sets of models: unadjusted, age and sex adjusted, and fully adjusted for all measured confounders. We have now made this clearer throughout the text in the methods, results and discussion sections. Please see below:

- Methods: "First, a parsimonious model adjusting for age and sex was constructed. Next, a fully adjusted model taking measured confounding variables into account was fitted (i.e. age, sex, parent social class, parent history of psychosis, cannabis use)."
- Results:
  - "The unadjusted, age- and sex-adjusted, and fully adjusted models for the associations between major discrimination and psychosis are presented in Table 2. After adjusting for age, sex, parent social class, parent history of psychosis, and cannabis use, there was no evidence of a difference in odds of psychosis after experiencing any major discrimination compared with no discrimination (OR=1.20, 95% CI: 0.91-1.59)."
  - "In fully adjusted models, there was a dose-response association between more types of major discrimination and increasing odds of psychosis (OR: 1.16, 95% CI: 1.02-1.31). participants reporting pervasive experiences of major discrimination (i.e. ≥ 3 types) had 1.79-fold greater odds of psychosis than those who experienced no discrimination (95% CI: 1.19-2.71)."

- "In fully adjusted models, minority ethnic groups had 1.42-fold greater odds of psychosis (95% CI: 1.08-1.85) compared with the ethnic majority (Table 2). In fully adjusted models stratified by minority ethnic groups and ethnic majority group, the association between pervasive experiences of major discrimination (i.e. ≥3 types) and odds of psychosis was OR=1.73 (95% CI: 1.12-2.68) for minority ethnic groups and OR=1.42 (95% CI: 0.65-3.10) for the ethnic majority."

- Table 2 Fully Adjusted Model asterisk (no new text): "*Separate models were fit for minority ethnic group, any discrimination, and types of discrimination; each model adjusted for age, sex, parent social class, parent history of psychosis, cannabis use;*"
- Discussion: "Reporting pervasive experiences of major discrimination was associated with increased odds of psychosis of around two-fold after adjusting for measured confounders (age, sex, parent social class, parent history of psychosis, cannabis use)."

2. They used the 'white' ethnic group as the ethnic majority group and when creating a dichotomous group they compiled the other ethnic groups into 'minority ethnic groups', however considering that this study was conducted across six different countries, including Brazil - is the 'white ethnic' group the majority ethnic group across all of the countries and if not, is it appropriate to designate the 'white ethnic' group as the reference or majority group.
Thank you for noting this. The 'white ethnic' group is the majority ethnic group in all 6 countries, which we now state this explicitly in the Methods section:
"*Ethnic Group*. Respondents provided self-reported ethnic categorizations relevant to each country's context, which were then collapsed into six categories for standardization across sites: Asian, Black, Mixed, North African, White, and Another. White is the majority ethnic group in all six countries included in this dataset. A binary variable was created to distinguish the ethnic majority (White) and minority ethnic groups (Asian, Black, Mixed, North African, Another) based on these classifications, as we were most interested in assessing whether there was a difference in the association across all minority ethnic groups compared with the ethnic majority."

My other point is that we cannot infer causality or the direction of the relationship. However, the authors have acknowledged.
Thank you. We agree completely that causality and direction cannot be inferred here.

REVIEWER #2

This study used a case-control design to examine the odds of perceived discrimination between people with psychosis and controls. The main analysis did not find a significant effect of perceived discrimination, however there was a higher odds of psychosis among people who experienced three or more discrimination events, as well as among ethnic minorities groups in stratified analyses. The current study is novel in that the effects of discrimination are explored among people from the ethnic majority as well, rather than limiting to ethnic minority groups. This novel aspect of the current study could be better emphasized and highlighted, as I think it is a significant strength.
We appreciate your kind assessment of this paper as well as highlighting this novel aspect of the study. We have added a line into the first paragraph of the Discussion:
"This is one of the first studies to show that perceived discrimination is also associated with increased risk of psychosis among the ethnic majority."

We have also added a line in the first paragraph of the Study Implications section:

"Social adversities affect risk across groups, including the ethnic majority as demonstrated by inclusion in this study, although the relative importance of social adversities appears to be greater for minority ethnic groups."

I have a number of comments and queries that I hope will be useful to the study team as they revise the manuscript:

A. The recruitment of cases is not well-described - it is stated that a subset of cases from an incidence study were recruited, but it doesn't describe how people were selected and what proportion of the total sample of cases were participating. This information is important for claims that this is a "population-based" case-control study.
The incidence sample comprised 2774 individuals with a first episode of psychosis. Of these, 1519 were approached, and 1130 were consented and assessed (41% of the total incidence sample). Reasons for non-participation among cases who were approached were refusal to participate, language barriers, and exclusion after consenting as they did not meet the age inclusion criteria. We have updated the description of the Study Population as follows:
"A subset of these incident cases was approached for participation in the concurrent case-control study to collect and analyze data on putative risk factors (41% of incidence sample)."

B. Information on the cross-cultural validity of the perceived discrimination tool should be provided - has this been established?
The Major Experiences of Discrimination measure originated in the United States and has been primarily used there and in the United Kingdom. Although it has been used in diverse samples within these countries, the cross-cultural validity in other countries has not been established yet. Therefore, we have added this as an additional line in the Limitations section:
"This measure has not yet been cross-culturally validated in all the countries included in this dataset."

C. The authors used parent social class as their adjustment variable for SES. Given that the sample ranged in age from 18 to 64 years, this is not the best choice, particularly for those over the age of 30 years. The authors are advised to use a more relevant variable for SES, or explore the impact of parental vs. own social class in sensitivity analyses.
Thank you for this question. We selected parent social class in part for theoretical reasons (as the literature indicates that early life experiences play a large role in onset of psychosis) but also for practical ones, as parent social class had less missing data (11%) compared to main social class (19% missing) and current social class (27% missing). However, as a sensitivity analysis, we have also re-run all of the major analyses (regression models, moderation, mediation) using the participant's main social class and are glad to report the estimates are all similar in direction, magnitude, and significance. For example:

	Adjusting for parent social class (reported in paper)	Adjusting for main social class (sensitivity analysis)
Any discrimination	1.20 (0.91. 1.59)	1.24 (0.89, 1.72)
3+ types of discrimination	1.79 (1.19, 2.71)	1.75 (1.19, 2.57)

We have added this into the text as follows:

- Methods: "Finally, a sensitivity analysis was conducted to substitute parent social class with participant social class."
- Results: "All results were similar in direction, magnitude, and significance in sensitivity analyses."

D. I'm not clear on the rationale for adjusting for "parent history of psychosis" in the multivariable models - further explanation of the role of this variable as a potential confounding factor would be useful.
Thank you for this question. Parent history of psychosis is associated with both the exposure and the outcome, which makes it a relevant confounding variable. The discrimination measure in this study is about “unfair treatment” not specific to race/ethnicity. Having a parent with mental illness can lead to greater discrimination both directly due to stigma and ostracization but also indirectly due to other social and economic consequences that contribute to discrimination. It is well-established that parent history of psychosis is linked to developing psychosis. We now clarify how we chose the confounders in the Methods section:

“Next, a fully adjusted model taking measured confounding variables into account was fitted (i.e. age, sex, parent social class, parent history of psychosis, cannabis use). These confounders were chosen *a priori* based on our literature review.”

E. I do not understand the statement "all comparisons between ethnic groups were restricted to controls to provide population-representative estimates, since the cases would over-represent ethnic minorities". I'm not clear on how this restriction would enable more representative estimates? Do the authors hypothesize that ethnic minorities with psychosis would have a different frequency of discriminatory events?
Yes, we do. First, ethnic minorities are disproportionately represented among cases and cases are more likely to experience discrimination than non-cases. Second, ethnic minorities who experience a higher frequency of discriminatory events may be more likely to have psychosis than ethnic minorities who have not developed psychosis in the general public (as is ultimately indicated by our findings). Therefore, for our bivariate descriptive comparisons of the prevalence of discrimination between the minority ethnic group and majority ethnic group were restricted to the controls. We have revised the statement as follows:
“all comparisons between ethnic groups were restricted to controls to provide population-representative estimates, since the cases are more likely to experience discrimination and also over-represent ethnic minorities."

F. The authors spend a large portion of the results section (approx. 2 pages) describing the prevalence of different types of perceived discrimination and the perceived reason for discrimination - describing the prevalence and testing for differences between people with and without psychosis was not one of the objectives of the current study, so I'd suggest moving these results to the appendix.
We agree that these sections are not part of the main objectives of the current study and have moved them to the Supplement and replaced with the following text:
“See Supplemental Table 1 for prevalence of the 12 individual types of major discrimination in the total sample, by case/control status, and by ethnic group status. See Supplemental Figure 1 for prevalence of the perceived reason for experiences of major discrimination (i.e., ethnicity, age, gender, mental illness, religion, sexuality, other) in the total sample, by case/control status, and by ethnic group status.”

G. The claim that there is a "dose-response" relationship between more types of major discrimination and odds of psychosis is overstated - the investigators found an association for 3+ discrimination types, but no association for 1 or 2 types of discrimination. To me, this is suggestive of a threshold effect rather than a dose-response relationship.
We appreciate your careful reading. We would like clarify our approach. As described in the Methods, we treated the number of types of major discrimination (0, 1, 2, 3+) as an ordinal variable to test the linear trend and then as indicator variables to assess the odds ratio for each

number of types. We did find the linear trend to be statistically significant, which indicates a dose-response relationship. This was originally presented in the Table as a p-value (which has been removed as per later comments), but we have now added this directly into the Results section. We have also included guarded statements to reflect these results:
"In fully adjusted models, there was a statistically significant linear trend suggestive of dose-response association between more types of major discrimination and increasing odds of psychosis (OR: 1.16, 95% CI: 1.02-1.31). Participants reporting pervasive experiences of major discrimination (i.e. ≥ 3 types) had 1.79-fold greater odds of psychosis than those who experienced no discrimination (95% CI: 1.19-2.71)."

Further, the use of the term "pervasive" to describe this category isn't entirely accurate - I would suggest "repeated" as a more accurate term. How were multiple discrimination events of the same type captured and handled in the analyses?
We appreciate this careful attention to language, as we also spent a lot of time thinking about how best to frame this. The measure we used does *not* capture multiple discrimination events of the same type, therefore using "repeated" would not be appropriate. What we want to capture here is the impact of experiencing discrimination across multiple major domains of life (e.g. in jobs, in housing, by the police) versus experiencing discrimination within a single domain, which could be perceived as an isolated or idiosyncratic experience.

We adopt the language of "pervasive discrimination" from Schmitt et al. 2014: "Schmitt and Branscombe (2002b) argued that the consequences of perceptions of discrimination depend on the degree to which discrimination is perceived to be isolated and idiosyncratic versus *pervasive*—meaning that discrimination is systemic and thus occurs frequently and across multiple contexts. Because discrimination is less avoidable if more pervasive across contexts, perceptions of pervasive discrimination should undermine feelings of control. In addition, pervasive discrimination, compared to discrimination that is seen as isolated, is more likely to be experienced as rejection and exclusion by dominant society. For these reasons, discrimination appraised as pervasive is especially likely to have a negative effect on well-being compared to discrimination that is seen as isolated (e.g., Schmitt, Branscombe, & Postmes, 2003)."

We have revised this in the Methods:
"For this paper, perceived experiences of ≥3 types of major discrimination will be described as 'pervasive experiences of discrimination' to distinguish it from a single isolated experience of discrimination (Schmitt et al., 2014)."

Minor Comments:
- The "another" ethnic group would be better called "other"
Some believe that the use of the term "other" contributes to the "othering" of racial/ethnic groups designated to this category, while "another" simply implies there is another racial/ethnic group not included in the ones listed thus far. Although we acknowledge this is a recent shift in language not yet widely used in academic literature, we know that language matters and hope that by using it in our paper we can contribute to making this most standard in our field.

- At several points throughout the manuscript, the authors use the term "cross-sectional" data - this is incorrect, as these are case-control data.
Thank you for noting this. We were using it as shorthand for data collected at a single moment of time but agree this term has a specific meaning in the field and have replaced it in both locations that it was previously used to say "data collected at a single moment of time".

- Table 1: please clarify the sample included in each group, and why the sample size varies

across the table. P-values should be removed, as comparing differences across these groups was not the objective of the study
This table includes the entire analytic sample. If we understand the question correctly, this concerns the total sample number compared to some of the individual variables. This is explained in the table notes: "*due to missing data, n may not add to the sample totals*". As missingness was limited for most covariates, we included those participants in the sample.

We have removed the p-values and associated table footnotes, although we note that the comparisons across these groups is relevant and presented in the first paragraph of the Results as part of understanding the study population and confirming that the case and control samples are quite different from each other.

- P-values should also be removed from Table 2 - they do not provide any additional information to what is already reflected in the 95% confidence interval
We have removed the p-values and deleted the associated table footnotes.

- The two figures are difficult to read and do not add much to the paper - suggest removing
We have removed both of the figures.

- The footnote on table 2 states - "Separate models were fit for minority ethnic group, any discrimination, and types of discrimination." If this is the case, which model are the ORs for the covariates from? It would be clearer if the other covariates were removed from the table (eg. age, sex, social class, etc) so as not to give the appearance that this was one fully adjusted model.
We have added the following to the end of the footnote: "*ORs for covariates are from the models for types of discrimination*"
We have removed the covariates that are not being adjusted, and in doing so, rearranged the table so the exposures are listed at the top and the covariates underneath them.

REVIEWER #3

The authors have used the EU-GEI data, a large case-control study of psychosis incidence across 5 European countries and Brazil, to investigate whether the perception of being discriminated against was associated with increased risk for a psychotic disorder. Additionally the authors investigated the relative contribution of discrimination to the increased risk for psychosis which is generally observed in ethnic minorities. The study manuscript is clearly written and well structured, and contributes to the literature by investigating these associations in a large international sample, using diagnoses rather than (sub-clinical) symptoms as the criterion. The sampling and investigational procedure was thorough and is well described here and elsewhere, and the authors are well aware of the limitations of their cross-sectional method, and the instrumentation to measure discrimination.
Thank you for your kind comments on the contributions and considered limitations of this paper.

On my reading of the manuscript I noted down a few rather minor comments which the authors may find helpful.
1. Methods: The statistical method is described as "multivariable mixed-effects logistic regression". To me the addition of 'multivariable' appears uncommon and I was not clear about its function here, is it to emphasize that the (final) model is adjusted for several possible confounders?
The purpose of the term was to indicate the adjustment of multiple confounders, but we have removed it here to eliminate confusion. In response to reviewer #1, we have made several

clarifications throughout the manuscript of the confounders being adjusted for in the models.

2. In the results section the authors use the formulation "There was weak evidence of a modest difference". I would advise a more strict formulation here and much prefer the formulation used later in the discussion "These limitations noted, our finding that broadly reporting any experience of major discrimination was not associated with increased odds of psychotic disorders". A similar note applies for:, "We found no strong evidence of interaction for pervasive experiences of major discrimination."
We agree with the reviewer and have revised this sentence accordingly: "…there was no evidence of a difference in odds of psychosis after experiencing any major discrimination compared with no discrimination."

3. Figure 2: When looking at mediation results in a figure I would expect to see a flow diagram. The current information content of the figure is limited and could be more efficiently represented by incorporating the 3 OR's in text
Based on this feedback and reviewer #2 above, we have removed this Figure. All 3 of the ORs are already listed in the text.

4. Discussion : "as confirmed in the recent EU-GEI incidence study (Jongsma et al., 2018)." Are the current study and the study referred to here based on the same data? If so, this could be made more clear.
These are related studies. The population-based incidence study is the parent study from which a subset of the cases was sampled. We have clarified this: "as confirmed in the recent EU-GEI incidence study (Jongsma et al., 2018) from which this case-control study is drawn."

Thank you again to all of their reviewers for their thoughtful and helpful feedback that have led to a strengthened manuscript.

Abstract

Background: Perceived discrimination is associated with worse mental health. Few studies have assessed whether perceived discrimination (i) is associated with risk of psychotic disorders, and (ii) contributes to an increased risk among minority ethnic groups relative to the ethnic majority.

Methods: We used data from the European Network of National Schizophrenia Networks Studying Gene-Environment Interactions Work Package 2, a population-based case-control study of incident psychotic disorders in 17 catchment sites across six countries. We calculated odds ratios (OR) and 95% confidence intervals (95% CI) for the associations between perceived discrimination and psychosis using mixed-effects logistic regression models. We used stratified and mediation analyses to explore differences for minority ethnic groups.

Results: Reporting any perceived experience of major discrimination (e.g., unfair treatment by police, not getting hired) was higher in cases than controls (41.8% vs. 34.2%). Pervasive experiences of discrimination (≥3 types) were also higher in cases than controls (11.3% vs. 5.5%). In fully adjusted models, the odds of psychosis were 1.20 (95% CI: 0.91-1.59) for any discrimination and 1.79 (95% CI: 1.19-1.59) for pervasive discrimination compared with no discrimination. In stratified analyses, the magnitude of association for pervasive experiences of discrimination appeared stronger for minority ethnic groups (OR=1.73, 95% CI: 1.12-2.68) than the ethnic majority (OR=1.42, 95% CI: 0.65-3.10). In exploratory mediation analysis, pervasive discrimination minimally explained excess risk among minority ethnic groups (5.1%).

Conclusions: Pervasive experiences of discrimination are associated with slightly increased odds of psychotic disorders, and may minimally help explain excess risk for minority ethnic groups.

Key words: discrimination, minority ethnic group, psychotic disorder, psychosis, first-episode, case-control, multi-country

Introduction

Perceived discrimination, the perception of unfair treatment of members of a social group, is associated with worse mental and physical health outcomes (Williams & Mohammed 2009; Krieger 2014; Schmitt et al., 2014; Lewis et al., 2015; Paradies et al., 2015). It is posited that minority ethnic groups have more pervasive and more severe experiences of discrimination (Schmitt et al., 2014; Paradies et al., 2015), regardless of whether or not they explicitly attribute this unfair treatment to their race or ethnicity (Williams & Mohammed 2009; Lewis et al., 2015). Discrimination is considered a key factor in driving mental health inequities among minority ethnic groups (Williams & Mohammed 2009; Krieger 2014; Schmitt et al., 2014; Lewis et al., 2015; Paradies et al., 2015). A meta-analysis confirmed that perceived ethnic discrimination is associated with worse mental health for minority ethnic groups in Europe, although this only included four studies on psychotic symptoms (de Freitas et al., 2018).

A recent systematic review identified 24 studies on the relationship between perceived discrimination and psychosis, which produced suggestive findings that discrimination may be associated with increased risk of psychosis and tentatively indicated a dose-response relationship (Pearce et al., 2019). While these studies provide preliminary support for a link between discrimination and psychosis, the current body of evidence is limited in at least three ways. First, the majority of studies were of subthreshold psychotic experiences or clinical high-risk status, not psychotic disorders. While this information is important, subthreshold experiences are not sufficient to predict who goes on to develop psychotic disorders (Fusar-Poli et al., 2013). Second, measures of discrimination included in previous studies have often only used one or a few items, restricted these experiences to the past year, and/or required attribution to race. Such measurement is unlikely to capture the full experience of discrimination or allow for testing of

dose-response relationships; requiring attribution to race also underestimates experiences of unfair treatment among minority ethnic groups (Williams & Mohammed 2009). Third, most previous study samples have typically lacked an ethnic majority comparison group, preventing investigation of how discrimination may uniquely affect psychosis risk in minority ethnic groups relative to the ethnic majority.

In this study, we analyzed data from Work Package 2 of the European Network of National Schizophrenia Networks Studying Gene-Environment Interactions (EU-GEI) study, a population-based incidence and case-control study of psychotic disorders and the largest international investigation of psychotic disorders in the last 40 years, to examine the relationship between perceived discrimination and psychotic disorders. We sought to test three hypotheses: (1) There will be an association between *any* experience of major discrimination and odds of psychotic disorders; (2) There will be a dose-response association between *more types* of major discrimination and increasing odds of psychotic disorders; (3) Experiencing more types of major discrimination will *partially explain* the association between minority ethnic groups and excess odds of psychotic disorders.

Methods

Study Population

Work Package 2 of the EU-GEI study ran from May 2010 to April 2015 and the incidence and first-episode case-control program included 17 clearly defined catchment areas across six countries (Brazil, France, Italy, Netherlands, Spain, United Kingdom) (Gayer-Anderson et al., 2020). The primary goal was to study genetic and socio-environmental interactions in the onset of psychosis. Catchment sites were selected for large migrant and minority ethnic populations and to represent a mix of urban and rural regions. Incidence data

included anyone who came into contact with specialist mental health services with a first-episode psychotic disorder. A subset of these incident cases was approached for participation in the concurrent case-control study to collect and analyze data on putative risk factors (41% of incidence sample). In analyses for this paper, we excluded 36 cases from the site in Paris (where no control participants were recruited) and 84 participants missing all discrimination data. Participants who were excluded from analyses had similar characteristics (e.g., age, sex, parent social class) to those included. Ethical approval was provided by research ethics committees in each site. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Written informed consent was obtained from all participants.

Variables

Case/Control Status. Cases were individuals aged 18 to 64 years residing in the specified catchment areas who made contact with specialist mental health services with a first-episode psychotic disorder (e.g., schizophrenia, schizoaffective disorder, bipolar disorder) based on the International Classification of Diseases, Tenth Edition (ICD-10) research diagnoses (codes F20-F33) during the time frame of the study (median 25 months, range 12 to 48 months depending on site). Individuals were excluded if they had previous contact with mental health services for psychosis, or if there was evidence that their psychotic symptoms were precipitated by an organic cause or due to acute intoxication. Controls were volunteers selected from the same catchment areas using a mixture of random and quota sampling to maximize representativeness, including randomly selecting from general practitioner lists and housing lists in some sites and more ad hoc approaches (e.g., leaflets at local stations, shops and job centers, Internet and

newspaper advertisements) in others. Controls were excluded if they reported a prior diagnosis of or treatment for any psychotic disorder (Gayer-Anderson et al., 2020). Some sites also 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.

Ethnic Group. Respondents provided self-reported ethnic categorizations relevant to each country's context, which were then collapsed into six categories for standardization across sites: Asian, Black, Mixed, North African, White, and Another. White is the majority ethnic group in all six countries included in this dataset. A binary variable was created to distinguish the ethnic majority (White) and minority ethnic groups (Asian, Black, Mixed, North African, Another) based on these classifications, as we were most interested in assessing whether there was a difference in the association across all minority ethnic groups compared with the ethnic majority.

Perceived Discrimination. Perceived discrimination refers to perceptions of unfair treatment. This study specifically addressed perceived lifetime experiences of discrimination that might have major interference with advancing socioeconomic position (referred to as "major discrimination"), rather than day-to-day, routine, and relatively minor experiences of unfair treatment. These experiences of major discrimination were assessed using a modified version of the Major Experiences of Discrimination Scale originally developed by Williams and colleagues (1997) for the Detroit Area Study in Michigan, USA. The scale has demonstrated good reliability and validity (Williams et al., 1997) and has been widely used in the literature (Kessler et al., 1999; Taylor et al., 2004). Respondents were asked whether they have ever *unfairly* experienced any of the following twelve events: being fired; not being hired; being denied a promotion; being stopped, questioned, or threatened by the police; being treated unfairly by the court system; being

discouraged in education; being prevented from renting or buying housing; experiencing poor treatment by neighbors or family; being denied a loan or preferable mortgage rate; receiving worse service than others; experiencing unfair treatment when getting medical care; and experiencing unfair treatment when using public transport. For each affirmative response, participants were then asked to select one reason why they believe they had been treated unfairly (gender, race or ethnicity, religion, mental illness, sexuality, age, other; a binary variable was created for each reason ever endorsed). For analysis, two aggregate variables of perceived lifetime experiences of major discrimination were created: 1) A binary variable for endorsement of any experience of major discrimination across the 12 items, and 2) a categorical variable for the number of different types of experiences of major discrimination grouped into 0, 1, 2, and ≥3 types consistent with prior studies (Oh et al., 2016). For this paper, perceived experiences of ≥3 types of major discrimination will be described as "pervasive experiences of discrimination" to distinguish it from a single isolated experience of discrimination (Schmitt et al., 2014).

Other Variables. Information on potential confounders was collected at the time of assessment and selected a priori based on their established relationships with perceived discrimination and psychosis: age (continuous), sex (male/female), parent social class (professional, intermediate, working-class, long-term unemployed), parent history of psychosis (yes/no), and cannabis use (never, past, current).

Statistical Analysis

All analyses were conducted in Stata 15 (StataCorp 2017). Frequency distributions of sociodemographic and lifestyle characteristics of participants were explored. Continuous variables were expressed as mean ± standard deviation (SD). Categorical variables were expressed as number (percent, %). Chi-square and t-tests were used to compare

sociodemographic characteristics, types of major discrimination, and reasons for major discrimination among cases versus controls and minority ethnic groups versus the ethnic majority (all comparisons between ethnic groups were restricted to controls to provide population-representative estimates since the cases would over-represent ethnic minorities).

To test the hypothesis of an association between *any* experience of major discrimination and case-control status, we used mixed-effects logistic regression models while accounting for clustering by catchment site. Inverse probability weights were used to account for oversampling of minority ethnic groups among the controls relative to the populations at risk. First, a parsimonious model adjusting for age and sex was constructed. Next, a fully adjusted model taking measured confounding variables into account was fitted (i.e., age, sex, parent social class, parent history of psychosis, cannabis use). These confounders were chosen *a priori* based on our literature review. A sensitivity analysis was conducted to substitute parent social class with participant social class.

To test the hypothesis of a dose-response association for number of types of discrimination and case-control status, we constructed the next model by treating the number of types of major discrimination (0, 1, 2, 3+) as an ordinal variable to test the linear trend and then as indicator variables to assess the odds ratio for each number of types.

To test the hypothesis that the binary and dose-response associations between perceived discrimination and case-control status were stronger among minority ethnic groups compared with the ethnic majority, each association was tested for modification by ethnic group by (i) running the analyses separately among minority ethnic groups and the ethnic majority (stratification) and (ii) assessing whether addition of cross-products between ethnic group and case status improved the fit of the model (likelihood ratio test).

Finally, to test the hypothesis that more types of discrimination partially explained the association between minority ethnic status and case-control status, exploratory mediation analysis was conducted by specifying ethnic group as the independent variable, case status as the dependent variable, and a binary variable of three or more versus two or fewer types of major discrimination as the mediating variable. We consider these analyses as exploratory since we are using data collected at a single moment of time that limit inferences about temporal ordering and also cannot adjust for exposure-mediator, exposure-outcome, and mediator-outcome confounding. This mediation model did not allow for adjustment for clustering by catchment site or sampling weights for the oversampling of minority ethnic groups among the controls. Bootstrapping was used to generate bias-corrected confidence intervals (1000 repetitions, seed specified as 1234) (Valeri & VanderWeele 2014; VanderWeele & Vansteelandt 2010). The odds ratios reflecting total effect (OR^{MTE}), natural direct effect (OR^{NDE}) and natural indirect effect (OR^{NIE}) are used to be consistent with the terminology of mediation analysis, not to imply causality. The proportion mediated was calculated by using the formula $(OR^{NDE}*(OR^{NIE} - 1)) / (OR^{NDE}*OR^{NIE} - 1)$ (VanderWeele & Vansteelandt 2010).

Results

The final analytic sample was 2,507 participants, of which 41.5% were cases (69.7% non-affective psychosis, 28.3% affective psychosis, 2.0% unspecified psychotic diagnoses) and 27.3% were classified as members of minority ethnic groups. Cases and controls differed on all measured sociodemographic characteristics. Cases were more likely to be younger ($t(2503)=10.2$, $p<0.001$), men ($\chi^2(1)=50.2$, $p<0.001$), from a minority ethnic group ($\chi^2(1)=66.5$, $p<0.001$), have parents who had psychosis ($\chi^2(1)=42.6$, $p<0.001$), have parents who were

working-class or long-term unemployed ($\chi^2(3)=23.9$, $p<0.001$), and have ever used cannabis ($\chi^2(2)=94.2$, $p<0.001$) (Table 1).

[Insert Table 1 here]

Lifetime Prevalence of Perceived Experiences of Major Discrimination

Over a third (37.3%) of participants reported any perceived experience of major discrimination, and this was higher in cases than in controls (41.8% vs. 34.2%, $\chi^2(1)=15.3$, $p<0.001$) and in minority ethnic groups than the ethnic majority (45.8% vs. 31.0%, $\chi^2(1)=23.9$, $p<0.001$, restricted to controls). Only 7.9% of participants reported pervasive experiences of discrimination (i.e. ≥3 different types of major discrimination), and this was higher in cases (11.3% vs. 5.5% in controls, $\chi^2(3)=33.7$, $p<0.001$) and minority ethnic groups (9.4% vs. 4.4% in ethnic majority, $\chi^2(3)=36.9$, $p<0.001$, restricted to controls). See Supplemental Table 1 for prevalence of the 12 individual types of major discrimination in the total sample, by case/control status, and by ethnic group status. See Supplemental Figure 1 for prevalence of the perceived reason for experiences of major discrimination (i.e. ethnicity, age, gender, mental illness, religion, sexuality, other) in the total sample, by case/control status, and by ethnic group status.

Association Between Any Experience of Major Discrimination and Psychosis

The unadjusted, age- and sex-adjusted, and fully adjusted models for the associations between major discrimination and psychosis are presented in Table 2. After adjusting for age, sex, parent social class, parent history of psychosis, and cannabis use, there was no evidence of a difference in odds of psychosis after experiencing any major discrimination compared with no discrimination (OR=1.20, 95% CI: 0.91-1.59).

Dose-Response Association of More Types of Major Discrimination and Psychosis

In fully adjusted models, there was a dose-response association between more types of major discrimination and increasing odds of psychosis (OR: 1.16, 95% CI: 1.02-1.31). Participants reporting pervasive experiences of major discrimination (i.e. ≥ 3 types) had 1.79-fold greater odds of psychosis than those who experienced no discrimination (95% CI: 1.19-2.71).

Differences in Associations for Discrimination and Psychosis by Ethnic Group

In fully adjusted models, minority ethnic groups had 1.42-fold greater odds of psychosis (95% CI: 1.08-1.85) compared with the ethnic majority (Table 2). In analyses stratified by minority ethnic groups and ethnic majority group, the association between pervasive experiences of major discrimination (i.e. ≥3 types) and odds of psychosis was OR=1.73 (95% CI: 1.12-2.68) for minority ethnic groups and OR=1.42 (95% CI: 0.65-3.10) for the ethnic majority. To test for interaction, we compared results from this model with those from a model with the interaction terms (cross-product with ethnic group) using a likelihood ratio test. We found no strong evidence of interaction for pervasive experiences of major discrimination (χ^2 = 5.96, p=0.11).

[Insert Table 2 here]

In exploratory mediation analysis, pervasive experiences of major discrimination (i.e. ≥ 3 types) minimally explained the association between ethnic group and risk of psychosis. Pervasive experiences of major discrimination only accounted for a small proportion (5.1%) of the total effect of being a member of a minority ethnic group on odds of psychosis (OR^{MTE}=1.90, 95% CI: 1.55- 2.34; OR^{NDE}=1.85, 95% CI: 1.50-2.30; OR^{NIE}=1.02, 95% CI: 1.00-1.07).

All results were similar in direction, magnitude, and significance in sensitivity analyses.

Discussion

This study is the largest to date to investigate the relationship between perceived discrimination and psychosis. We extend previous investigations by including participants with a diagnosis of a psychotic disorder; an established scale that measures lifetime experiences of major discrimination that does not require attribution to race; and an ethnic majority comparison group. While over a third of participants reported ever experiencing major discrimination, a much smaller proportion (7.9%) reported pervasive experiences of major discrimination (i.e. ≥3 different types). Reporting pervasive experiences of major discrimination was associated with increased odds of psychosis of around two-fold after adjusting for measured confounders (age, sex, parent social class, parent history of psychosis, cannabis use). This is one of the first studies to show that perceived discrimination is also associated with increased risk of psychosis among the ethnic majority. Among controls, who are expected to represent the underlying source population, reporting pervasive experiences of major discrimination was twice as common among minority ethnic groups compared with those among the ethnic majority. Exploratory mediation analyses suggested that these higher levels of pervasive experiences of major discrimination might help explain a small part of the excess risk for psychosis among minority ethnic groups, and also suggest that perceived discrimination is relatively rare and only a small part of what is likely a larger constellation of social adversities that cumulatively contribute to excess risk among minority ethnic groups.

Study Limitations

The case-control design limits any inferences about causality since it is collected at a single moment of time; however, embedding the case-control study within a population-based incidence study is a powerful and efficient approach to measure exposures at the presumed onset of the outcome. Case-control studies are typically the most feasible study designs for rare

outcomes such as psychosis but are subject to recall bias. It is well established that mood-dependent recall, including due to current symptoms, influences recollection of prior life events. This is particularly a consideration in a first-episode study, where cases are identified based on current symptoms and may not yet have fully recovered. Within psychotic disorders, symptoms of paranoia in particular may influence retrospective perceptions of unfair treatment. This could lead to an overestimation of the association, including for dose-response relationships (Dohrenwend 2006). However, it would not be appropriate to adjust for paranoia as discrimination also leads to paranoia symptoms (Pearce et al., 2019) and so it is likely to be on the causal pathway between discrimination and psychosis. Some research suggests that severe events tend to be recalled better than less severe ones, as might be the case for the major experiences of discrimination reported here (Williams & Mohammed 2009). Nevertheless, current paranoia remains a major limitation as it may influence reporting of perceived lifetime experiences of major discrimination.

Ethnic group is a crude proxy of the social status of groups of people classified as members of minority ethnic groups (Bhopal 1997) and misses variability in socioeconomic status, health status, exposure to adversity, timing and context of migration and reception. This applies both across ethnic groups and across national boundaries. Nonetheless, it provides important preliminary evidence about the potential consequences of relatively lower social status and is strengthened by comparison to the ethnic majority. Clinical diagnosis of psychotic disorder required contact with specialist mental health services, which does not capture all individuals with psychosis. However, it is considered to be fairly comprehensive at measuring the treated incidence of psychosis in these countries (Jongsma et al., 2018). Importantly, using research diagnoses expands upon prior research that predominantly relied on subthreshold

psychotic experiences, which have an indeterminate relationship with subsequent psychotic disorder diagnoses. Like most research, the measure of discrimination relied on self-report. However, many of the proposed mechanisms emphasize the importance of *perceiving* treatment by society as unfair, and pervasively so. This measure has not yet been cross-culturally validated in all the countries included in this dataset. The measure also did not capture all dimensions of discrimination (e.g., structural discrimination, other forms of major discrimination, any measures of chronic, everyday discrimination, and experiences not perceived as discriminatory by the individual) and therefore likely underestimates experiences of discrimination, yet it is a more comprehensive measure than most prior studies investigating discrimination and psychosis.

Perceived Discrimination and Psychosis

These limitations noted, our finding that broadly reporting any experience of major discrimination was not associated with increased odds of psychotic disorders aligns with the one prior case-control study that also used clinical diagnoses (Veling et al., 2008; Pearce et al., 2019) and suggests this may not be a sufficient risk factor on its own. The finding that experiencing multiple types of major discrimination (i.e. pervasive experiences of discrimination) was associated with increased risk of psychotic disorders aligns with the recent systematic review that identified multiple studies that also found dose-response relationships using subthreshold psychotic experiences (Pearce et al., 2019). One of these prior studies also used the Major Experiences of Discrimination Scale, albeit a nine-item version restricted to items attributed to race or ethnicity, and also found ≥3 types of major discrimination was associated with the highest risk for psychotic symptoms (Oh et al., 2016). Social adversities such as perceived discrimination are postulated to influence risk of psychosis via both biological processes (e.g., stress dysregulation, abnormal dopaminergic functioning) (Van Winkel et al., 2013; Berger &

Sarnyai 2015; Morgan & Gayer-Anderson 2016; Misiak et al., 2017; Murray et al., 2017) and psychological mechanisms (e.g., affective dysfunction, maladaptive cognitive schema) (Bentall et al., 2014; Collip et al., 2008; Howes & Murray 2014; Morgan & Gayer-Anderson 2016; Misiak et al., 2017; Williams et al., 2018).

Study Implications

While advances in genetics and neurobiology offer critical insights into the onset and progression of psychosis, there is now growing evidence for the additional role of social adversities (Murray et al., 2017). Social adversities affect risk across groups, including the ethnic majority as demonstrated by inclusion in this study, although the relative importance of social adversities appears to be greater for minority ethnic groups. Current findings support this idea that greater experiences of social adversities such as perceived discrimination may contribute to the excess risk of psychosis among minority ethnic groups (Morgan et al., 2010; Dykxhoorn & Kirkbride 2018; Morgan et al., 2019). Recent global meta-analyses have found being a migrant and/or member of a minority ethnic group are consistently associated with increased risk of psychotic symptoms (Leaune et al., 2019) and psychotic disorders (McGrath et al., 2004; Selten et al., 2019), as confirmed in the recent EU-GEI incidence study (Jongsma et al., 2018) from which this case-control study is drawn. These rates vary both by region of ethnic origin and the specific catchment region, further supporting differences due to the social context (Termorshuizen et al. 2020). Self-reported experiences of major discrimination operationalize one aspect of potential unfair treatment for individuals perceived as members of minority ethnic groups within these contexts. Further, even when the prevalence of these types of major experiences are similar across ethnic groups with psychotic disorders, minority ethnic groups are more likely to attribute them to discrimination based on race or ethnicity (Gilvarry et al., 1999).

It is important to note that the higher prevalence of social adversities among minority ethnic groups are part of the broader fabric of racism that leads to systemic, avoidable, and unfair inequalities in power, resources, capacities and opportunities across racial or ethnic categorizations perceived as inferior (Paradies et al., 2015; Williams et al., 2019). Racism occurs simultaneously across multiple levels including structural (e.g., institutions, policies), interpersonal (between individuals), and internalized (negative beliefs and stereotypes applied to self) levels. For example, it is postulated that minority ethnic groups experience greater economic disadvantage, a sense of being a member of a devalued, low-status group, and the personal experiences of racial discrimination (Nazroo 2003). But studies including our own typically rely only on self-reported perceptions of interpersonal discrimination and therefore underestimate the full consequences of structural racism on health. The types of perceived major discrimination measured in this study hint at a further social disadvantage, as each domain can have a cascade of consequences of their own (e.g., being unfairly targeted by the police affecting employment opportunities, being unfairly fired preventing the purchase of basic needs). This may help contextualize why the exploratory mediation analysis found that discrimination only explained a small proportion of excess risk for psychosis among minority ethnic groups. It is worth considering the role of discrimination as a risk factor for psychosis among minority ethnic groups within the constellation of other social adversities (e.g., Jongsma e al. 2020).

In this context, the higher prevalence of multiple different types of discrimination among minority ethnic groups could contribute to stronger feelings of distrust and hostility, as these experiences of unfair treatment start to feel pervasive rather than isolated events (Schmitt et al., 2014). It has been posited that greater exposure to systemic social adversities over time, particularly those involving high levels of interpersonal threat, hostility, and violence, could help

explain the excess rates of psychotic disorders in some minority ethnic groups (Morgan et al., 2019). This could also be exacerbated by additional unfair treatment of members of minority ethnic groups *with psychosis*, such as more harmful entries into care (e.g., compulsory admission, police and criminal justice contact) (Halvorsrud et al., 2018). This becomes complex given the symptoms of psychosis such as paranoia, in which individuals have persistent concerns that others intend to cause them harm. It will be crucial to parse symptoms of psychosis such as paranoia and delusions from a reasonable response to prior experiences of discrimination or else risk additional harms by the very institutes that are supposed to support these individuals.

Future studies should consider how perceived discrimination fits into the broader constellation of social adversities that may interactively increase the risk of psychosis. Much of the evidence to date for the role of social adversities on risk of psychosis points to the role of early life adversities, the influence of early life adversities on later life adversities, and the cumulative experience of adversities across the life course (e.g., Varese et al., 2012; Morgan et al., 2014; Stilo et al., 2017), so it will be valuable to assess multiple social adversities simultaneously. Future studies should expand their measures of discrimination to include structural discrimination, additional domains of major discrimination, and chronic, everyday experiences of discrimination. They should also consider related consequences of perceived experiences of major discrimination, such as changes in employment, housing, and social relationships, which could lead to further social disadvantage and also increase the risk of psychosis. These future studies should consider protective factors that may attenuate the risk of psychosis among members of minority ethnic groups even after experiences of discrimination.

Conclusions

In this international investigation of psychotic disorders, pervasive experiences of major discrimination were associated with almost two-fold increased odds of a psychotic disorder. This appears to be driven in part by the much higher prevalence of pervasive experiences of discrimination among minority ethnic groups. This study bolsters prior ones by including psychotic disorder diagnoses, a more robust measure of discrimination, and an ethnic majority comparison group. Future studies should continue to investigate how additional aspects of discrimination, in combination with other social adversities, might help explain the excess risk of psychosis among minority ethnic groups.

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Table 1. Sociodemographic characteristics of the EU-GEI case-control sample by case status and by minority ethnic group status

	All (N = 2507)		**Case vs. control (N = 1040 cases)**		**Minority vs. majority (N = 683 minorities)**	
	n	**Total %**	**Case %**	**Control %**	**Minority %**	**Majority %**
Age in years*	34.1 (12.3)		31.2 (10.6)	36.2 (12.9)	31.5 (11.0)	35.1 (12.6)
Catchment site						
London	395	15.8	18.1	14.1	29.4	10.6
Cambridge	146	5.8	3.9	7.2	2.2	7.2
Amsterdam	197	7.9	9.2	6.9	13.8	5.6
Gouda/Voorhout	207	8.3	9.4	7.4	2.8	10.3
Madrid	75	3.0	3.6	2.6	1.5	3.6
Barcelona	65	2.6	2.7	2.5	0.6	3.3
Oviedo	76	3.0	2.6	2.7	1.8	3.5
Valencia	80	3.2	4.6	2.2	1.2	3.9
Créteil	154	6.1	5.2	6.8	11.4	4.2
Puy de Dôme	62	2.5	1.4	3.2	0.7	3.1
Bologna	129	5.2	6.3	4.4	2.6	6.1
Palermo	151	6.0	5.0	6.7	1.3	2.8
Ribeirão Preto	493	19.7	18.3	20.6	29.1	16.1
Santiago	65	2.6	2.6	2.6	0.1	3.5
Verona	156	6.2	4.3	7.6	0.6	8.3
Cuenca	56	2.2	1.7	2.6	0.9	2.7
Ethnic group						
White	1823	72.8	64.1	78.9	0	100
Black	279	11.1	15.8	7.8	40.8	0
Mixed	219	8.7	10.0	7.8	32.1	0
Asian	63	2.5	3.0	2.2	9.2	0
North African	67	2.7	4.1	1.6	9.8	0
Another	55	2.2	3.0	1.6	8.1	0
Sex						
Female	1177	46.9	38.6	52.9	45.8	47.4
Male	1330	53.1	61.4	47.1	54.2	52.6

	All (N = 2507)		Case vs. control (N = 1040 cases)		Minority vs. majority (N = 683 minorities)	
	n	Total %	Case %	Control %	Minority %	Majority %
Parent social class						
Professional	657	29.3	25.9	31.5	24.2	31.1
Intermediate	611	27.2	26.1	28.0	25.7	27.8
Working class	958	42.7	46.4	40.3	48.8	40.5
Unemployed	17	0.8	1.6	0.2	1.3	0.6
Parent with psychosis						
No	2145	96.1	92.9	98.3	95.5	96.3
Yes	88	3.9	7.1	1.7	4.5	3.7
Cannabis use						
Never	1128	45.7	35.6	52.8	50.2	44.1
Past use	963	39.0	42.6	36.6	32.8	41.4
Current use	376	15.2	21.9	10.6	16.9	14.6
Major discrimination						
None	1571	62.7	58.2	65.8	50.2	67.4
1 type	504	20.1	20.2	20.0	22.3	19.3
2 types	235	9.4	10.4	8.7	12.9	8.1
3+ types	197	7.9	11.3	5.5	14.6	5.3

**Mean (SD); due to missing data, n may not add to the sample totals*

Table 2. Associations between major discrimination and psychosis in the EU-GEI case-control sample

	Sample		Unadjusted		Age- & Sex-Adjusted		Fully Adjusted*	
	N	**%**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Minority ethnic group								
No	1823	72.8	*Reference*		*Reference*		*Reference*	
Yes	683	27.2	1.58	1.21, 2.07	1.41	1.06, 1.87	1.42	1.08, 1.85
Any discrimination								
No	1571	62.7	*Reference*		*Reference*		*Reference*	
Yes	936	37.3	1.27	0.91, 1.78	1.36	0.99, 1.88	1.20	0.91, 1.59
Discrimination types**								
None	1571	62.7	*Reference*		*Reference*		*Reference*	
1 type	504	20.1	1.11	0.79, 1.57	1.16	0.83, 1.62	1.08	0.77, 1.51
2 types	235	9.4	1.19	0.72, 1.96	1.30	0.78, 2.19	1.14	0.69, 1.87
3+ types	197	7.9	2.02	1.25, 3.24	2.26	1.46, 3.50	1.79	1.19, 2.71
Age	2505	99.9			0.94	0.93, 0.96	0.94	0.93, 0.96
Sex								
Female	1177	46.9			*Reference*		*Reference*	
Male	1330	53.1			1.52	1.33, 1.75	1.42	1.15, 1.76
Parent social class								
Professional	657	29.3					*Reference*	
Intermediate	611	27.2					1.18	0.91, 1.53
Working class	958	42.7					1.56	1.15, 2.12
Long-term unemployed	17	0.8					7.02	2.20, 22.44
Parent with psychosis								
No	2145	96.1					*Reference*	
Yes	88	3.9					3.52	2.39, 5.19
Cannabis use								
Never	1128	45.7					*Reference*	
Past	963	39.0					1.54	0.99, 2.37
Current	376	15.2					1.89	1.10, 3.24

DISCRIMINATION, ETHNIC GROUPS & PSYCHOSIS

**Separate models were fit for minority ethnic group, any discrimination, and types of discrimination; each model adjusted for age, sex, parent social class, parent history of psychosis, cannabis use; ORs for covariates are from the models for types of discrimination*

Perceived major experiences of discrimination, ethnic group, and risk of psychosis in a six-country case-control study

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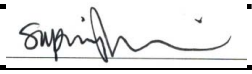
Signature*:		**Date*:**	1/22/2021

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