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Translating the epidemiology of psychosis into public mental health: evidence, challenges and future prospects

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Genetic and environmental factors are associated with psychosis risk, but the latter present more tangible markers for prevention. We conducted a theoretical exercise to estimate the proportion of psychotic illnesses that could be prevented if we could identify and remove all factors that lead to increased incidence associated with ethnic minority status and urbanicity. Measures of impact by population density and ethnicity were estimated from incidence rate ratios [IRR] obtained from two methodologically-similar first episode psychosis studies in four UK centres. Multilevel Poisson regression was used to estimate IRR, controlling for confounders. Population attributable risk fractions [PAR] were estimated for our study population and the population of England. We considered three outcomes; all clinically relevant ICD-10 psychotic illnesses [F10–39], non-affective psychoses [F20–29] and affective psychoses [F30–39]. One thousand and twenty-nine subjects, aged 18–64, were identified over 2.4 million person-years. Up to 22% of all psychoses in England (46.9% within our study areas) could be prevented if exposures associated with increased incidence in ethnic minority populations could be removed; this is equivalent to 66.9% within ethnic minority groups themselves. For non-affective psychoses only, PAR for population density was large and significant (27.5%); joint PAR with ethnicity was 61.7%. Effect sizes for common socio-environmental risk indicators for psychosis are large; inequalities were marked. This analysis demonstrates potential importance in another light: we need to move beyond current epidemiological approaches to elucidate exact socio-environmental factors that underpin urbanicity and ethnic minority status as markers of increased risk by incorporating gene-environment interactions that adopt a multi disciplinary perspective.

The search for the causes of schizophrenia and other psychotic illness, including the affective psychoses, has elucidated a new set of aetiological truisms in the last five years. First, no single gene of large effect is associated with psychosis risk. Rather, as witnessed by recent, large genome-wide association studies (International Schizophrenia Consortium *et al*, 2009), a plethora of genes – each of small effect

– are likely to shape individual risk of psychosis (O'Donovan *et al*, 2009). Second, there is likely to be considerable shared genetic liability to schizophrenia and bipolar disorder (Lichtenstein *et al*, 2009; Craddock *et al*, 2009) or, more broadly speaking, between the so-called non-affective and affective psychoses. Third, traditional heritable risk calculations for psychosis – placed at around 80–85% (Cardno *et al*, 1999) – do not solely report genetic liability, but include any gene-environment

interactions that may also be shared (van Os *et al*, 2008; McGrath & Selten, 2008). More recently, one study has revised true genetic heritability estimates to around 60% (Lichtenstein *et al*, 2009). Fourth, incidence rates of non-affective psychoses are elevated for people born, brought-up and living in more urban areas (Mortensen *et al*, 1999; Lewis *et al*, 1992; Kirkbride *et al*, 2006). Finally, incidence rates of all psychotic illnesses are raised in immigrant groups and their offspring (Cantor-Graae & Selten, 2005), independent of important confounders and biases (Kirkbride *et al*, 2008a). The exact magnitude of this risk varies by ethnicity (Fearon *et al*, 2006; Veling *et al*, 2006), gender (Kirkbride *et al*, 2008a) and along other socio-environmental gradients (Boydell *et al*, 2001), but effect sizes are estimated to be between 1.5 and 11.0; far larger than for any identified single gene and equivalent to the effect sizes associated with rare chromosomal deletions (International Schizophrenia Consortium, 2008), such as 22q11 deletion syndrome (Murphy *et al*, 1999).

These latter two points strongly suggest that a significant socio-environmental aetiology underpins schizophrenia and other psychotic illnesses (Allardyce & Boydell 2006), either through independent mechanisms, or more probably interacting with genetic susceptibility to psychosis (van Os *et al*, 2008; Mittal *et al*, 2008). Indeed, a range of socio-environmental markers measured across the life course, including discrimination (Veling *et al*, 2007), markers of social fragmentation (Allardyce *et al*, 2005; Kirkbride *et al*, 2008b), isolation (Boydell *et al*, 2001) and other forms of social disadvantage are associated with increased rates of psychotic illness (Morgan *et al*, 2008; Morgan *et al*, 2007; Werner *et al*, 2007). Psychiatric genetics has been slow to acknowledge the contribution of environmental influences on psychosis risk, despite eloquent, impassioned and empirically-rooted calls to do so (McGrath, 2008; McGrath & Richards, 2009).

Here, we had the opportunity to conduct a theoretical exercise, using data from two large, well-designed epidemiological studies of first episode psychosis to estimate the proportion of psychotic illnesses that could theoretically be prevented if we could remove the suite of factors that increased risk associated with black and minority ethnic (BME) status and urbanicity. We undertook this theoretical exercise to show:

- that the potential public mental health impact of socio-environmental factors are greater than for any genetic variant

- that socio-environmental factors are more easily preventable and modifiable than genetic factors
- and that psychiatric research should no longer consider genetic or environmental correlates in isolation (van Os *et al*, 2008).

Methods

We estimated measures of impact associated with urbanicity around the time of onset, and ethnicity, for various psychotic illnesses. Data were pooled from two methodologically-similar, robust epidemiological studies of first episode psychosis in England, based on the WHO 10-country study (Jablensky *et al*, 1992); the Aetiology and Ethnicity in Schizophrenia and Other Psychoses [ÆSOP] and the East London First Episode Psychoses [ELFEP] studies (Kirkbride *et al*, 2006; Fearon *et al*, 2006; Coid *et al*, 2008). A brief overview is provided below, with reference to the features of the present investigation (Kirkbride *et al*, 2006; Fearon *et al*, 2006; Coid *et al*, 2008).

Measures of impact

We estimated two measures of impact from our dataset for ethnicity, urbanicity and their joint effects; the population attributable risk fraction [PAR] and the attributable fraction in the exposed [AF_e]. Urbanicity was estimated using small area population density estimates (see below). The PAR provides an estimate of the proportion of cases that could be prevented if the exposure(s) under investigation could be successfully identified and removed from the population. The AF_e is the proportion of cases in the exposed group that could be prevented under the same conditions. Interpretation of these measures of impact is based on the following assumptions:

- the relationship between exposure and outcome is causal
- all confounders are known and adjusted for
- all exposures are perfectly measured
- removal of the exposure will lead to prevention of outcome.

For the purposes of this theoretical exercise, we assume that the first three assumptions are met (see *Discussion*). However, we acknowledge from the outset that the last assumption is invalid, since we are studying markers of increased risk – ethnicity and urbanicity – that act as known latent variables for a suite of unknown, underlying risk factors for psychosis. Nevertheless, this analysis remains important because it allows us to quantify the theoretical public mental health

impact that removing such factors would have on the incidence of psychosis. Given that it is socio-environmental, rather than genetic, factors that are more modifiable targets for the prevention of psychosis, our theoretical analysis serves to highlight the importance of incorporating social and environmental factors into aetiological models of psychosis risk.

Measures of impact are calculated by taking incidence rate ratios [IRR] for any risk factors of interest and combining these with the proportion of the population exposed/unexposed to such factors. We estimated two sets of measures of impact from our data; internal estimates from our dataset (set one), relevant to the population at-risk in the ÆSOP and ELFEP studies, and extrapolated estimates to the population of England (set two). Set one asks the question: if we could remove all risk factors associated with increased rates of psychoses in urban areas or BME groups, and assuming the conditions above were met, what proportion of cases in our study areas could we prevent? Set two asks the question: if we could remove these factors, what proportion of cases in England could we prevent?

Different formulae are required to answer these two questions, given their application to different denominator populations. For set one we used the formula proposed by Greenland and Drescher (1993), which produces internally-valid PAR estimates based on adjusted IRR. This formula accounts for the distribution of other co-variables in the model and can be used when you wish to estimate the joint PAR for more than one exposure. This formula cannot be used to extrapolate PAR estimates to an external population, so an alternative, classical method was adopted for set two:

$$PAR = \frac{P_e(IRR-1)}{P_e(IRR-1)+1}$$

Where P_e is the proportion of the population exposed to the factor of interest and IRR is the unadjusted incidence rate ratio. For multiple independent categorical variables (ie. ethnicity) this is extended to:

$$PAR = \frac{\sum_{i=0}^k p_i(IRR_i - 1)}{1 + \sum_{i=0}^k p_i(IRR_i - 1)}$$

Where the subscript i refers to the i th exposure level, P_i is the proportion of the source population

in the i th exposure level and IRR_i is the unadjusted incidence rate ratio in the i th exposure level (Rockhill *et al*, 1998). An assumption of this method is that there is no confounding in the data, so we could not calculate joint PAR estimates for ethnicity and urbanicity using this method.

Case ascertainment

The ÆSOP study was conducted in south east London, Bristol and Nottinghamshire; the former was exclusively urban, Bristol included urban and suburban environments and Nottinghamshire contained a mixture of urban, suburban and rural environments. The ÆSOP study was conducted over 24 months in south east London and Nottingham (September 1997–August 1999) and the first nine months of this period in Bristol. The ELFEP study was conducted in inner-city east London over 24 months in three neighbouring boroughs: City and Hackney (December 1996–November 1998), Newham, and Tower Hamlets (both December 1998–November 2000). Ethical approval was obtained from local research ethics committees in each centre.

All subjects who presented to services during the study period meeting the following criteria were included:

- aged 18–64 years
- resident within study area
- first episode of psychosis
- absence of organic basis to illness.

International Statistical Classification of Diseases 10th revision (ICD-10) (World Health Organization, 2007) diagnoses were made by consensus from a panel of clinicians. Inter-rater reliability was high (Kirkbride *et al*, 2006). We inspected case notes to exclude the possibility that subjects presented to both studies. Here, we considered three outcomes; all clinically relevant psychoses (ICD-10 F10–39), non-affective psychoses (F20–29), and the affective psychoses (F30–39).

We recorded data on age at first contact, sex, ethnicity, highest-ever occupational status and postcode. Ethnicity was ascribed to one of 16 categories from the 2001 census, as previously reported (Kirkbride *et al*, 2008a; Fearon *et al*, 2006). We collapsed this into an eight-category ethnicity variable: white British, other white ethnicities, black Caribbean, black African, South Asian (Indian, Pakistani and Bangladeshi), mixed white and black Caribbean, other mixed ethnicities and all other ethnic groups. We also considered a dichotomous ethnicity variable to calculate PAR

estimates for all BME groups versus the white British group. We assigned occupation into one of six categories provided by *The National Statistics Socio-Economic Classification* (NS-SEC) (Office for National Statistics, 2005); the occupational-based socio-economic classification used in the 2001 census (Office for National Statistics, 2003). Postcode at first-presentation was linked to Office for National Statistics' 'statistical ward' to estimate neighbourhood population density (urbanicity).

Population at-risk

For each statistical ward in the *ÆSOP* (n=180) and *ELFEP* (n=60) study, we estimated the population at-risk, aged 18–64 years, from the 2001 UK census. The census population was doubled in all centres to account for the two-year study period, except for Bristol where it was multiplied by 0.75 (nine months). Population density was estimated by dividing the total population (all ages) in each statistical ward in the 2001 census by its area (in hectares) to yield people per hectare (pph).

Statistical analyses

We conducted random intercepts Poisson regression to obtain incidence rate ratios [IRR] for population density and ethnicity. Random intercepts models acknowledge the hierarchical structure of the dataset (people within neighbourhoods), allowing the baseline incidence of psychoses to vary between wards, but assuming that the association between population density and illness is constant between wards. Population density was fitted as a continuous variable at statistical ward-level. For each outcome, we also included age (10 categories: 18–24 and subsequent five-year age bands until 55–64), sex and socio-economic status as *a priori* individual-level confounders. We treated the natural logarithm of the denominator population in each ward as an offset in our models. All modelling was conducted in Stata (version 9) using the XTPOISSON command. PAR estimates for set one were calculated using the AFLOGIT command. Since this command cannot be directly used following XTPOISSON, we refitted our models using standard Poisson modelling (POISSON command) with a clustering function included at ward level to account for intra-ward correlation. Both methods produced analogous IRR (data available from authors) and allowed us to estimate PAR estimates using the formula outlined above (Greenland & Drescher, 1993). PAR estimates for set two were calculated in Microsoft Excel.

Results

Sample characteristics

We identified 1,029 cases of any clinically relevant syndrome during over 2.4 million person-years of follow-up (equivalent to 4.0% of the population at-risk of England) (**Table 1**, overleaf). Overall, we surveyed 10.6% of the BME population aged 18–64 in England, rising to over 24% and 18% of the black African and black Caribbean populations respectively. Over 70% (n=725) of cases received a diagnosis of non-affective disorder, 26.7% (n=295) affective psychoses, with substance-induced psychoses (ICD-10 F10-19) accounting for the remainder of the sample (n=29). We did not consider substance-induced psychoses as a separate outcome in this study due to small numbers. Seventy-six per cent of cases presented to services in south east or east London, which by comparison accounted for only 57.3% of the total population at-risk.

For regression analyses, we excluded 72 people for whom ward-level population density could not be obtained, either because they were of no fixed abode (n=28) or because postcode data were otherwise incomplete (n=44). Excluded subjects were more likely to be men (Chi2 test on 1 degree of freedom: 4.56, p=0.03), but did not differ in terms of age (Wilcoxon ranksum test, p=0.69) or ethnicity (Chi2: 1.42, p=0.23) from included subjects.

Measures of impact for all clinically relevant psychoses

In our study areas, the PAR associated with BME status was 46.9% for all clinically relevant psychoses (**Table 2**, overleaf). In other words, if we could identify and remove all the exposures that increased the risk of psychoses for BME groups, we could prevent up to 46.9% of all first episode psychoses in the *ÆSOP* and *ELFEP* study regions. Extrapolating this finding to the English population, we estimated that up to 21.6% of all cases could be prevented if these factors could be identified and removed. Within BME groups themselves, this would be equivalent to the prevention of up to 66.9% of new cases (AF_e).

For specific ethnic groups, the largest impact on the overall prevention of psychoses in England would occur if we could remove the exposures that were associated with increased risk in black Caribbean (5.7%), Asian (4.9%) and non-British white groups (4.1%). The latter two groups had relatively modest increased rates of psychoses (for example, Asian unadjusted IRR: 2.3; 95% CI: 1.8, 2.8), but their relative importance in public health terms was explained by their respective population

Table 1 Sociodemographic characteristics of pooled /ESOP-ELFEP sample, by DSM-IV diagnosis

	All clinically relevant psychoses (F10–33) (%)	Non-affective psychoses (F20–29) (%)	Affective psychoses (F30–33) (%)	Substance-induced psychoses (F10–19) (%)	Study denominator* (person-years) (%)	English denominator* (person-years) (%)	% of English denominator in study
Total	1,029 (100.0)	730 (70.9)	272 (26.4)	29 (2.8)	2,404,240 (100.0)	59,981,766 (100.0)	4.0
Ethnicity							
White British	367 (35.7)	245 (33.6)	97 (35.7)	25 (92.6)	1,538,956 (64.0)	51,782,396 (86.3)	3.0
BME [†] total, of which:	662 (64.3)	485 (66.4)	175 (64.3)	2 (7.4)	865,284 (36.0)	8,199,370 (13.7)	10.6
White other	104 (10.1)	74 (10.1)	30 (11.0)	0 (0.0)	206,859 (8.6)	2,781,164 (4.6)	7.4
Black Caribbean	196 (19.1)	155 (21.2)	41 (15.1)	0 (0.0)	151,308 (6.3)	842,135 (1.4)	18.0
Black Africa	153 (14.9)	116 (15.9)	37 (13.6)	0 (0.0)	149,904 (6.2)	608,310 (1.0)	24.6
South Asian	126 (12.2)	93 (12.7)	33 (12.1)	0 (0.0)	229,699 (9.6)	2,463,683 (4.1)	9.3
Mixed white and black Caribbean	24 (2.3)	11 (1.5)	13 (4.9)	0 (0.0)	16,857 (0.7)	160,023 (0.3)	10.5
Mixed, other ethnicities	12 (1.2)	6 (0.8)	4 (1.5)	2 (7.4)	33,500 (1.4)	381,936 (0.6)	8.8
Other ethnicities	47 (4.6)	30 (4.1)	17 (6.3)	0 (0.0)	77,157 (3.2)	962,119 (1.6)	8.0
Place						Population density (people per hectare)	
South east London (/ESOP)	295 (28.7)	219 (30.0)	75 (27.6)	1 (3.7)	547,868 (22.8)	88.1	
Nottingham (/ESOP)	195 (19.0)	110 (15.1)	60 (22.1)	25 (92.6)	779,082 (32.4)	8.9	
Bristol (/ESOP)	55 (5.3)	39 (5.3)	15 (5.5)	1 (3.7)	248,740 (10.3)	24.0	
East London (ELFEP)	484 (47.0)	362 (49.6)	122 (44.9)	0 (0.0)	828,550 (34.5)	78.8	

[†]BME: black and minority ethnic

*Population at-risk estimated over two-year period in south east London, east London and Nottingham and nine months in Bristol. Data for England adjusted accordingly

Table 2 Incidence rate ratios and population attributable risks for all clinically relevant psychoses

	Adjusted IRR‡ (95% CI)	Population attributable risk fraction [PAR] (%) (Set 1)*	Unadjusted IRR (95% CI)	Population attributable risk fraction [PAR] (%) (Set 2)*	Attributable Fraction in the exposed [AFe] (%) (Set 2)*
Ethnicity					
White British	1.0 (ref)	-	1.0 (ref)	-	-
BME total [†] of which:	2.3 (2.0, 2.7)	46.9	3.0 (2.6, 3.5)	21.6	66.9
White other	1.7 (1.3, 2.1)	4.9	1.9 (1.5, 2.4)	4.1	48.2
Black Caribbean	4.1 (3.4, 5.0)	18.7	5.3 (4.4, 6.3)	5.7	81.0
Black African	3.0 (2.4, 3.7)	10.0	3.9 (3.2, 4.8)	2.9	74.4
South Asian	1.4 (1.1, 1.8)	4.6	2.3 (1.8, 2.8)	4.9	55.8
Mixed white and black Caribbean	3.5 (2.3, 5.4)	5.1	5.9 (3.8, 9.0)	1.3	82.9
Mixed, other ethnicities	1.2 (0.6, 2.1)	0.5	1.5 (0.8, 2.7)	0.3	35.5
Other ethnicities	1.7 (1.2, 2.5)	3.1	2.2 (1.9, 3.5)	1.9	54.8
Urbanicity					
Population density (1 person per hectare change)	1.003 (1.001, 1.005)	19.3	-	-	-
Ethnicity and place combined					
	-	56.6	-	-	-

[†]BME: black and minority ethnic
[‡]Adjusted incidence rate ratio [IRR] for age, sex, socio-economic status and ethnicity/place
*Set one – PAR estimates for study denominator in AESOP and ELFEP studies (see **Table 1**)
*Set two – PAR and AFe estimates extrapolated to population at-risk in England (see **Table 1**)

sizes in England (**Table 1**); a pattern reversed for the black Caribbean group. Within our study areas, a slightly different pattern emerged, with largest PAR estimates associated with black ethnic groups (Set one, **Table 2**), who made up a greater proportion of the population at-risk. We also observed very high attributable fractions in the exposed (AFe) for specific ethnic groups. Our data suggested that up to 75% of cases could be prevented in black Caribbean, black African and mixed white and black Caribbean groups, and approximately half of cases in nearly all other BME groups, if the factors associated with increased risk of psychoses in these groups could be identified and removed.

With regard to urbanicity, we estimated that if we could identify and remove all the risk factors that underpinned the association between population density and psychoses risk, we could prevent 19.3% of cases (**Table 2**). We estimated that the synergistic prevention of factors allied to both urbanicity and ethnicity would prevent 56.6% of all clinically relevant psychoses in our study areas.

Measures of impact for non-affective psychoses

For the non-affective psychoses, broadly similar PAR estimates were obtained with regard to ethnicity (**Table 3**, overleaf). The impact of population density, however, was considerably greater than before (PAR: 27.5%, **Table 3**,

overleaf), as was its combined impact with ethnicity (PAR: 61.7%).

Measures of impact for the affective psychoses

By contrast, there appeared to be no significant association between population density and the affective psychoses (IRR: 1.001; 95% CI: 0.998, 1.004; $p=0.62$). The associated PAR estimate was also small and non-significant (PAR=6.4%; $p=0.70$). However, up to an estimated 52.4% of affective psychoses could be prevented in our study population if we could identify and remove all the factors associated with the increased risk in BME populations (**Table 4**, overleaf). The equivalent figure for the population of England was 21.8%, of which the non-British white, Asian and black Caribbean groups had the largest specific PARs (5.1%; 4.8%; and 4.1% respectively).

Discussion

Principal findings

To our knowledge this is the first study to have simultaneously estimated measures of impact for the joint and independent effects of ethnicity and urbanicity on psychoses in England. Our data suggest that up to 22% of cases of all psychotic illnesses could be prevented if we could identify and remove all exposures associated with the increased risk of psychoses in BME populations in England; equivalent to a reduction of nearly 67%

Table 3 Incidence rate ratios and population attributable risks for non-affective psychoses

	Adjusted IRR [‡] (95% CI)	Population attributable risk fraction [PAR] (%) (Set 1) [*]	Unadjusted IRR (95% CI)	Population attributable risk fraction [PAR] (%) (Set 2) [#]	Attributable Fraction in the exposed [AF _e] (%) (Set 2) [#]
Ethnicity					
White British	1.0 (ref)	-	1.0 (ref)	-	-
BME total [†] of which:	2.4 (2.0, 2.9)	48.1	3.3 (2.8, 3.9)	24.0	69.8
White other	1.7 (1.3, 2.2)	4.8	2.0 (1.5, 2.7)	4.4	50.0
Black Caribbean	5.0 (3.8, 6.4)	22.4	6.3 (5.1, 7.9)	7.0	84.2
Black African	3.2 (2.5, 4.2)	10.9	4.4 (3.4, 5.6)	3.3	77.2
South Asian	1.6 (1.2, 2.1)	5.2	2.5 (1.9, 3.2)	5.8	60.2
Mixed white and black Caribbean	2.6 (1.4, 4.8)	2.9	4.3 (2.3, 7.8)	0.9	76.6
Mixed, other ethnicities	0.9 (0.4, 1.9)	-0.4	1.2 (0.5, 2.6)	0.1	14.5
Other ethnicities	1.6 (1.0, 2.6)	2.2	2.1 (1.4, 3.2)	1.7	51.9
Urbanicity					
Population density (1 person per hectare change)	1.004 (1.001, 1.006)	27.5	-	-	-
Ethnicity and place combined					
	-	61.7	-	-	-
[†] BME: black and minority ethnic [‡] Adjusted incidence rate ratio [IRR] for age, sex, socio-economic status and ethnicity/place [*] Set 1 – PAR estimates for study denominator in ÆSOP and ELFEP studies (see Table 1 , p8) [#] Set 2 – PAR and AF _e estimates extrapolated to population at-risk in England (see Table 1 , p8)					

Table 4 Incidence rate ratios and population attributable risks for affective psychoses

	Adjusted IRR [‡] (95% CI)	Population attributable risk fraction [PAR] (%) (Set 1) [*]	Unadjusted IRR (95% CI)	Population attributable risk fraction [PAR] (%) (Set 2) [#]	Attributable Fraction in the exposed [AF _e] (%) (Set 2) [#]
Ethnicity					
White British	1.0 (ref)	-	1.0 (ref)	-	-
BME total [†] of which:	2.6 (2.0, 3.5)	52.4	3.0 (2.4, 3.9)	21.8	67.1
White other	2.1 (1.3, 3.2)	6.7	2.2 (1.4, 3.3)	5.1	53.9
Black Caribbean	3.4 (2.3, 5.0)	12.1	4.0 (2.7, 5.9)	4.1	75.2
Black African	3.2 (2.1, 4.8)	9.3	3.7 (2.4, 5.8)	2.7	73.3
South Asian	1.7 (1.1, 2.6)	5.3	2.2 (1.5, 3.3)	4.8	55.5
Mixed white and black Caribbean	7.8 (4.2, 14.3)	11.1	11.4 (6.5, 20.0)	2.7	91.3
Mixed, other ethnicities	1.6 (0.6, 4.5)	1.5	1.9 (0.7, 5.2)	0.6	47.4
Other ethnicities	2.8 (1.6, 5.0)	6.5	3.1 (1.7, 5.2)	1.4	67.9
Urbanicity					
Population density (1 person per hectare change)	1.001 (0.998, 1.004)	6.4	-	-	-
Ethnicity and place combined					
	-	55.3	-	-	-
[†] BME: black and minority ethnic [‡] Adjusted incidence rate ratio [IRR] for age, sex, socio-economic status and ethnicity/place [*] Set 1 – PAR estimates for study denominator in ÆSOP and ELFEP studies (see Table 1 , p8) [#] Set 2 – PAR and AF _e estimates extrapolated to population at-risk in England (see Table 1 , p8)					

of new cases within BME populations themselves. Our data suggest that removing exposures associated with an increased risk of psychoses in black Caribbean, non-British white and Asian populations in England would lead to the greatest prevention of psychoses in the population. Within the AËSOP and ELFEP study areas themselves, PAR estimates for ethnicity were substantially higher, reflecting the concentration of BME groups in these communities. If we could identify and remove the factors associated with urbanicity for non-affective psychoses (measured here using population density) that increased incidence, we could prevent up to 27% of cases in these communities. The joint PAR for removing all risk factors associated with ethnicity and urbanicity in relation to non-affective psychoses was over 60% in our study.

Comparison with previous research

Harrison and colleagues (1997) suggested that if the factors associated with increased risk of psychoses in the black Caribbean group could be identified and removed, 19% of the overall incidence of psychoses in their study population could have been prevented. This figure was almost identical to that observed in our study for the same ethnic group (**Table 2**, p9). With regard to urbanicity, Harrison and colleagues (2003) urge that '[w]e should ... be cautious in generalizing the population attributable risk (PAR) for "urban" place of birth from estimates determined in studies carried out in one country'. Nevertheless, and with this caveat in mind, the PAR for non-affective psychosis associated with urban birth in Denmark (34.6%) (Mortensen *et al*, 1999) and the Netherlands (31%) (Marcelis *et al*, 1998) are remarkably similar to the equivalent PAR estimates for urbanicity at onset in our sample. Our data support the previous literature regarding the absence of association between affective psychoses and urbanicity (Kirkbride *et al*, 2007; Scully *et al*, 2004; Pedersen & Mortensen, 2006).

Strengths and limitations of the study

The use of measures of impact is not without controversy (Rockhill *et al*, 1998), and we recommend caution in the interpretation of our PAR estimates. In estimating PARs, a number of assumptions are made and it is salient to discuss whether these are valid here. PAR estimates assume that we have perfectly measured all other confounders and risk factors. We controlled for age, sex, socio-economic status and either urbanicity or ethnicity in our analyses, but we recognise that other, unmeasured confounders may be important,

including a family history of psychoses and other stressful life events over the life course (Morgan *et al*, 2007; Morgan *et al*, 2008). It is worth noting, however, that such 'confounders' may be the exact factors we wish to elucidate from the urbanicity and ethnicity effects. We acknowledge that it is unlikely that psychosocial risk factors are often sufficient to cause psychosis, but rather interact with neurodevelopmental or genetic vulnerability; in some cases they may not even be necessary aspects to causation. Nevertheless, we have used the best available data to estimate PARs for ethnicity and urbanicity in England and quantified the attached public mental health opportunities.

To ensure we did not extrapolate beyond our findings, we have been careful to follow guidance provided by Rockhill and colleagues (1998), including using the most appropriate method of PAR calculation given our data. We believe that the use of unadjusted IRR in our set two calculations was appropriate as there was only limited evidence of confounding by age, sex and socio-economic status (see **Tables 2–4**, pp9–10). In estimating the joint effects of ethnicity and urbanicity we did not erroneously sum PARs, but calculated their combined effects having adjusted for correlation between them.

We considered the generalisability of our findings, where possible, to the wider population of England. Given the greater concentration of BME populations in our study areas than in England as a whole, our PAR estimates were lower when applied to the rest of the country. We assumed that the increased incidence of psychoses observed in our study areas for BME groups applied to other such groups in England, given the consistent literature on this subject (Cantor-Graae & Selten, 2005). Urban populations were over-represented in our study area compared to the remainder of England, highlighting the need for future empirical studies to determine variation in incidence rates in rural populations, though our Nottinghamshire study centre included some rural populations. Our estimates provide some handle on the potential public health impact that such strategies could have. Public mental health gains may prove to be much larger if the factors that underpin raised rates of psychotic illness in BME groups or urban areas are also present in the white British group or rural populations, since removal of these exposures from the population would have an effect across all levels of exposure.

We were not able to address the public mental health challenge of substance-induced psychosis in the present study given the small sample size and

homogeneous group with respect to demographic factors. Further, our studies did not collect detailed measures of the role of substance abuse, including cannabis, in psychosis and we were, therefore, unable to address the public mental health impact of drug use associated with preventing psychotic illness. However, applying a modelling-based approach to our ÆSOP data, Hickman and colleagues (2009) have previously attempted to estimate the number of cannabis users that would be needed to prevent a single case of schizophrenia. They found that this number was at least 2,800, and probably higher, suggesting that preventing cannabis use would only have a modest effect in preventing schizophrenia.

The public mental health challenge

The public mental health estimates we have outlined here pose a considerable challenge. Ethnic minority status and urban living present two non-specific exposures that more truly index a suite of other underlying risk factors, potentially having their critical effects on psychosis at different times across the life course and, in likelihood, operating in interactive ways with predisposing genetic susceptibility and even mediated by ongoing epigenetic processes (van Os *et al.*, 2008; Tsankova *et al.*, 2007). Although understanding both the genetic and environmental correlates of severe mental illness, and their interactive effects, will be crucial to our understanding of the aetiology, management and outcome of psychosis, it is the elucidation of socio-environmental factors that will offer more tangible benefits to the prevention of illness. Socio-environmental variables are eminently more modifiable and removable from the population than any posited candidate susceptibility gene or common genetic variant, making them more readily amenable to prevention strategies. At present, designing prevention strategies that target urban living or ethnic minority status are unlikely to yield practical, meaningful or cost-effective reductions in the incidence of psychotic illness. However, our theoretical estimates serve to illustrate the public mental health importance of acknowledging the role of social and environmental factors in the aetiology of psychotic illnesses.

Our estimates also highlight two broad domains through which we should be able to more thoroughly investigate specific environmental effects on psychosis, and their interaction with susceptibility genes (Morgan & Hutchinson, 2009). We suggest that immigration and ethnic minority status, rather than urbanicity, presents

the more putative direction through which to study environmental effects on psychoses; effect sizes are generally larger, there are fewer issues associated with social drift and this risk indicator is associated with a range of psychotic illnesses that are not limited to schizophrenia. Further, epidemiological studies of migration and psychosis are now moving beyond 'immigration' or ethnic minority status as simple indicators of risk by placing these factors in a broader context. For example, there is considerable support for the ethnic density hypothesis that suggests that the risk of schizophrenia increases for ethnic minority groups as they live in communities with fewer members of their own ethnic group (Boydell *et al.*, 2001; Kirkbride *et al.*, 2008b; Veling *et al.*, 2008). In our study in south London (Kirkbride *et al.*, 2008b), we also found that greater ethnic fragmentation – the absence of residential cohesion between people of the same ethnic group in a given community – was associated with higher rates of schizophrenia, adjusted for confounders including socio-economic deprivation. There is also evidence that groups that face greater levels of discrimination (Veling *et al.*, 2008) or neighbourhoods where social cohesion (trust between neighbours) is low (Kirkbride *et al.*, 2008b) face higher rates of psychosis. This research should be instrumental in shaping putative hypotheses regarding the onset of psychosis, supporting as it does pathways that implicate chronic exposure to social stressors as important, such as the proposed dopamine hypothesis of schizophrenia. Understanding more about the social experiences of migrants and their offspring – such as the social, economic and cultural pressures faced by these groups – in combination with possible variation in genetic vulnerability to psychosis, will help us to understand which aspects of immigration and ethnic minority status are most strongly associated with psychosis risk.

Future aetiological studies of schizophrenia and other psychoses will need to be sensitive to contextual variation in the milieu of socio-environmental factors that may impinge upon the life course. Important contributions from epidemiology, genetics and the neurosciences will be needed to elucidate other complex issues in the aetiology of psychotic illnesses, including gene-environment interactions, multiple levels of causation, timing of exposure across the life course and the exact biological pathways and systems involved in the onset of psychotic symptoms. This challenge will not be easy, however, and large samples or innovative study designs will be required that synthesise methodologies and perspectives

across psychiatric research (van Os & Rutten, 2009). Large samples from prospectively-collected birth cohort studies generally represent the gold standard in this regard, but given the absolutely low incidence of psychotic illnesses these studies are likely to prove too large and expensive to achieve the sample sizes required to test the complex aetiological processes likely to be important. Fortunately, other innovative designs are emerging, including experimental 'virtual reality' studies of environmental effects (Freeman, 2008) and large multi-site case-control studies capable of testing putative gene-environment interactions (European Network of Schizophrenia Networks for the Study of Gene-Environment Interactions, 2008).

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