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| **Box S2: Principle hypotheses to explain raised rates of psychotic disorder in migrant groups and their offspring** | **Hypothesis title** | **Hypothesis description** | **TYPE OF HYPOTHESIS†** | **Proposed by (YEAR)** | **Evidence for‡** | **Evidence against‡** | **Notes** |
| H1 | Predisposition to migrate | People at genetic disposition to psychosis were more likely to migrate | Reverse causality | Ødegaard [153] (1932) | Initial observations of Ødegaard [153] | Selten *et al*.’s natural experiment rejected hypothesis [160]  Raised rates in second- (& later-? i.e. 26) generation groups (i.e.10, 86,102,S1)  Migration highly complex task for people predisposed to psychosis [194] |  |
| H2 | High rates in sending country | Elevated rates in country of origin would explain higher rates in immigrants | Reverse causality | Cochrane & Bal [S2] (1987) | None | Incidence rates of schizophrenia in the Caribbean comparable to those in host UK & Dutch population [162,163,164,S3]. Hospitalised rates in Ireland higher than those for Irish migrants to UK [S2] | Few comparative studies have been conducted other than the UK vs. Caribbean studies noted. Irish comparative study [S2] only based on hospitalized rates. Other studies would be informative i.e. rates in Morocco vs. Moroccan migrants in the Netherlands |
| H3 | Socio-demographic differences | Age, sex, martial status & socioeconomic status [SES] differences between host & immigrant groups explain differences | Confounding | Cochrane & Bal [S2] (1987) | Young, male groups over-represented in initial migrant groups. Also known to be at increased risk of psychosis [9] | Control for age & sex [10,73,86,117,149,157,S1,S4,S5, latterly SES [26,155,156]. Marital status a consequence, not cause of psychosis [S2] |  |
| H4 | Misdiagnosis of psychotic symptoms | Psychiatrists in host country may misdiagnosis psychotic symptoms in migrant groups, unfamiliar with their socio-cultural norms, or tendency to over-diagnosis migrants with schizophrenia vs. other psychotic disorders | Bias | Cochrane & Bal [S2] (1987) | Early evidence of institutionalized racism in mental health services [165], particularly with regard to pathways to care [S6].  Psychotic symptoms may be more prevalent in Caribbean migrants [S7]  Poor inter-rater reliability between English & Jamaican psychiatrist [166] | Standardized diagnoses used in research, often quasi-blind to ethnicity of subject [1].  Raised rates of psychotic disorders not limited to schizophrenia [10, 73,120].  Inter-rater reliability was poor but not racially biased [166] | Rates of psychotic disorders in migrants persisted despite improved study designs & standardized diagnoses. Separate to the problem of institutionalized racism – see [150] for controversies surrounding this area. Cultural variation in symptom interpretation needs further research |
| H5 | Migratory & post-migratory factors | Several, but involving negative consequences of migration, acculturation & post-migratory living as relevant. Stress/vulnerability is posited as potential biological mechanism. | Confounding | Cochrane & Bal [S2] (1987),  Bhugra [S8,S9] (2000, 2004),  Jones & Fung [S10] (2005) | Ethnic density effect implicates social support as protective [54,94,171]  Higher rates of psychosis in BME groups which experience greater discrimination [168]  Neighbourhoods with more ethnic fragmentation have higher rates of psychosis [97]  Social adversity confounds relationship between psychosis & migrancy [S11]  Greater impact of social disadvantage in black Caribbean migrants than white British [182] | Other purportedly stress-induced disorders not raised for immigrants (i.e. depression) [S2,S12]  Immigrants experience similar levels of stress but variation in rates of psychosis is marked [S2]  Not conclusive evidence on discrimination [170] | Cochrane & Bal’s [S2] assertion that experience of migratory factors is similar across all immigrants is unlikely to now hold given likely genetic variation in stress vulnerability & differential experiences of migration along other socio-demographic & -cultural dimensions (i.e. family structure, social support, networks) |
|  | **Hypothesis title** | **Hypothesis description** | **TYPE OF HYPOTHESIS†** | **Proposed by (YEAR)** | **Evidence for‡** | **Evidence against‡** | **Notes** |
| H6 | Life course factors & neuro-development | Factors across the life course, including pre- & peri-natally, and through childhood have greater impact in migrants. Includes vitamin D hypothesis: a change in maternal vitamin D exposure after migration alters offspring neurodevelopment | Confounding | Eagles [S13] (1991),  McGrath [S14],  Jones & Fung [S10] (2005) | Separation from parents during childhood has greater impact in black Caribbean migrants than white British [183]  Prenatal hypovitaminosis D associated with schizophrenia risk in general [193], but… | No evidence that pre - & peri-natal problems have greater role in migrant than native groups [S12]  No current evidence directly linking migration, hypovitaminosis & psychosis | Evidence is mixed, depending on type of risk factor & period of life course. Further research required. |
| H7 | Substance abuse | Greater substance misuse in migrants accounts for higher rates | Confounding | Jones & Fung [S10] (2005) | None | Little evidence cannabis used more in black Caribbean than white patients [S15] or general population (i.e. [S16,S17,S18], or substance use more generally [S19]) | Putative link between cannabis & schizophrenia [146] combined with misconception that cannabis consumption was more prevalent in black Caribbean fuelled “hypothesis” |
| H8 | Psychological hypotheses | Interpretation of life events have greater impact on psychosis in migrant groups | Mediating factor | Jones & Fung [S10] (2005) | Tendency to attribute life events to an external locus may lead to onset of paranoid symptoms in some migrant groups. Evidence is weak [S20]. | No differences in number of life events experienced by UK white vs. black Caribbean migrants [S21] | Difficult to exclude this hypothesis & may mediate or have some overlap with other hypotheses (i.e. H5, H6, H10). |
| H9 | Genetic predisposition | Genetic factors explain higher rates in migrant groups | Genetic confounding | Jones & Fung [S10] (2005) | None | Morbid risk is similar for offspring of both black Caribbean migrants & white group in UK [S22,S23]. Larger morbid risk in second-generation migrants suggests environmental, not genetics pressures alone.  Rates of psychosis in Caribbean comparable to those in host UK population [162,163,164] | Genetic factors alone are unlikely to explain differences in rates between migrants & host population but genetic susceptibility in combination with environmental exposures (i.e. interaction – see Hypothesis 10 might be important) |
| H10 | Gene-environment interactions & epigenetic processes | People with underlying susceptibility genes for psychosis at increased risk if exposed to stressful environmental factors i.e. migration & other post-migratory factors. May be regulated epigenetically i.e. changes to gene expression following changes to environmental stimuli after migration | Interaction | Rutter [S24] (2002),  Broome *et al.* [S25] (2005),  Dealberto [S26] (2007) | Little explicit evidence either way. Ethnic density effect is proxy for interaction between individual phenotype (i.e. BME status) & exposure to environmental stressors (i.e. 54,94,171). No direct study of genes vs. environment in psychosis & migrants but studies are underway [S27] | Little explicit evidence either way. | Promising avenue for future research. More studies required. |

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