Physical health among persons with untreated psychotic disorder in diverse settings of the Global South.

ABSTRACT

Background

There is limited information on the prevalence and profile of comorbid physical health conditions in persons with untreated psychotic disorder in countries of the Global South.

Aim

To investigate the frequency of occurence and association of physical health indicators with untreated psychotic disorder in three diverse settings in the Global South.

Methods

Data were collected as part of the International Research Programme on Psychoses in Diverse Settings (INTREPID II), a population-based incidence and case-control study conducted in selected catchment areas in India, Nigeria, and Trinidad. Cases were aged 18-64 years with an untreated psychotic disorder diagnosed according to ICD 10 criteria. Control participants were matched for age, sex, and neighbourhood. Physical health measurements were acquired using the WHO STEPwise approach to non-communicable disease risk factors surveillance instrument (WHO STEPS). We estimated adjusted odds ratios (aOR) using unconditional logistic regression.

Results

We included 225, 209, and 212 case-control pairs, respectively in Kancheepuram (India), Ibadan (Nigeria), and Northern Trinidad. Among cases, we found marked variations in health behaviours and physical health indicators across settings. In case-control comparisons within settings, cases were more likely to report poor diet (aORs of 1.31 [Trinidad] to 3.70 [Ibadan]), current smoking (aORs of 2.21 [Kancheepuram] to 3.35 [Trinidad]), and physical inactivity (aORs of 0.23 [Ibadan] to 0.62 [Kancheepuram]). However, we found no strong evidence that indicators of cardiometabolic comorbidity were consistently more common among cases compared with controls (i.e.,cases across

sites were less likely than controls to have high blood pressure (aORs of 0.65 [Ibadan] to 0.76 [Trinidad]) and to be overweight (aORs of 0.70 [Kancheepuram] and 0.85 [Trinidad]), but were more likely than controls to have diabetes (aOR 1.94) and raised C-reactive protein levels (aOR 2.31) in Ibadan. By contrast, cases were more likely than controls to be underweight in all sites (aORs of 1.76 [Trinidad] to 3.67 [Ibadan]). In Kencheepuram (aOR 1.60) and Ibadan (aOR 2.66), cases were more likely to have a positive blood test for infection. These findings were broadly similar after accounting for health behaviours.

Conclusion

In three settings in the Global South, persons with untreated psychotic disorder were more likely to report poorer health behaviours, to be underweight, and experience more infections, possibly reflecting severe economic and social disadvantage in the settings of this study.

Keywords: Global South; Multimorbidity; Psychotic disorder; Underserved populations.

1. INTRODUCTION

Mental disorders are often associated with physical health comorbidities *(Firth et al., 2019)*. Comorbidity of physical health problems with psychotic disorder increases disability due to both conditions and contributes to premature mortality (Olfson et al., 2015; Solmi et al., 2024). There is a three-fold standardised relative mortality increase between people with psychotic disorder and the general population (Gatov et al., 2017; Solmi et al., 2024). Much of this variance is attributable to the differential burden of physical health conditions (Liu et al., 2017; Melo et al., 2022; Olfson et al., 2015), including persisting disparities, globally, in identification and treatment of physical health comorbidities among those with psychotic disorders. These inequalities may be more pronounced in populations with less effective access to healthcare (McNamara et al., 2018), and in many low and middle income countries (LMICs) where the burden of both psychotic disorder and physical health conditions is growing (Opoku et al., 2019).

Studies conducted in Europe and North America report an association between belonging in socioeconomically deprived ethnicities and both psychotic disorder (Radua et al., 2018) and poor physical health (Quinones et al., 2019). Yet, there is limited information on the risk of comorbid physical illness in persons living with untreated psychotic disorder in settings of the Global South. Specifically, it is currently unknown whether the frequency of occurence of physical health conditions among people with untreated psychotic disorder varies according to the socioeconomic profile of the setting in which they live. The aim of the present study is to investigate the frequency of occurence and association of both self-reported and directly measured physical health indicators with untreated psychotic disorder in three diverse settings in the Global South.

Data for this study were collected as part of the International Research Programme on Psychoses in Diverse Settings (INTREPID II), a population-based incidence and case-control study conducted in selected catchment areas in India, Nigeria, and Trinidad. In India, the study took place in four urban and rural sub-districts in Kancheepuram (Chengelpettu, Thiruporur, Uthiramerur and Maduran) in southern India, near Chennai, with a total population of 997,492 residents. The settings in Nigeria included three local government areas (L.G.A) within and around the Ibadan metropolis of Oyo state in the south-west of the country, with a total population of 861,504: Ibadan North East, Ibadan South East (both predominantly urban) and Ona-Ara (a mix of rural and sub-urban areas). In Trinidad, the catchment area comprised seven municipalities spanning urban and rural areas in the North, with a total population 705,296: Port of Spain, Arima, Chaguanas, Tunapuna/Piarco, San Juan/Laventille, Diego Martin and Sangre Grande. Population data were taken from the most recent census in each

country, which was 2006 in Nigeria and 2011 in India and Trinidad. We hypothesised that: 1) the types and prevalence of physical health problems in persons with untreated psychotic disorder will vary by setting, reflecting economic categories of countries, and 2) in all settings, physical health problems will be more common in cases compared with controls.

2. METHODS

INTREPID II study procedures were approved by the ethical review boards of King's College London, London, UK; London School of Hygiene and Tropical Medicine, the Schizophrenia Research Foundation (SCARF), Chennai, India; the University of Ibadan/University College Hospital, Ibadan, Nigeria; the University of the West Indies, St Augustine, Trinidad; and the North West, North Central, and Eastern Regional Health Authorities of Trinidad.

2.1. Participants

In each catchment area, we sought to identify all individuals aged 18-64 years with an untreated psychotic disorder over a two-year period through health services, traditional and faith healers, and key informants (Roberts et al., 2020). Psychotic disorder was defined according to ICD-10 criteria, and included substance induced psychosis. Eligible participants were antipsychotic naïve or treated for less than one continuous month prior to case identification. Exclusion criteria were: transient psychotic symptoms, moderate or severe learning disability, and dementia defined by ICD-10 criteria.

Controls were matched for age (±5 years of index case), sex, and residence in the same catchment area. As no sampling frame was available to randomly select potential controls, the ten nearest neighbourhood households were mapped for each case, listing all residents by sex and age. All households were then approached in random order to identify potential controls for the case. This continued until an eligible control was identified. Exclusion criteria for controls were: current or past ICD-10 psychotic disorder, moderate or severe learning disability, and dementia as defined by ICD-10 criteria. Additional details of our case finding procedures are described elsewhere (Morgan et al., 2023; Morgan et al., 2015). Written informed consent was obtained from all eligible individuals after the procedure of the study was explained to them either in English or the local languages. Capacity to provide consent was assessed by trained researchers.

2.3. Data collection

Data on sociodemographic characteristics, past and current symptoms, including duration of symptoms, were collected from cases, relatives, and clinical records (where available). We used translated versions of the MRC Sociodemographic Schedule, the WHO Personal and Psychiatric History Schedule (PPHS) (Jablensky et al., 1992), and the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (Wing et al., 1990) for data collection. Screening for psychosis for both cases and controls was conducted using the Screening Schedule for Psychosis (Jablensky et al., 1992). For cases, the presence of psychosis was subsequently confirmed using the SCAN (Wing et al., 1990). The SCAN, which incorporates the Present State Examination, has been used extensively in previous research on psychoses across multiple settings (Gupta et al., 2013; van der Zeijst et al., 2021). Diagnoses were made by consensus based on information collected using the SCAN. Duration of untreated psychosis was assessed using the PPHS and defined as the time between onset of psychotic symptoms (ie, symptoms meeting criteria for a rating of 2 [clinically relevant] in the psychosis sections of the SCAN) and date of identification. Date of onset was derived from this, by subtracting the duration of untreated psychosis from age at identification.

All assessments were conducted by researchers fluent in the local languages after undergoing extensive training on the study protocol (Roberts et al., 2020). For relevant assessments, we conducted interrater reliability (IRR) exercises. Researchers rated videos of assessments; these were compared with ratings developed by the principal investigators. For the assessments in this article, researcher ratings were within acceptable margins of principal investigator ratings: SCAN 87% (range, 85%-88%) and PPHS 76% (range, 73%-84%).

2.4. Ascertainment of physical health indicators

We used the WHO STEPwise approach to non-communicable disease risk factors surveillance instrument (WHO STEPS) (World Health Organization, 2022) to assess diet, hypertension, diabetes, raised cholesterol, head injury, C-reactive protein, and BMI (height, which was measured in metres using a stadiometer to the nearest 0.01metres, and weight in kilograms using an electronic weighing scale to the nearest 10th). The WHO STEPS is comprised of a questionnaire and physical and biochemical measurements. We therefore had data on self-report physical health indicators and on direct measurements.

Self-report data included: receipt in the previous two weeks of, aspirin or statin for heart disease

(Heart attack, angina, cerebrovascular accident or incident), medications for hypertension, or for diabetes; physical activity (i.e., engaging in moderate or more vigorous intensity work, sports, fitness, recreation and other lifestyle activity such as walking or cycling for at least 10 minutes continuously)*;* poor diet (i.e., not eating fruit or vegetables in a typical week in the past year; collected by presenting a nutrition card depicting local fruits and vegetables and asking respondents how many times they ate fruit or vegetables in a typical week in the past year); current infection (i.e., unexplained fever that had lasted for more than two weeks); and head injury (i.e., ever suffered a head injury that caused them to be unconscious).

Direct measurements included: Hypertension (i.e., defined as an average, across three blood pressure measurements, of systolic > 130mmHg or Diastolic>85 mmHg); BMI, with underweight defined as body mass index (BMI) < 18.5kg/m^2 and overweight or obesity was defined as BMI ≥25 kg/m^2; biochemical measures, using blood samples, of blood glucose and lipid profiles (i.e., total cholesterol, high density lipoprotein cholesterol, and triglycerides) and antibodies for several infectious diseases. We recorded the time of day the blood sample was taken and whether the respondent had anything to eat or drink apart from water in the past 12 hours. Diabetes was defined as a HbA1C test of 6.5% or above. Dyslipidaemia was defined as 12 hours fasting total cholesterol of >190.0 mg/dl, high density lipoprotein cholesterol < 39.8 mg/dl for men and 50.0 mg/dl for women mg/dl, or triglycerides >150.4mg/dl. Abnormal CRP was defined as peripheral C-reactive protein of ≥5 mg/dl. Infection was operationalised by a positive blood screen for any of hepatitis C, malaria, dengue, or chikungunya.

2.5. Missing data

Data were not available for self reported infection in Trinidad. A comparison of study participants who provided a blood sample for directly measured indicators and those without blood samples is presented in Supplementary Table 1. There were no notable differences in missingness by age, gender, ethnicity, or diagnosis. The number of missing data for each physical health indicator is presented in Supplementary Table 2. Few data were missing for indirect indicators of physical health collected by interview. Substantive data (up to ~ 50%) were missing for direct indicators, reflecting rates of consent to provide blood samples.

In line with all planned INTREPID II analyses, to handle missing data and avoid dropping observations, we used multiple imputation by chained equations (Azur et al., 2011) for analyses of case-control comparisons within settings. The imputation models included all variables in the main analyses and

several auxiliary variables. All physical health variables had missing data and these were imputed, except for self report physical health in Kancheepuram. Post-imputation analyses combined estimates across 25 imputed data sets using Rubin's rule (Azur et al., 2011; White et al., 2011). For completeness, we include complete case analyses in Supplementary Table 3.

2.6. Statistical analyses

We summarised socio-demographic, heath behaviour, and physical health (self-reported, and directly measured) variables using frequencies and percentages or means and standard deviations (SD), as appropriate. We conducted unconditional logistic regression analyses to estimate adjusted odds ratios (aOR) and 95% confidence intervals (CI) for the association of psychotic disorder with six self-reported and six directly measured physical health variables. We adjusted, first, for matching variables (age and sex)and, second, for potential confounders (current smoking, alcohol use, and physical activity). We used unconditional logistic regression adjusting for matching variables as such models can be more efficient in retaining all participants in analyses and limit loss of power in situations where data for one of the matched cases or controls is missing (Pierce, 2012). Analyses were conducted using Stata MP version 16.0 (StataCorp, 2019).

3. RESULTS

3.1. Participants characteristics

We identified and recruited 225, 209, and 212 eligible cases in the Kancheepuram, Ibadan, and Trinidadian catchment areas, respectively. The demographic and clinical characteristics of cases and controls are presented in Table 1. Age and sex were similar for cases and controls, reflecting matching by these variables. Among cases, there were variations across sites in diagnosis (i.e., non-affective psychoses: Kancheepuram, 65.3%; Ibadan, 80.4%; and Trinidad, 59.9%), mode of onset (i.e., acute onset: Kancheepuram, 63.1%; Ibadan, 80.4%; and Trinidad, 51.9%), and duration of untreated psychosis (DUP) (i.e., median: Kancheepuram, 4.6 years (Interquartile range [IQR] 1.6-11.4); Ibadan, 2.2 years (IQR 0.3-5.1); and Trinidad, 1.4 years (IQR 0.1-8.2). The minimum and maximum duration of psychosis, respectively were Kancheepuram 0.05 years (i.e., 2 weeks) and 36 years, Ibadan 0.03 years (i.e., 1 week) and 26 years, and Trinidad 0.03 years (i.e., 1 week) and 44 years.

[Insert Table 1]

3.2. Frequency of physical health indicators among cases, by setting

Among cases, we found variations in frequency of occurence of reported health behaviours and physical health indicators between settings (Table 2; Figure I).

Smoking and alcohol use were more commonly reported among cases in Trinidad (46.3% and 29.8% , respectively) compared with Kancheepuram (28.4% and 13.8% and Ibadan (11.8% and 14.8%). Physical activity profiles were also better in Trinidad (69.7% compared with Kancheepuram (16.4% and Ibadan (47.5% . Of particular note, levels of physical activity (16.4%) were especially low and poor diet especially high (50.2%) in Kancheepuram.

Self reports of all indicators of poor physical health were more common among cases in Trinidad compared with Kancheepuram and Ibadan (Table 2): cardiovascular disease (7.2%), hypertension (16.8%), diabetes (7.3%), and head injury (18.6%).

Direct indicators of hypertension, diabetes and infection were more common than indicated for self report in Kancheepuram and Ibadan (Table 2; Figure 1). Using direct measures, there were notable variations across settings. For example, hypertension, being underweight, and diabetes weremost common in Kancheepuram, for some by a large percentage (e.g., hypertension: 20.8% vs. 8.9% in Ibadan and 14.7% in Trinidad; diabetes: 13.6% vs. 2.9% Ibadan and 6.5% Trinidad.

[Insert Table 2; Figure 1]

3.3. Case-control comparisons

The frequency of occurence of reported health behaviours and physical health indicators in cases and controls across settings are presented in Table 3.

[insert Table 3]

In all settings, cases were more likely than controls to be current smokers and have a poor diet (with adj. ORs of around 2 to 3 in each setting) and less likely to engage in physical activity (with adj. ORs ranging from 0.23 to 0.62) or use alcohol, especially in Trinidad and Ibadan adj. ORs=0.37 and 0.39).

(Table 4; Supplementary Table 2)

Due to low numbers reporting some indicators, we did not compare all self-reported indicators of poor physical health by case-control status. In Table 4 we present (with wide confidence intervals in some estimates): (1) lower odds of self-report hypertension among cases than controls in Kancheepuram (adj. OR0.26, 95% CI 0.13-0.53) and Ibadan (adj. OR 0.74, 95% CI 0.34-1.61); (2) lower odds of self-report diabetes among cases than controls in Kancheepuram (adj. OR 0.40, 95% CI 0.15-1.07); (3) higher odds of self-report infection among cases than controls in Ibadan (adj. OR 5.51, 95% CI 2.05-14.83); and (4) higher odds of self-report head injury among cases thancontrols in Trinidad (adj. OR 1.56, 95% CI 0.85-2.87).

Using direct measures, we found no strong evidence, in any of the settings, that indicators of cardiometabolic syndrome were consistently more common among cases compared with controls (Table 3). Rather, cases were less likely than controls to have hypertension (adj. ORs ranged from 0.31 [Ibadan] to 0.70 [Kancheepuram]), less likely to be overweight (adj. ORs 0.85 [Kancheepuram] and 0.69 [Trinidad]) and less or no more likely to have dyslipidemia (high cholesterol), diabetes, and abnormal CRP. By contrast, in Ibadan, cases were more likely than controls to have these markers (adj. ORs ranged from 1.65 for dyslipidemia to2.03 for diabetes). In all sites, cases were more likely than controls to be underweight (adj. ORs ranged from 1.44 [Trinidad] to 2.99 [Ibadan]). In Kencheepuram (adj. OR 1.61, 95% CI 0.92-2.81) and Ibadan (adj. OR 2.74, 95% CI 1.64-4.59), cases were more likely to have a current infection.

[insert Table 4]

Finally, there were no substantive differences between complete case analyses (see Supplementary Table 2) and analyses presented in Table 4 using imputed data.

4. DISCUSSION

We found distinct patterns of associations between health behaviours, physical health indicators, and untreated psychotic disorder in three diverse settings of the Global South. There were some differences in patterns and associations for self-report and direct measures, possibly indicating under-treatment and under-reporting. This noted, broadly, our findings point to worse physical health on

several, but not all, indicators for cases in Kancheepuram compared with Ibadan and Trinidad. In case-control comparisons, we found no strong evidence that cardiometabolic syndrome was more common among cases in any of the settings. However, to varying extents, in all settings cases were more likely to report poorer health behaviours, to be underweight, and experience more infections.

4.1. Methodological considerations

These findings must be interpreted with due consideration of methodological strengths and limitations. We investigated the frequency of occurence of a variety of health behaviours and physical health indicators among individuals with untreated psychotic disorder and compared these with population-based controls in three diverse settings in the Global South. We adjusted analyses first for age and sex, and then for health behaviours, including current smoking, alcohol consumption, and physical activity. Our case finding approach varied between and within settings of the study. For example, while 98.4% of cases in Trinidad were identified from biomedical mental health services, 83.6% in Kancheepuram comprised persons who were identified through community informants and, in Ibadan, 51% were recruited from traditional or faith healing facilities. It is feasible that approaches to case detection that relied on traditional and folk sector informants may be less efficient compared with identification within biomedical services. There is thus a realistic chance that we may have missed some cases with untreated psychotic disorder in some of the catchment sites.

It is important to note that, with the exception of head injury, the data on self-reports of physical health indicators is based on receipt of medication or treatment for these conditions. We note the potential for recall bias in the ascertainment of some of these indicators. As less severe concussive injuries may or may not be associated with loss of consciousness, our approach may be more likely to identify more severe head injury. Also,while unexplained fever may not always be indicative of infection, it will be highly suggestive in the settings of the present study. Data were not available for self reported infection in Trinidad. This may be partly because the country is not listed as an area with risk of human transmission of some infections, including chikungunya(Simon et al., 2023). The small overall numbers of individuals self-reporting indicators of poor physical health in the present study means there is wide uncertainty in several of these estimates. Here, persons with untreated psychotic disorder in Trinidad, almost all of whom were recruited from professional settings, reported higher levels of physical health comorbidity. In so far as self-report relies on attendance at and diagnosis by clinical services, this may reflect differences in access to health care across the sites. For example, persons living in settings with greater access to

biomedical healthcare services may be more likely to obtain information about their health status and therefore provide more reliable self-report of their health (Sen, 2002). Yet, the possibility exists that a greater disease burden may be present in the more socio-economically deprived settings where access to biomedical health care services may not be universal. Consistent with this proposition, we found higher prevalence and association of directly measured physical health conditions with untreated psychotic disorder in our Kancheepuram and Ibadan samples.

Some physical health variables had missing values, for example, when some respondents did not provide samples for blood indices. We thus could not rule out the possibility that missing or unavailable information may have affected our estimates of prevalence of the relevant physical health indications. We compared study participants who provided blood samples for directly measured indicators and those without blood samples and, because the missing data pattern was not uniform, we performed multiple imputations using the iterative chained equations approach (White et al., 2011) to impute the missing items in analyses of case-control comparisons within settings. This strategy is in line with all planned INTREPID II analyses to handle missing data and avoid dropping observations.

4.2. Physical health and psychoses

These methodological limitations noted, our findings are reflective of the global literature, suggesting a high frequency of dyslipidaemia and other cardiometabolic risk factors in the general population (Opoku et al., 2019) as well as among persons with psychotic disorder (Rodrigues et al., 2021). The frequency of occurence of these conditions has increased in LMICs relative to trends in HICs (Gaziano et al., 2010; Opoku et al., 2019). Consistent with this, we found a high frequency of both dyslipidaemia and raised C-reactive protein levels in both persons with untreated psychotic disorder and controls.

Increased frequency of dyslipidaemia and other cardiometabolic risk factors in persons with psychotic disorder may result from treatment with antipsychotic medications (DE Hert et al., 2011). However, our study population had no or very limited exposure to anti-psychotics. Consistent with findings in the present study, the pooled effect size in two previous meta-analyses (Ayerbe et al., 2018; Vancampfort et al., 2016) of studies examining the risk of hypertension in psychotic disorder did not suggest an association between the two conditions. Nevertheless, the importance of studies examining these associations in settings such as those in this report is highlighted by the fact that, while some reports in Europe and North America have suggested a genetic link between psychosis,

especially schizophrenia, and cardiometabolic risk and disease, the view has also been expressed that such link may not apply to more genetically diverse populations (Lv et al., 2022; Strawbridge et al., 2021) as may be the case in our study participants.

Globally, the association between comorbid undernutrition, including poor dietary intake and being underweight (World Health Organization, 2024), with psychotic disorder has received little attention. Existing studies in the literature are hospital based, characterised by small sample sizes and wide variations in reported prevalence (Sugawara et al., 2018). Particularly striking is the limited evidence regarding undernutrition in patients with psychotic disorder in settings outside Europe, North America, and Australia. In the present study, we found a pattern in which undernutrition was more common in Kancheepuram and Ibadan compared with the higher income setting in Trinidad. Persons with untreated psychotic disorder had between two- and four times the odds of this nutritional condition compared with controls. A previous comparative cross-sectional study investigated undernutrition in 51 incident cases of psychotic disorder and general population control pairs derived from door-to-door survey of a rural Indian community (Padmavati et al., 2010). Approximately 45.1% of subjects in that study had undernutrition compared with 13.1% in controls. Notably, the mean DUP of subjects with untreated psychotic disorder in the prior Indian study was 127 months with a range of 12 to 480 months (Padmavati et al., 2010). In the present study, participants from Kancheepuram were median ten years older than in the other sites, and had correspondingly higher DUP. While the reasons for undernutrition in psychotic disorder is not fully understood, factors such as stress, poverty and other indices of social disadvantage which are common in the context of persistently untreated psychosis may lead to reduced nutrient intake and weight loss (Fouque et al., 2008; Onu & Osuji, 2020; Sugawara et al., 2018).

The observed raised C-reactive protein levels deserve a mention. Changes in circulating CRP levels are associated with dyslipidaemia and other risk factors for cardiovascular diseases (Saito et al., 2003). Separately, increased peripheral C-reactive protein in schizophrenia has been proposed as a psychotic state dependent phenomenon (Fernandes et al., 2016; Ohaeri et al., 1993). A large meta-analysis of 26 heterogenous studies of a broad spectrum of patients with schizophrenia concluded that peripheral C-reactive protein is increased in psychotic disorder regardless of use of antipsychotics (Fernandes et al., 2016). We did not find a uniform direction of association between raised C-reactive protein with untreated psychotic disorder across sites in the present study.

To conclude, we found higher frequency of occurence of physical health conditions and strong associations with untreated psychotic disorder in diverse settings of the Global South. While conditions representing cardiometabolic risk factors did not demonstrate consistent association with psychotic disorder in these settings, persons with untreated psychotic disorder had approximately three times the odds of undernutrition when compared with neighbourhood controls who were marched for age, sex and lifestyle factors. Findings in this report may reflect the vulnerability of persons with psychosis to severe adverse social and economic conditions as well as limitations in access to evidence based diagnostic and treatment services. Further studies are needed to examine factors, beyond lifestyle choices, that drive variations in physical health comorbidity with untreated psychotic disorder in diverse settings.

CRediT author statement

Akin Ojagbemi: Formal analysis, Writing - Original Draft, Writing - Review & Editing. **Olufemi Idowu:** Data Curation, Formal analysis. **Bola Olley**: Project administration, Investigation. **Georgina Miguel Esponda:** Project administration. **Tessa Roberts**: Conceptualization, Methodology. **Sujit John**: Resources, Investigation. **Vijaya Raghavan**: Resources, Investigation, **Joni Lee Pow**: Resources, Investigation. **Casswina Donald**: Resources, Investigation. **Olatunde Ayinde**: Resources, Investigation. **Joseph Lam**: Data Curation, Formal analysis. **Paola Dazzan**: Writing - Review & Editing. **Fiona Gaughran**: Writing - Review & Editing. **the INTREPID group**: Resources. **Alex Cohen**: Conceptualization, Methodology, Writing - Review & Editing. **Helen A. Weiss**: Data Curation, Formal analysis, Writing - Review & Editing. **Robin M. Murray**: Conceptualization, Methodology, Writing - Review & Editing. **Rangaswamy Thara**: Conceptualization, Methodology, Resources, Supervision. **Gerard Hutchinson**: Conceptualization, Methodology, Resources, Supervision. **Craig Morgan**: Conceptualization, Methodology, Funding acquisition, Supervision, Writing - Review & Editing. and **Oye Gureje**: Conceptualization, Methodology, Resources, Supervision, Writing - Review & Editing.

Funding

This programme is funded by the UK Medical Research Council (MRC) (MRC Reference: MR/PO25927/1). The authors acknowledge financial support from the National Institute for Health Research (NIHR) Specialist Biomedical Research Centre for Mental Health at South London and Maudsley NHS Foundation Trust and King's College London, and the ESRC Centre for Society and Mental Health at King's College London (ESRC Reference: ES/S012567/1). This programme builds on research funded by the Wellcome Trust (WT094525). The first author (A.O.) is supported by the NIHR and Wellcome Global Health Research Partnership International Intermediate Fellowship (Ref: 220684/Z/20/Z).

Ethical Approvals

Ethical approvals for all aspects of the programme were provided by ethics review boards at each lead institution and, where necessary, by other relevant bodies. In the UK: King's College London, UK (Reference: HR-17/18-5601); London School of Hygiene and Tropical Medicine, UK (Reference: 15807). In India: Health & Family Welfare Department, Government of Tamil Nadu (Letter No.14248/EAPI-2/2018-2, Dated 28.05.2018); Institutional Ethics Committee of SCARF (Date of issue: 28.11.2017); Institutional Ethics Committee, Madras Medical College (No.19082019, Dated 06.08.2019). In Nigeria: University of Ibadan and University College Hospital Ethics Committee (Registration number: NHREC/05/01/2008a; Study number: UI/EC/18/0099), Ibadan, Nigeria; Institute for Advanced Medical Research & Training (IAMRAT), College of Medicine (Reference: UI/EC/18/0099). In Trinidad, Eastern (Reference: PHO: 24/1), North Central (Reference: 185-43 CD), and North West (approved on 9 July 2018, no reference number issued) Regional Health Authorities.

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Table 1. Demographic and Clinical Characteristics of the Cases and (as appropriate) Controls.

	Kancheepuram				Ibadan				North Trinidad			
	Cases (n 225)		Controls (n 225)		Cases (n 209)		Controls (n 209)		Cases (n 212)		Controls (n 212)	
Age (median, IQR)	44	34-50	42	35-51	34	26-41	33	25-41	31	24-40	31	23-38
	n	%	n	%	n	%	n	%	n	%	n	%
Gender												
Men	90	40.0	90	40.0	116	55.5	116	55.5	122	57.5	122	57.5
Women	135	60.0	135	60.0	93	44.5	93	44.5	90	42.5	90	42.5
Ethnicity												
Indian	225	100	225	100	-	-	-	-	41	19.3	45	21.2
Mixed	-	-	-	-	-	-	-	-	59	27.8	54	25.5
African	-	-	-	-	209	100	209	100	112	52.8	111	52.4
Other	-	-	-	-	-	-	-	-	-	-	2	0.9
Diagnosis												
Non-affective	147	65.3	-	-	168	80.4	-	-	127	59.9	-	-
Affective	9	4.0	-	-	17	8.1	-	-	81	38.2	-	-
Psychosis NOS	69	30.7	-	-	24	11.5	-	-	4	1.9	-	-
Mode of Onset												
Acute	142	63.1	-	-	156	80.4	-	-	110	51.9	-	-
Insidious	83	36.9	-	-	38	19.6	-	-	102	48.1	-	-
DUP												
<=2 yrs	66	29.3	-	-	102	49.0	-	-	114	53.8	-	-
> 2 yrs	159	70.7	-	-	106	51.0	-	-	98	46.2	-	-

Table 2. Health related behaviours and physical health indicators by setting, cases only.

	Kancheepuram[1]	Ibadan[2]	Trinidad[3]	X^2 (df)	p
Health Behaviours: Self-report	Case N=225 n (%)	Case N=209 n (%)	Case N=212 n (%)		
Current Smoker					
No	161 (71.6)	179 (88.2)	108 (53.7)	58.49 (2)	< 0.001
Yes	64 (28.4)	24 (11.8)	93 (46.3)		
Current Alcohol Use					
No	194 (86.2)	173 (85.2)	141 (70.2)	21.49 (2)	< 0.001
Yes	31 (13.8)	30 (14.8)	60 (29.8)		
Physical Activity					
No	188 (83.6)	105 (52.5)	50 (30.3)	123.12 (2)	< 0.001
Yes	37 (16.4)	95 (47.5)	136 (69.7)		
Poor Diet					
No	112 (49.8)	165 (82.1)	139 (71.3)	52.40 (2)	< 0.001
Yes	113 (50.2)	36 (17.9)	56 (28.7)		
Health Indicators: Self-report					
Medication for heart disease					
No	225 (100.0)	190 (97.4)	180 (92.8)	18.36 (2)	< 0.001
Yes	0 (0)	5 (2.6)	14 (7.2)		
Medication for Hypertension					
No	210 (93.3)	185 (93.4)	173 (83.2)	23.42 (2)	< 0.001
Yes	15(6.7)	13 (6.5)	35 (16.8)		
Medication for Diabetes					
No	219 (97.3)	192 (98.0)	179 (92.8)	8.50 (2)	0.014
Yes	6 (2.7)	4 (2.0)	14 (7.3)		
Infection[a]					
No	224 (99.6)	183 (90.1)	*	20.24 (1)	< 0.001
Yes	1 (0.4)	20 (9.9)	*		
Head Injury					
No	225 (100.0)	187 (95.4)	158 (81.4)	56.05 (2)	<0.001
Yes	0 (0)	9 (4.6)	36 (18.6)		
Health Indicators: Direct measure					
Hypertension[b]					
No	141 (79.2)	184 (91.1)	134 (85.4)	10.75 (2)	0.005
Yes	37 (20.8)	18 (8.9)	23 (14.7)		
BMI (kg/m^2)					
<18.5 (underweight)	47 (26.9)	50 (24.9)	14 (9.4)	37.93 (4)	< 0.001
18.5-24.9 (normal)	79 (45.1)	111 (55.2)	65 (43.6)		
≥25 (overweight/obesity)	49 (28.0)	40 (19.9)	70 (47.0)		
Diabetes[c]					
No	95 (86.4)	165 (97.1)	100 (93.5)	11.81 (2)	0.003

	Yes	15 (13.6)	5 (2.9)	7 (6.5)		
Dyslipidaemia[d]						
	No	30 (25.2)	44 (24.2)	41 (37.6)	6.77 (2)	0.034
	Yes	89 (74.8)	138 (75.8)	68 (62.4)		
Abnormal C- reactive protein[f]						
	No	90 (86.5)	103 (60.6)	56 (52.3)	30.33 (2)	< 0.001
	Yes	14 (13.5)	67 (39.4)	51 (47.7)		
Infection[e]						
	No	66 (55.5)	74 (43.5)	75 (69.4)	17.98 (2)	< 0.001
	Yes	53 (44.5)	96 (56.5)	33 (30.6)		

BMI= Body Mass Index,[a]Self reported unexplained fever that has lasted more than two weeks, ,[b]Systolic blood pressure >135 mmHg or diastolic blood pressure >85 mmHg, [c]HbA1C ≥6.5%, [d]Fasting total cholesterol ≥190.0mg/dl or high density lipoprotein <39.8 mg/dl for men and <50.0 mg/dl for women, or triglycerides ≥150.4mg/dl,[e]Positive blood test for hepatitis c, dengue fever, malaria, chikinguya, [f]C-reactive protein equal to or greater than 5 mg/dl,* Data not collected in Trinidad

[1] Missing Data: Kancheepuram: Hypertension (measured) 47; Diabetes 115; Dyslipidemia 106; Infection (measured) 106; CRP 121; BMI 50.

[2] Missing Data: Ibadan: Cardiovascular 14; Hypertension (self-report) 11; Diabetes (self-report) 13; Poor Diet 8; Infection (self-report) 6; Head Injury 13; Hypertension (measured) 7; Diabetes (measured) 39; Dyslipidemia 27; Infection (measured) 39 ; CRP 17 ; BMI 8; Smoking 6 ; Alcohol Use 6 ; Physical Activity 9.

[3] Missing Data: Trinidad: Cardiovascular 18; Hypertension (self-report) 18; Diabetes (self-report) 19; Poor Diet 17; Head Injury 18; Hypertension (measured) 55; Diabetes (measured) 105; Dyslipidemia 103; Infection (measured) 104; CRP 105; BMI 63; Smoking 11; Alcohol Use 11; Physical Activity 17.

Table 3. Health related behaviours and physical health indicators by setting and case-control status.

	Kancheepuram		Ibadan		Trinidad	
Health Behaviours	Case n 225 n (%)	Control n 225 n (%)	Case n 209 n (%)	Control n 209 n (%)	Case n 212 n (%)	Control n 212 n (%)
Current Smoker						
No	161 (71.6)	188 (83.6)	179 (88.2)	192 (92.3)	108 (53.7)	157 (75.1)
Yes	64 (28.4)	37 (16.4)	24 (11.8)	16 (7.7)	93 (46.3)	52 (24.9)
Current Alcohol Use						
No	194 (86.2)	187 (83.1)	173 (85.2)	167 (79.9)	141 (70.2)	107 (51.2)
Yes	31 (13.8)	38 (16.9)	30 (14.8)	42 (20.1)	60 (29.8)	102 (48.8)
Physical Activity						
No	188 (83.6)	171 (76.0)	105 (52.5)	45 (21.5)	50 (30.3)	29 (13.9)
Yes	37 (16.4)	54 (24.0)	95 (47.5)	164 (78.5)	136 (69.7)	180 (86.1)
Poor Diet						
No	112 (49.8)	154 (68.4)	165 (82.1)	197 (94.3)	139 (71.3)	168 (80.4)
Yes	113 (50.2)	71 (31.6)	36 (17.9)	12 (5.7)	56 (28.7)	41 (19.6)
Health Indicators: Self-report						
Medication for heart disease						
No	225 (100.0)	223 (99.6)	190 (97.4)	201 (97.1)	180 (92.8)	198 (95.7)
Yes	0 (0)	1 (0.5)	5 (2.6)	6 (2.9)	14 (7.2)	9 (4.4)
Medication for Hypertension						
No	210 (93.3)	175 (77.8)	185 (93.4)	187 (89.5)	173 (83.2)	156 (80.4)
Yes	15(6.7)	50 (22.2)	13 (6.5)	22 (10.5)	35 (16.8)	38 (19.6)
Medication for Diabetes						
No	219 (97.3)	206 (91.6)	192 (98.0)	205 (98.6)	179 (92.8)	196 (94.2)
Yes	6 (2.7)	19 (8.4)	4 (2.0)	3 (1.4)	14 (7.3)	12 (5.8)
Infection[a]						

No	224 (99.6)	224 (99.6)	183 (90.1)	203 (97.1)	*	*
Yes	1 (0.4)	1 (0.4)	20 (9.9)	6 (2.9)	*	*
Head Injury						
No	225 (100.0)	223 (99.1)	187 (95.4)	208 (100.0)	158 (81.4)	181 (87.4)
Yes	0 (0)	2 (0.9)	9 (4.6)	0 (0)	36 (18.6)	26 (12.6)
Health Indicators: Direct measure						
Hypertension[b]						
No	141 (79.2)	136 (71.6)	184 (91.1)	163 (78.0)	134 (85.4)	144 (79.6)
Yes	37 (20.8)	54 (28.4)	18 (8.9)	46 (22.0)	23 (14.7)	37 (20.4)
BMI (kg/m^2)						
<18.5 (underweight)	47 (26.9)	16 (8.4)	50 (24.9)	21 (10.1)	14 (9.4)	9 (4.9)
18.5-24.9 (normal)	79 (45.1)	98 (51.3)	111 (55.2)	138 (66.4)	65 (43.6)	72 (38.9)
≥25 (overweight/obesity)	49 (28.0)	77 (40.3)	40 (19.9)	49 (23.6)	70 (47.0)	104 (56.2)
Diabetes[c]						
No	95 (86.4)	76 (76.0)	165 (97.1)	120 (99.2)	100 (93.5)	122 (96.1)
Yes	15 (13.6)	24 (24.0)	5 (2.9)	1 (0.8)	7 (6.5)	5 (3.9)
Dyslipidaemia[d]						
No	30 (25.2)	17 (15.9)	44 (24.2)	44 (33.6)	41 (37.6)	39 (30.5)
Yes	89 (74.8)	90 (84.1)	138 (75.8)	87 (66.4)	68 (62.4)	89 (69.5)
Abnormal C- reactive protein[f]						
No	90 (86.5)	72 (72.7)	103 (60.6)	92 (76.0)	56 (52.3)	34 (26.6)
Yes	14 (13.5)	27 (27.3)	67 (39.4)	29 (24.0)	51 (47.7)	94 (73.4)
Infection[e]						
No	66 (55.5)	66 (61.7)	74 (43.5)	81 (66.9)	75 (69.4)	87 (68.0)
Yes	53 (44.5)	41 (38.3)	96 (56.5)	40 (33.1)	33 (30.6)	41 (32.0)

BMI= Body Mass Index,[a]Self reported unexplained fever that has lasted more than two weeks, ,[b]Systolic blood pressure >135 mmHg or diastolic blood pressure >85 mmHg, [c]HbA1C ≥6.5%, [d]Fasting total cholesterol ≥190.0mg/dl or high density lipoprotein <39.8 mg/dl for men and <50.0 mg/dl for women, or triglycerides ≥150.4mg/dl, [e]Positiveblood test for hepatitis c, dengue fever, malaria, anaemia, chikinguya, [f]C-reactive protein equal to or greater than 5 mg/dl,* Data not collected in Trinidad

[1] Missing Data: Kancheepuram: Cardiovascular 1 (1 cases, 0 controls); Raised Cholesteral 1 (0 cases, 1 control); Head Injury 2 (0 cases, 2 controls); Hypertension (measured) 82 (47 cases, 35 controls); Diabetes (measured) 240 (115 cases, 125 controls); Dyslipidemia 224 (106 cases, 118 controls); Infection (measured) 224 (106 cases, 118 controls); CRP 247 (121 cases, 126 controls); BMI 84 (50 cases, 34 controls)

[2] Missing Data: Ibadan: Cardiovascular 16 (14 cases, 2 controls); Hypertension (self-report) 11 (11 cases, 0 controls); Diabetes (self-report) 13 (13 cases, 0 controls); Raised Cholesteral 14 (13 cases, 1 control); Poor Diet 8 (8 cases, 0 controls); Infection (self-report) 6 (6 cases, 0 controls); Head Injury 14 (13 cases, 1 control); Hypertension (measured) 7 (7 cases, 0 controls); Diabetes (measured) 127 (39 cases, 88 controls); Dyslipidemia 105 (27 cases, 78 controls); Infection (measured) 127 (39 cases, 88 controls); CRP 69 (17 cases, 52 controls); BMI 9 (8 cases, 1 control); Smoking 7 (6 cases; 1 control); Alcohol Use 6 (6 cases, 0 controls); Physical Activity 9 (9 cases, 0 controls)

[3] Missing Data: Trinidad: Cardiovascular 23 (18 cases, 5 controls); Hypertension (self-report) 22 (18 cases, 4 controls); Diabetes (self-report) 23 (19 cases, 4 controls); Raised Cholesteral 54 (31 cases, 23 controls); Poor Diet 20 (17 cases, 3 controls); Head Injury 23 (18 cases, 5 control); Hypertension (measured) 86 (55 cases, 31 controls); Diabetes (measured) 190 (105 cases, 85 controls); Dyslipidemia 187 (103 cases, 84 controls); Infection (measured) 188 (104 cases, 84 controls); CRP 189 (105 cases, 84 controls); BMI 90 (63 cases, 27 control); Smoking 14 (11 cases; 3 control); Alcohol Use 14 (11 cases, 3 controls); Physical Activity 20 (17 cases, 3 controls)

Table 4. Associations between untreated psychotic disorder and physical health comorbidities in diverse settings of the global south (with imputed data).

	Kancheepuram*				Ibadan				Trinidad			
Behaviours	Adj. OR 1	95% CI	Adj. OR 2	95% CI	Adj. OR 1	95% CI	Adj. OR 2	95% CI	Adj. OR 1	95% CI	Adj. OR 2	95% CI
Current Smoker												
No	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-
Yes	2.31	1.40-3.82	2.21	1.28-3.82	1.67	0.84-3.34	3.26	1.34-7.95	2.81	1.81-4.36	3.35	2.07-5.43
Current Alcohol												
No	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-
Yes	0.72	0.40-1.32	0.65	0.33-1.25	0.67	0.39-1.16	0.39	0.19-0.80	0.44	0.29-0.66	0.37	0.24-0.59
Physical Activity												
No	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-
Yes	0.62	0.38-0.99	0.72	0.44-1.18	0.23	0.15-0.36	0.23	0.15-0.37	0.37	0.22-0.62	0.39	0.22-0.66
Poor Diet												
No	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-
Yes	2.22	1.50-3.27	1.87	1.25-2.79	3.63	1.82-7.21	3.70	1.77-7.75	1.69	1.06-2.68	1.31	0.79-2.18
Indicator: Self	Adj. OR 1	95% CI	Adj. OR 2	95% CI	Adj. OR 1	95% CI	Adj. OR 2	95% CI	Adj. OR 1	95% CI	Adj. OR 2	95% CI
Heart disease												
No	*	*	*	*	1.00	-	1.00	-	1.00	-	1.00	-
Yes	*	*	*	*	1.01	0.30-3.41	1.39	0.39-4.94	1.84	0.75-4.53	1.47	0.56-3.89
Hypertension												
No	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-
Yes	0.24	0.13-0.45	0.26	0.13-0.53	0.64	0.31-1.32	0.74	0.34-1.61	1.24	0.73-2.12	1.35	0.75-2.42
Diabetes												
No	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-
Yes	0.28	0.11-0.73	0.40	0.15-1.07	1.83	0.39-8.51	1.68	0.30-9.45	1.35	0.60-3.05	1.28	0.53-3.08
Infection[a]												

	No	*	*	*	*	1.00	-	1.00	-	*	*	*	*
	Yes	*	*	*	*	3.79	1.49-9.65	5.51	2.05-14.83	*	*	*	*
Head Injury													
	No	*	*	*	*	*	*	*	*	1.00	-	1.00	-
	Yes	*	*	*	*	*	*	*	*	1.61	0.92-2.81	1.56	0.85-2.87
Indicator: Direct													
Hypertension[b]													
	No	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-
	Yes	0.70	0.43-1.35	0.67	0.41-1.10	0.31	0.17-0.58	0.33	0.17-0.64	0.65	0.35-1.19	0.76	0.40-1.46
BMI (kg/m^2)													
	18.5-24.9	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-
	<18.5	2.83	1.55-5.16	2.55	1.37-4.74	2.99	1.69-5.29	3.67	1.97-6.82	1.44	0.60-3.46	1.76	0.68-4.54
	≥25	0.85	0.52-1.38	0.70	0.42-1.16	0.99	0.60-1.63	0.91	0.53-1.59	0.69	0.42-1.13	0.85	0.49-1.50
Diabetes[c]													
	No	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-
	Yes	0.53	0.28-1.01	0.58	0.29-1.14	2.03	0.33-12.29	1.94	0.29-12.82	1.26	0.37-4.27	1.02	0.27-3.79
Dyslipidaemia[d]													
	No	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-
	Yes	0.61	0.31-1.20	0.62	0.30-1.27	1.65	0.99-2.75	1.98	1.10-3.58	0.66	0.37-1.18	0.57	0.30-1.08
Abnormal CRP[e]													
	No	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-
	Yes	0.47	0.24-0.95	0.47	0.22-0.99	1.99	1.18-3.38	2.31	1.30-4.11	0.31	0.18-0.52	0.33	0.19-0.60
Infection[e]													
	No	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-
	Yes	1.61	0.92-2.81	1.60	0.90-2.84	2.74	1.64-4.59	2.66	1.55-4.56	0.88	0.47-1.63	0.94	0.48-1.84

Adj. OR 1: adjusted for age and sex

Adj. OR 2: adjusted for age, sex, smoking, alcohol use, physical activity, and diet

Notes: BMI: Body Mass Index, [a]Self reported unexplained feve that has lasted more than two weeks, [b]Systolic blood pressure >135 mmHg or diastolic blood pressure >85 mmHg, [c]HbA1C ≥6.5%, [d]Fasting total cholesterol ≥190.0mg/dl or high density lipoprotein <39.8 mg/dl for men and <50.0 mg/dl for women, or triglycerides ≥150.4mg/dl, [e]Positive blood test for hepatitis c, dengue fever, malaria, anaemia, chikinguya, [f]C-reactive protein equal to or greater than 5 mg/dl,*Data not collected or outcomes occurred in fewer than 10 cases and controls.

* For Kancheepuram, data on self-report physical health not imputed (very few missing data)