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Article (Accepted Version)

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**Effect of lifestyle, medication and ethnicity on cardiometabolic risk in the year following the first episode of psychosis: A prospective cohort study.**

**Fiona Gaughran\*, Daniel Stahl\*, Dominic Stringer, Poonam Gardner-Sood, David Hopkins, John Lally, Zerrin Atakan, Kathryn Greenwood, Anita Patel, Shubulade Smith, Margaret Heslin, Brendon Stubbs, Stefania Bonaccorso, Anna Kolliakou, Oliver Howes, David Taylor, Marta Di Forti, Anthony David, Robin M Murray^, Khalida Ismail^ on behalf of the IMPACT team**

**Corresponding author:** Dr Fiona Gaughran MD, FRCPI, FRCP, FRCPsych, Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience (IoPPN), King's College London, London, United Kingdom and National Psychosis Service, South London and Maudsley NHS Foundation Trust, London, United Kingdom.

Tel: +44 203 228 4418

Email: [Fiona.p.gaughran@kcl.ac.uk](mailto:Fiona.p.gaughran@kcl.ac.uk)

Fax: +44 203 28 4312

**Affiliations**

1. Dr Fiona Gaughran MD, FRCPI, FRCP, FRCP(E), FRCPsych, Lead Consultant Psychiatrist, National Psychosis Service, South London and Maudsley NHS Foundation Trust and Reader, Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, Kings College London, Denmark Hill, London, United Kingdom.
2. Dr Daniel Stahl, Senior Lecturer in Biostatistics, Biostatistics Department, Institute of Psychiatry, Psychology and Neuroscience, Kings College London, Denmark Hill, London, United Kingdom.

3. Dr David Hopkins BSc, MB, ChB, FRCP. Department of Diabetic Medicine, King's College Hospital NHS Foundation Trust, King's Health Partners, London, UK
4. Mr. Dominic Stringer, Statistician, Department of Biostatistics and Health Informatics, Institute of Psychiatry, Psychology and Neuroscience, Kings College London, Denmark Hill, London, United Kingdom.
5. Dr. Zerrin Atakan, MD, FRCPsych. Hon. Senior Lecturer, Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, Kings College London, Denmark Hill, London, United Kingdom
6. Dr Kathryn Greenwood, PhD, DClinPsy, Clinical Research Fellow, Sussex Partnership NHS Foundation Trust, and Hon Senior Research Fellow, School of Psychology, University of Sussex.
7. Professor Anita Patel Director, Anita Patel Health Economics Consulting Ltd, London UK AND Honorary Professor, Queen Mary University of London, London, United Kingdom
8. Dr Shubulade Smith, MBBS MD FRCPsych. Clinical Senior Lecturer, Department of Forensic and Neurodevelopmental Science, Institute of Psychiatry, Psychology and Neuroscience, Kings College London, Denmark Hill, London United Kingdom and Consultant Psychiatrist, Forensic Services, South London and Maudsley NHS Foundation Trust, London, UK.
9. Dr Poonam Gardner-Sood, PhD, University College London, London, United Kingdom
10. Dr John Lally, MB MSc MRCPsych, Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience (IoPPN), King's College London, London, and the Royal College of Surgeons in Ireland.
11. Dr Margaret Heslin, Research Fellow, Honorary Lecturer, Kings' Health Economics, Institute of Psychiatry, Psychology & Neuroscience at King's College London
12. Dr Brendon Stubbs, PhD, BSc (Hons), MSc, MCSP, Health Service and Population Research Department, Institute of Psychiatry, King's College London, London, United Kingdom and Physiotherapy Department, South London and Maudsley NHS Foundation Trust, London, United Kingdom
13. Dr. Stefania Bonaccorso, Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, Kings College London, Denmark Hill, London, United Kingdom

14. Dr. Anna Kolliakou, Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, Kings College London, Denmark Hill, London, United Kingdom
15. Prof. Oliver Howes, Professor of Molecular Psychiatry, MRC London Institute for Medical Sciences and Institute of Psychiatry, Psychology and Neuroscience, Kings College London, and the South London and Maudsley NHS Foundation Trust Denmark Hill, London, United Kingdom
16. Prof. David Taylor, Director of Pharmacy and Pathology; Head of Pharmaceutical Sciences Clinical Academic Group, King's Health Partners, South London and Maudsley NHS Foundation Trust
17. Dr. Marta Di Forti, MRC Clinician Scientist, Dept of Social, Genetic and Developmental Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, United Kingdom. Department of Psychiatry, Experimental Biomedicine and Clinical Neuroscience (BIONEC), University of Palermo, Italy and the South London and Maudsley NHS Foundation Trust
18. Professor Anthony S David, FRCPsych, FR CP, MD. University College London, United Kingdom
19. Professor Robin M Murray Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, Kings College London, United Kingdom. Department of Psychiatry, Experimental Biomedicine and Clinical Neuroscience (BIONEC), University of Palermo, Italy and the South London and Maudsley NHS Foundation Trust
20. Professor Khalida Ismail, Professor of Psychiatry and Medicine, Dept of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, Kings College London, Denmark Hill, London, United Kingdom

**Competing interests:**

FG has received honoraria for advisory work and lectures or CME activity support from Roche, BMS, Lundbeck, Otsuka, Janssen and Sunovion, is a collaborator on an NHS Innovations project co-funded by Janssen and has a family member with professional links

to Lilly and GSK, including shares. RMM has received honoraria for lectures from Lundbeck, Otsuka, Janssen and Sunovion. MDF has received honoraria for lectures from Janssen and Sunovion. ZA has received honoraria for advisory work and lectures from Roche, Sanofi, Lilly and Otsuka. ODH has received investigator-initiated research funding from and/or participated in advisory/ speaker meetings organised by Astra-Zeneca, Autifony, Biogen, BMS, Eli Lilly, Heptares, Jansenn, Lundbeck, Lyden-Delta, Otsuka, Servier, Sunovion, Rand and Roche. DT has received funding for lectures and research from Janssen, Otsuka, Servier, Lundbeck, Sunovion. All other authors declare they have no conflict of interest.

## Funding

This paper summarises independent research funded by the National Institute for Health Research (NIHR) under its IMPACT Programme (Grant Reference Number RP-PG- 0606-1049) in collaboration with Genetics and Psychosis Project funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. BS and FG are, in part, supported by the Maudsley Charity and the National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care South London (NIHR CLAHRC South London) at King's College Hospital NHS Foundation Trust. The views expressed in this publication are those of the authors and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health.

## **Abstract (word count=242/250)**

### **Background**

The first episode of psychosis (FEP) is a critical period in the emergence of cardiometabolic risk.

### **Aims**

We set out to explore the influence of individual and lifestyle factors on cardometabolic outcomes in early psychosis.

### **Method**

A prospective cohort study of 293 UK adults presenting with FEP investigating the influence of socio-demographics, lifestyle (physical activity, sedentary behaviour, nutrition, smoking, alcohol, substance use), and medication on cardiometabolic outcomes over the following 12 months.

### **Results**

Rates of obesity and glucose dysregulation rose from 17.8% and 12% respectively at baseline to 23.7% and 23.7% at one year. Little change was seen over time in the 76.8% tobacco smoking rate or the quarter who were sedentary for over 10 hours daily. We found no association between lifestyle at baseline or type of anti-psychotic medication prescribed with either baseline or one-year cardiometabolic outcomes. Median Hba1c rose by 3.3 mmol/mol in participants from Black and minority ethnic (BME) groups, with little change observed in their white counterparts. At 12 months, one third of those with BME heritage exceeded the threshold for pre-diabetes (HbA1c >39mmol/mol).

### **Conclusion**

Unhealthy lifestyle choices are prevalent in early psychosis and cardiometabolic risk worsens over the next year, creating an important window for prevention. We found no evidence however that preventative strategies should be preferentially directed based on lifestyle habits. Further work is needed to determine whether clinical strategies should allow for differential patterns of emergence of cardiometabolic risk in people of different

ethnicities.

**Key words:** First episode psychosis, cardiometabolic risk, weight, glucose dysregulation, ethnicity

Word count 3899/4000

## **Introduction**

People with psychotic illnesses die prematurely, mostly from natural causes, with markedly raised standardized mortality ratios for cardiovascular disease (3.6; 95%CI, 3.5-3.6), with young adults (4.5; 95%CI, 4.1-4.8), women (4.6; 95%CI, 4.5-4.7), and people of white ethnicity (4.9; 95% CI, 4.8-5.0) especially at risk (1). Cardiometabolic dysregulation is evident even from the early stages of psychosis (2) and increases in the months after first presentation, with olanzapine having the most marked effect (3). Clozapine also affects metabolism, with 55% exhibiting glucose dysregulation within three months of starting (4). A recent meta-analysis reported that antipsychotics were associated with greater weight gain in Asian as opposed to Western studies, although very few studies looked directly at the effects of ethnicity (5). Evidence is needed to determine whether or not interventions to modify cardiometabolic risk can be targeted in first episode psychosis (FEP). Few studies have investigated whether health behaviours at presentation including diet, physical activity and substance use *predict* subsequent deterioration in cardiometabolic status. An exception is a recent prospective study of 101 people with FEP (6) which found that low aerobic fitness was a significant risk factor for metabolic syndrome (MetS). Overall however, insufficient prospective observational studies have attempted to disentangle the impact of lifestyle on the emergence of cardiometabolic risk to reliably inform the development and targeting of effective preventative strategies.

The main aims of this study were therefore to a) to determine the prevalence of cardiometabolic risk factors in an ethnically diverse population at first presentation with psychosis; b) to describe the emergence of additional cardiometabolic risk over the year following first presentation with psychosis and c) to determine the relationship between

lifestyle factors (diet, sedentary behaviour, smoking, substance use) and antipsychotic medication, in particular olanzapine and clozapine use, on cardiometabolic risk both at baseline and at 12 months follow up. We hypothesised that there would be an association between baseline lifestyle choices and (a) cardiometabolic risk at baseline and (b) prospectively in change in cardiometabolic risk over a one-year follow-up period. We also hypothesised that the emergence of glucose and lipid dysregulation would be greater in those prescribed the dibenzodiazepines, clozapine or olanzapine, compared to other antipsychotics.

## **Methods**

### **Setting and Design**

A prospective observational cohort of people was followed up for 12 months after their first presentation with psychosis. The study took place in inpatient and Early Intervention in Psychosis community mental health teams in three English Mental Health NHS services.

### **Eligibility criteria**

Inclusion Criteria were as follows: a) aged between 16 and 65 years; b) within 6 months of first presentation with psychosis (ICD-10 codes F20-29 and F30-33) c) proficient in English with no requirement for an interpreter. Patients were excluded if they were pregnant or had a major medical illness or neurological disease; diagnosed severe learning disability; an organic cause for their psychosis; or previous contact with health services for the presence of psychosis. All participants were included in the study only after giving written, confirmed consent. The study protocol was approved by the Joint South London and Maudsley and the Institute of Psychiatry NHS Research Ethics Committee (08/H0807/53).

### **Assessments**

Patients were assessed at baseline and after 12 months. Sociodemographic data were recorded at baseline, namely age, sex, ethnicity (self-report) and years of education. The operational criteria checklist for psychotic and affective illness (OPCRIT) was used to assess type of mental health state over the lifetime (7). All other measures were recorded at both time points. Selected clinical measures unaffected by fasting state (weight, blood pressure,



HbA1c, cholesterol, HDL) were recorded where available and utilized in analyses at baseline if the relevant measure post-dated the onset of psychosis and preceded the research measures, being thus less likely to have been affected by the introduction of psychotropic medication. Follow-up clinical measures were utilised if research measures for that period were missing.

### **Psychopathology**

Mental health status was measured using the Positive and Negative Symptom Scale (PANSS) (8), Global Assessment of Functioning (GAF) (9), Clinical Global Impression Scale (CGI) (10), Calgary Depression score (11), and the Young Mania Rating Scale (YMRS) (12).

### **Pharmacological History**

Type(s) (British National Formulary definitions) of psychotropic medication and duration of antipsychotic (in days) were retrospectively extracted from electronic medical records.

### **Cardiometabolic measures**

Metabolic measures comprised anthropometric measures of weight, height, body mass index (BMI), waist circumference and blood pressure (BP), as well as fasting blood samples for glucose, glycated haemoglobin (HbA1c), lipids and c-reactive protein (CRP). Standardized techniques were used to measure height, blood pressure and weight. Where available, the BP values are the second BP measurements (first reading presented in 75/219 participants at baseline; and 39/147 at 12 months). Waist circumference was measured at the umbilicus with the patient standing.

Obesity was defined by the World Health Organisation (WHO) reference standard (BMI  $\geq 30$  kg/m<sup>2</sup>) and overweight as BMI  $\geq 25$  kg/m<sup>2</sup> (WHO [http://www.who.int/healthinfo/indicators/2015/chi\\_2015\\_67\\_adults\\_overweight.pdf?ua=](http://www.who.int/healthinfo/indicators/2015/chi_2015_67_adults_overweight.pdf?ua=)). Diabetes was diagnosed based on a HbA1c of  $\geq 48$  mmol/mol ( $\geq 6.5\%$ ), or a fasting glucose  $\geq 7.0$  mmol/l or a prior diagnosis of diabetes. In keeping with recent guidance from the American Diabetes Association, an HbA1C of 39-47 mmol/mol (5.7-6.4%) was taken to indicate glucose dysregulation or a high risk of diabetes (13). The IDF definitions of other

cardiometabolic risk factors were used (14). Insulin resistance was presented using the homeostasis model assessment (HOMA-IR), calculated from fasting glucose and insulin levels. Inflammation was estimated using high sensitivity C-reactive protein (CRP) as a marker.

### **Physical activity and Dietary intake**

Physical activity was assessed by the International Physical Activity Questionnaire (15), which has been validated in psychosis (16). The self-report Dietary Instrument for Nutrition Education (DINE)(17) was used to assess dietary patterns over the previous week. Additional questions were included to account for sugar intake, the consumption of take-away food, carbonated drinks and adding either salt or sugar to food/drinks.

### **Substance use**

Cigarette and tobacco consumption was measured using the Nicotine Dependence questionnaire (18) and alcohol use with the Alcohol Use Disorders Identification Test (19), where scores of 8 or more indicate hazardous and harmful alcohol use. A modified Cannabis Experience Questionnaire (CEQ-4) was used to enquire about lifetime and current use of substances (20, 21) and a urine drug screen requested.

### **Statistical Analysis**

Descriptive data are presented in tabular form. Pairwise comparisons were done using t-tests for continuous and chi-squared tests for categorical outcomes.

Baseline associations between continuous scores for lifestyle and cardiometabolic factors were investigated using unadjusted and adjusted linear regression models. To account for different patterns of missingness, we used multiple imputation by chained equations prior to these analyses, using the lifestyle factors (DINE Saturated Fat Score, AUDIT Hazardous Drinking score, Number of hours sitting per day and whether taking Olanzapine), cardiometabolic factors (Cholesterol, Diastolic Blood Pressure, HbA1c, Waist Circumference, BMI, HDL and Triglycerides), age, gender, ethnicity and pre-baseline number of days on antipsychotic medication in the multiple imputation model. We used the **mi impute chained**

command in Stata version 15.1, with 50 imputed datasets for each MI model. Binary variables were imputed using logistic regression, using augmented logistic regression where perfect prediction was detected (22). Continuous variables were imputed using linear regression unless they appeared non-normal, in which case the predictive mean matching imputation method, drawing from 5 nearest neighbours, was used (23).

Imputed datasets were then used to examine cross sectional associations between each lifestyle factor and cardiometabolic factor separately using linear regression, unadjusted and adjusted for pre-specified potential confounders of CVD risk, namely age, gender, ethnicity and pre-baseline number of days on antipsychotic medication. We further explored the cross-sectional associations between use of dibenzodiazepine medications (yes/no) prior to baseline and cardiometabolic factors at baseline using the same model and potential confounders.

For each outcome (change in cardiometabolic factor) at 12 months we employed separate multiple imputation models (using the same method as above) using the outcome and the same variables at baseline. We then explored for each baseline lifestyle factor, separately, whether they were associated with change in cardiometabolic factors over the 12 months follow up period, unadjusted, and then adjusted for the above potential confounders, investigating associations between use of dibenzodiazepine medications between baseline and 12 months (yes/no) and cardiometabolic factors in the same way.

We separately assessed whether cardiometabolic factors at baseline differed between a) medicated participants with less or greater than 14 days of antipsychotic medication prior to baseline and b) medicated and un-medicated participants prior to baseline.

To account for multiple testing a stricter alpha of 0.01 was pre-specified as the significance level (24). Tests with a p value between 0.01 and 0.05 were discussed as a trend and conclusions should be treated as explorative. Sensitivity analyses were carried out for all the analyses using complete cases from the full dataset, and also using a reduced dataset (with only participants with <5 variables of interest missing) prior to using multiple imputation to check the extent to which the original multiple imputation was plausible.

## **Results**

We screened 11705 for eligibility; 971 were eligible of whom 321 (32.1%) consented to participate (263 declined, 50 transferred, 337 uncontactable). Twenty-eight were excluded after consent when further information became available, leaving 293 eligible people, (mean (SD) age, 30.6 (10.5) years) in the study at baseline, 46.4% of whom were of white ethnicity; 36.9% black and 7.8% Asian. Sixteen withdrew at baseline, and 251 completed baseline measures with 26 remaining in the study but missing or declining data collection at that timepoint. A further 10 participants withdrew during the study, one died and 140 dropped out (51 uncontactable, 73 declined, 11 missed and 5 in prison), with 125 completing 12-month follow-up assessments. Demographic and clinical characteristics are reported in supplementary table 1.

Twelve-month follow up was completed on 125 patients with additional selected anthropometric and blood measures taken from clinical records where available and required. There were no differences in baseline demographics or cardiometabolic measures between those who had 12-month follow up assessments (N=125) and those who did not (N=168) (supplementary table 4).

### **Cardiometabolic and lifestyle factors in the year following onset of psychosis**

Rates of obesity, hypertriglyceridaemia, diabetes, raised CRP, and low HDL cholesterol all rose over the first year of illness, while the proportion of people with HbA1c in the glucose dysregulation range almost doubled (tables 1, 2, supplementary tables 2, 7 and figure 1;). Rates of tobacco smoking were high (tables 2, 3); smokers consumed a median of 10 cigarettes per day, with little change over time. Combining both self-report and urinary drug screen data, 49.5% (102/206) of participants were current users of cannabis at baseline, while 23/183 (12.6%) reported current usage of 'other recreational drugs'. The corresponding figures at 12 months were 38.1% (40/105) and 12/102 (11.8%) respectively. From baseline to 12 months, 12 (11.3%) participants initiated cannabis use while 16 (15.5%) stopped using cannabis.

Data were available on antipsychotic prescriptions prior to baseline for 242 (82.6%) participants. 22% (54/242) were antipsychotic free before baseline, while a further 65

(26.9%) had received antipsychotics for less than 2 weeks. The median duration of antipsychotic treatment for those prescribed antipsychotics pre-baseline was 21 days (IQR 9.0-55.5 days) (mean (SD) =43.3 days (53.3)), with most (94.7%; n=178/188) prescribed second-generation antipsychotics. Overall, 128 people were prescribed olanzapine across the year, 102 as their first anti-psychotic. Of those on olanzapine at baseline (N=89; median dose 10mg (IQR, 10, 75; range 2.5-25)), 71% (52/73) remained on olanzapine at follow-up. At follow-up, 66 people were prescribed olanzapine, at a median dose of 12.5mg (N=45, IQR 10, 17.5; range 2.5-30). All but 15 had been prescribed anti-psychotic medication over the course of the study, for a median of 378 (IQR 302-434)/mean of 354.6 (SD 138.9) days, with those receiving olanzapine prescribed it for a median of 236 (IQR 61-388)/ mean of 239.6 (SD 169.8) days. No patients were prescribed clozapine. We did not have data on somatic medications prescribed over the course of the follow-up.

Participants medicated prior to baseline had higher baseline average waist circumferences (+7.7 cm [95% CI: 2.0,13.4], p=0.009) compared to those unmedicated. Those who had received over two weeks antipsychotic medication prior to baseline had higher total cholesterol (+0.5 mmol/L [0.1, 0.8 95% CI]) (p=0.007) than those prescribed antipsychotics for less than 2 weeks (excluding those prescribed no antipsychotic) (Supplementary Table 3).

At baseline, 57% consumed a carbonated drink daily, half (50%) drinking more than one 500ml bottle per day, while 21.4% of the total sample drank diet carbonated drinks daily. Three-quarters (75.7%) consumed tea on a daily basis, most (90.8%) taking more than one cup, with 44% of the sample adding 2 teaspoons or more of sugar to each cup of tea. Salt was added to food during cooking by 66.5% of participants. 78.5% of the sample consumed take-away meals, three-quarters of whom (75.8%) did so more than once weekly.

### **Relationship between lifestyle/medication and cardiometabolic outcomes at baseline and 12 months follow up.**

Baseline DINE fat scores, sedentary behaviour, AUDIT scores and pre-baseline olanzapine use were not significantly associated with any of the baseline cardiometabolic outcomes either unadjusted or after adjusting for potential confounders (supplementary table 6). Nor did the

linear regression models show any association between baseline lifestyle factors and change in any of the cardiometabolic outcomes over 12 months either unadjusted or after adjusting for potential confounders (table 4). Nor was there evidence of a difference in change in cardiometabolic outcomes by 12 months between those participants prescribed olanzapine between baseline and 12 months and those not (unadjusted and adjusted) (table 4).

Sensitivity analyses using complete cases only gave similar results with no evidence of any associations. Sensitivity analyses using a reduced dataset prior to imputing also gave similar results.

### **Effects of gender and ethnicity**

Rates of central obesity at baseline were higher in women (62.7%; n=37/59) than in men (35.3%; n=36/102), ( $\chi^2= 11.34$  p=0.001), with a trend towards women from BME groups having larger waists than their white counterparts (t=2.37, p=0.02), this gap increasing over time in the paired sample subgroup (supplementary table 5). White men overall gained a mean of 4.9cm in waist circumference over the year, while men from black and minority ethnic (BME) groups gained 1.6cm ( table 3), with similar findings in the paired sample subgroup (supplementary table 5). There was no relationship between ethnicity and BMI. There was a trend towards lower total cholesterol at 12 months (p=0.04) in BME patients.

Though HbA1c levels at baseline were comparable, BME patients exhibited a significant increase in median HbA1c levels over 12 months (p<0.01), rising by 3.3 mmol/mol. In contrast, no change was evident in white patients (table 3). Where only complete paired datasets were included in the analysis, median HbA1c rose in white patients by 1.1 mm/mol and by 3.3mmol/mol in participants from BME groups (supplementary table 5). HbA1c levels above 39mmol/mol were seen in 10% (4/40) of white participants and 34% (18/53) of those from BME groups at 12 months. There was no significant difference in ethnicity between those prescribed olanzapine and those not ( $\chi^2(3)=3.10$ , p=0.376).

### **Discussion**

This comprehensive large-scale cohort study of patients with first episode psychosis prospectively considers the relationship between lifestyle factors, medication and cardiometabolic trajectories. Weight gain is the most obvious problem for many patients both cosmetically and for their health – here 17.8% were obese at onset, rising to 23.7% within one year. A case has recently been made for obesity to be recognised as a chronic disease (25) to allow the preventative strategies needed at a population level; in psychosis, the rapidity of weight gain over the first year offers an unrivalled opportunity for prevention, with diet, exercise and medication being key targets. We noted high consumption of saturated fat, carbonated, high-sugar drinks, sweetened beverages and added salt. Calorie intake was further augmented by alcohol use (Table 2). Although neither fat intake nor alcohol use in the early weeks of psychosis predicted longer term outcomes in our population, the Keeping the Body in Mind program has successfully worked with dieticians and exercise physiologists to prevent weight gain using lifestyle interventions for all early in the disease process (26).

We also found early emergence of glucose dysregulation; by one year twice as many people had HbA1c levels at or above the ADA glucose dysregulation range (Tables 1, 2). Diabetes is highly predictive of cardiometabolic disease and can have especially significant health impacts in people with psychosis, given the other practical challenges they may face.

There was a remarkably high baseline prevalence of tobacco smoking of 76.8%. Smoking confers an almost five-fold risk of mortality in people with schizophrenia (27). Further, nicotine dependence after psychosis onset predicts both poor medication adherence and non-remission of psychosis (28). It is therefore worrisome that we saw little reduction in smoking rates over time. Since this work was completed, many UK mental health hospitals have become smoke free environments (29) and although a recent trial has demonstrated that smoking cessation can be achieved in the community, work remains to be done to sustain quitting (30). Rates of current cannabis use and lifetime use of other substances were high, in keeping with previous work (20).

People with psychosis engage in low levels of physical activity (31). Although physical activity at baseline did not predict cardiometabolic outcome in our study, by 12 months 40% of the sample were engaging in the 150 minutes of physical activity per week recommended by the World Health Organisation (WHO, 2014). Worryingly however, sedentary behavior changed

little and CRP levels increased over time. Sedentary behavior is associated with inflammation in psychosis (32), while inflammation is in turn linked to cardiometabolic disease (33). Both exercise and sedentary behavior are important targets for health promotion with studies underway to examine ways of changing patterns of behavior in clinical settings (34).

Our regression analyses revealed no relationship between cardiometabolic outcomes and lifestyle, nor any effect of dibenzodiazepine medication, despite the high risk of weight gain demonstrated with olanzapine in other settings (3). A high proportion were prescribed olanzapine as a first anti-psychotic, a practice now not recommended (35). Of note, no participants were prescribed clozapine in the first year of their illness, in keeping with the reported mean lag time to starting clozapine of 47.7 months (SD = 49.7) (36). The omission of clozapine is noteworthy as 23% of people presenting with their first episode of psychosis are treatment resistant from illness onset (37).

Our sensitivity analyses illustrated the rapidity of cardiometabolic change in early psychosis; those exposed to antipsychotic medication for more than 14 days before baseline had higher cholesterol levels than those on antipsychotics for less than a fortnight, whilst those exposed to any antipsychotic medication had a larger waist circumference at baseline than did the antipsychotic naive.

### **Effects of ethnicity and gender**

Males of white ethnicity appeared to have a particular vulnerability to emergence of central obesity, increasing their mean waist size by 4.9cm, while men of other ethnicities gained a more modest 1.6cm. These changes are clinically significant and the variation between ethnic groups was in keeping with findings in established psychosis (38). Central obesity is a better predictor of CVD risk than is general obesity (39), so this may relate to the lower hazard ratios seen for all-cause mortality in black African, black Caribbean and South Asian patients with SMI compared to their white British counterparts (40).

Women were at risk of central obesity throughout, with 72.7% in that category by one year, again consistent with the local figure of 95% seen in women with established psychosis (38). Central adiposity in females is predictive of all-cause mortality in white, but not black women (41)



Minority ethnic groups appeared vulnerable to emergent glucose dysregulation, with highly clinically relevant increases in median HbA1c of 3.3mmol/mol (Table 3, supplementary table 5), but no change seen in white patients. Within the non-diabetic range, this reflects a highly clinically significant shift in glycaemia in the BME group, with one third exceeding the ADA HbA1c threshold for pre-diabetes (13)( $>39\text{mmol/mol}$  (5.7%)), although it is useful to note that some would not have been identified as at risk by current NICE Guidelines (<https://www.nice.org.uk/guidance/PH38/chapter/Recommendations#risk-identification-stage-1>). This change in glucose regulation in a relatively young population over just one year highlights the risk of accelerated emergence of diabetes in people of non-white ethnicity, and is in keeping with a recent large cross-sectional analysis of London primary care (42) data which showed a 3-10 fold relative risk of T2DM in young people with SMI.

### *Strengths and limitations*

This is to our knowledge the most comprehensive study to date examining the effects of lifestyle choice on emergent cardiometabolic risk. In conducting this study, we recruited an incident sample of people presenting to both inpatient and community services for the first time with psychosis and followed them up for one year, thereby capturing the period with the greatest change in physical health. The diverse nature of the population studied allows exploration of the effect of ethnicity on emergence of cardiometabolic risk. The use of multiple imputation on a reduced dataset allowed confidence in the results while retaining generalizability (43).

The study must be interpreted taking into account a number of methodological aspects. Over half our patients required acute inpatient care at the time of recruitment and many had received treatment for some weeks before being well enough to consent to inclusion. To minimise this effect and minimise missing data, we therefore sought permission to use clinical data, where available and comparable, as well as adjusting for the number of days prescribed anti-psychotics before baseline in our analyses. Also, in follow-up studies there is a risk that attrition may not be random. Therefore, considerable efforts were made to minimise loss to follow-up with contact made with 81% (217/268) of the then eligible participants at 12-months, although 73 participants declined 12-month follow-up. There was recompense for

time but no financial incentivisation to remain in the study. Analysis showed no differences in baseline demographic or clinical attributes between completers and non-completers. The supplementary tables include a descriptive table of complete paired measures. We also note that while 89 people were prescribed olanzapine at baseline, some did not sustain that prescription throughout the study period, possibly because of emergent metabolic effects. Finally, the number of statistical tests carried out was reasonably large and although we took a more conservative threshold of statistical significance, we cannot completely discount the possibility of Type I errors.

## Conclusion

Our results identify that cardiometabolic risk factors are already pronounced in those presenting to FEP services and worsen over the first year under standard care. No baseline behaviour predicted risk of worsening cardiometabolic parameters, but a greater degree of emergent glucose dysregulation was observed in those from black and minority ethnicity groups.

## Contributors

FG, DS, DH, ZA, KG, AP, SS, AD, RMM and KI were grant holders who devised the study content and design, participated in data analysis and interpretation of results and drafted and reviewed the manuscript. OH, DT, MDF made substantial contributions to the conception and/or design of the work; SB, PS, JL, BS, MH, AK, MDF made substantial contributions to the study conduct, protocol and study documents along with the acquisition and interpretation of data for the project. DSt, DS were study statisticians, leading on data analysis for the work. All authors were involved in drafting or revising the work critically for important intellectual content, giving final approval for the version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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