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Physical health of individuals with and without schizophrenia: a study based on GEN SCRIP (Genetics of Schizophrenia in Pakistan) data

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Abstract

Introduction: Individuals with schizophrenia are at a high risk of physical health co-morbidities and premature mortality. Cardiovascular and metabolic causes are an important contributor. Studies from across the world show that there are gaps in monitoring, documenting and managing these physical health conditions among schizophrenia patients in healthcare. Patients themselves because of their condition may not be aware of these co-morbidities and may not be able to follow a life style that prevents and manages the complications. In many low and middle income countries including Pakistan, the bulk of burden of care for schizophrenia fall on the families.

Objectives: To describe the rate of self-reported physical health problems and risk factors associated with cardiovascular and metabolic disorders in cases of schizophrenia compared with a group of healthy controls.

Design: We are conducting a case control, cross-sectional multicenter study of schizophrenia in Pakistan.

Settings: Multiple data collection sites across country for patients i.e. public and private psychiatric OPDs (Out Patient Departments), specialized psychiatric care facilities and psychiatric wards of Teaching and District level hospitals. Healthy controls enrolled from community.

Participants: We report a total of 6838 individuals' data with (N 3,411 (49.9%)) cases of schizophrenia compared with a group of healthy controls (N 3,427 (50.1%)).

Results: Body mass index (BMI) and rate of smoking is higher in schizophrenia patients than controls. Problems with vision, joint pain and high cholesterol is higher in controls. The cases

describe more problems in the category “other”. The cases also report a higher rate of digestive problems and epilepsy but the difference is not statistically significant.

Conclusions: In light of prior literature, we hypothesise that physical health problems are under recognized and under reported in patients with schizophrenia in Pakistan.

Key words

Physical health, schizophrenia, mental health, low and middle income countries, Pakistan, self-report, metabolic syndrome, antipsychotics

Strengths and limitations of this study

- It is a multicentre study, includes individuals from different geographical locations, ethnicities and socioeconomic class and uses a strict quality control mechanism for data collection.
- It is, to our knowledge, the biggest study on physical health in schizophrenia in Pakistani population.
- Our sampling technique was not random.
- Our study results are based on self-reports which can be affected by the variation in pattern of reporting among individuals.
- Our questionnaire did not cover all the physical conditions, so we might have missed some.

INTRODUCTION

Individuals suffering from schizophrenia are at an increased risk of developing co-morbid non-psychiatric physical health disorders. This includes infections like tuberculosis, HIV, Hepatitis B and C [1,2], osteoporosis [3], digestive system disorders [4,5], respiratory system disorders [6–8], neurological diseases like movement disorders [9,10] and epilepsy [11,12]. World Health Survey, a large cross-sectional general population study of 242,952 individuals utilizing random sampling from 48 Low- and Middle-Income Countries (LMICs), including Pakistan, assessed the prevalence of nine different physical health disorders; arthritis, angina pectoris, asthma, diabetes, chronic back pain, visual impairment, hearing problems, edentulism, and tuberculosis. Twenty-two hundred and twenty-four participants (1.1 %) reported that they had been diagnosed with schizophrenia/psychosis. The adjusted odds ratio for individuals with psychosis was 4.05 (95% CI, 3.25-5.04) for multimorbidity defined as two or more of these disorders [13]. The most widely studied physical health conditions are cardiovascular and metabolic disorders. Several systematic reviews and meta-analyses show clear evidence of increase in risk of 1.4-2 times across all cardiovascular and metabolic diseases in individuals suffering from schizophrenia [14], resulting in significantly higher premature mortality [15]. About 60% of the excess mortality is because of physical health problems in severe mental illness [16,17]. The evidence from High Income Countries (HICs) shows that the mortality gap between schizophrenia and general population is increasing, mainly due to cardiovascular disease [18]. Evidence from LMICs also suggests that the average potential years of life lost for persons with severe mental illness is about 28 years [19]. In a study from Ethiopia people with severe mental illness died 30 years prematurely and half of these deaths were because of infectious diseases [19].

Excess morbidity and mortality is a result of some, potentially, modifiable risk factors including smoking [20], obesity [21] and sedentary life style [22]. Lack of access to appropriate health care is another contributor [23,24]. Patients with severe mental illness are less likely to seek help for their physical health problems [25,26] and the quality of care they receive is inferior than the people without mental illness [27–29]. In individuals with schizophrenia, chronic diseases like diabetes mellitus, dyslipidemia, hypertension are under-diagnosed and under treated [30], blood pressure and cholesterol is less likely to be recorded by GPs [31]. Consequences of mental illness like cognitive impairment, social isolation and suspiciousness may deter patients from seeking help [29].

Most studies from well-developed health care systems have focussed on cardiovascular diseases or on metabolic disorders in people with schizophrenia [32–34]. People with psychosis are generally at high risk of multimorbidity, including physical health conditions, such as arthritis, chronic back pain which may not increase the risk of premature mortality, but will have significant negative impact on quality of life [35]. Despite the increased knowledge of heightened mortality from high risk conditions such as diabetes, the research on multimorbidity (i.e., two or more physical health comorbidities) in people with psychosis is still limited.

The prevalence of and risk factors for developing disorders of physical health are well established, but the data from LMIC is sparse [14].

South Asian populations living in India and Pakistan have very high incidence of metabolic diseases, such as hypertension, type 2 diabetes, and vascular disease [36].

We report data from a large cohort of people with schizophrenia on multimorbidity and smoking. As part of a large, ongoing, multicenter, case-control study of the genetics of schizophrenia (GEN-SCRIP: GENetics of SChizophRenia In Pakistan), we have assessed co-morbidity of different physical health conditions, BMI and history of smoking. We aim to compare the self-reported physical health status of individuals with schizophrenia with those without the illness.

METHODS

This paper is based on the analysis of data from a genetic case control study. The focus of the paper is self-reported physical health problems and risk factors for cardiovascular and metabolic disease. We compare the cases with controls. The data was collected between August 2018 and September 2019.

Sites

We collected data from 24 sites in the country. These sites are spread across the country. Table 1 provide the province wise detail of centers.

Province	Cities	Total clinics
Khyber Pakhtunkhwa	Dadar, Peshawar, Mardan	7
Punjab	Faisalabad, Gujranwala, Khushab, Sargodha, Lahore, Multan, Sahiwal, Rahim Yar Khan, Sialkot	13
Sindh	Hyderabad, Karachi	3
Capital area	Islamabad	1

Table 1 sites in different provinces

These centers are spread across the country and cover different ethnic and racial groups. Some of these are public sector hospital and clinics and others are private sector clinics. Patients were recruited both from outpatients and inpatient departments. Ethics approval was taken from Institutional Research Ethics Board of teaching hospitals and National Bioethics Committee of Pakistan.

Interviewers

The interviewers have graduate level education in psychology or pharmacy. They received training in administration of the study instruments (Screening Questionnaire and Diagnostic Interview for Psychosis and Affective Disorders (DI-PAD))[37]. Their data collection was supervised till they achieved an inter-rater reliability measured as Fleiss' kappa of 0.8 or more. The training typically lasted for four days to achieve that. Our senior diagnosticians were trained in New York City by our collaborating team and they then trained rest of the team. We use the same stringent quality control system for data collection.

Physical health assessment

The physical health assessment consisted of following three aspects.

1. Body Mass Index (BMI)

Both for cases and controls we measured the height and weight and used that for calculation of BMI.

2. Assessments of physical health conditions

We used a Screening Questionnaire that has been developed for this purpose by our collaborating group Genomic Psychiatry Cohort Consortium in the United States. The consortium was

established in 2008 and they have collected nearly 65,000 participants for various studies. They have used the Screening Questionnaire in these studies. The Screening Questionnaire includes 32 questions and screens for mania, psychosis, depression, anxiety disorder, alcohol, nicotine and other substance use history. It is based on questions from well-validated interviews. In addition, there is a section on demographic information (i.e., age, gender and self-identifying race and ethnicity) and a section on medical conditions and disorders.

During adaptation of the Screening Questionnaire we used colloquial language for different disorders. For example, instead of diabetes we used the word "sugar" that is widely understood by lay people. The GPC was established in 2008 with about 10,000 existing participants from earlier studies it is now approaching 65,000 participants.

3. Smoking status

The Screening Questionnaire has a section on smoking that we used for collection of information about smoking.

Psychiatric assessment

For detailed psychopathological assessment of the cases, a semi-structured interview was conducted using DI-PAD i.e. Diagnostic Interview for Psychosis and Affective Disorders - an 83 items interview schedule. It contains questions about psychopathology for psychotic and affective disturbances, premorbid adjustments of the patient, family history, treatment history and a section for interviewer ratings based on observations during the process. The screener and DI-PAD were developed by collaborators in the United States [37]. The questions for the DI-PAD are from Diagnostic Interview for Genetic Studies (DIGS) [38]. We translated and back translated the DI-PAD and the screener.

The process of translation was managed by a committee of bilingual researchers and linguists (AA, AN, MS, FN, FH, TN, MA). The instruments were in English and we translated them in Urdu. We initially commissioned three independent forward translations. These were reviewed by the committee and one consensus draft was provided to a separate group for back translation. The back translation was compared with the original draft and discrepancies identified were addressed through a second iteration of translation. The translation was then reviewed by five bilingual researchers in the field and their feedback was incorporated in the translated version. We then field tested the translated version in fifty participants. The feedback from interviewers was incorporated in the translation for further improvement. The final translated version was approved by the committee.

Information from each participant was gathered from multiple sources, if available; interviews with patients and family members, clinical records and team.

Participants and Data collection

Informed consent was taken from all participants. Patients fulfilling the DSM-V criterion for schizophrenia or schizoaffective disorder depressed type were enrolled. Exclusion criteria for the cases was (1) Poly-substance or any other abuse except cannabis before the onset of psychosis (2) acute toxic psychosis (3) patients with a history of severe head injury (4) onset of schizophrenia after the age of 50 (5) neurological disorder prior to onset of psychotic symptoms (6) psychotic depression (7) psychotic symptoms secondary to any medical conditions (8) schizophrenia Co-occurring with intellectual disability (9) schizoaffective manic type. A record of the excluded patients was also maintained.

Controls

We aimed to enrol controls who did not have a personal or family history (in first degree relatives), of schizophrenia, Major Depression or Bipolar Disorder. We administered the Screening Questionnaire to these subjects. We used purposive sampling to recruit controls from matched communities. The controls had to be unrelated biologically to each other and to the cases. We identified controls by advertising in educational institutions, professional training institutes and in the community. The lower limit for the age in controls was 23.

Quality control

A stepwise standard operating procedure was designed and followed to make the process of enrollment uniform and alike among all sites. The data entered by interviewers was checked by a trainer/supervisor on daily basis and any issues were resolved by a face to face or telephone conversation. Ten percent of patients from each center were randomly selected and recalled for a repeat, independent interview by another trainer/supervisor. If a center enrolled less than one hundred patients, then we recalled a minimum of ten patients for a second interview. If we identified any issues with an interviewer in a center, we provided them additional training.

Data analysis

We used R version 3.6.1 (https://cran.r-project.org/bin/windows/base/old/3.6.1/) for data analysis. For categorical variables we provide percentages. We performed Fisher exact test or t test as appropriate.

We report frequencies of various physical health issues. This information is based on self and family report. We performed logistic regression with cases control status as outcome measure

and age and gender as covariates. We report odds ratios and p values for Wald's test. The other category in health issues covers anything not included in the list.

We calculated body mass index (BMI) from height and weight. We used logistic regression with age and gender as covariates to examine the differences between cases and controls.

In the screening questionnaire there are four questions about smoking. We report the difference between cases and controls and use logistic regression with age and gender as covariates.

RESULTS

The total number of cases was 3,411 (49.9%) and total number of controls was 3,427 (50.1%). The mean age of cases was 33.50 (SD 10.0) years and of controls it was 26.04 (SD 6.86) years.

Participants

Table 2 provides the age and gender distribution of participants. There are more males in control group and more females in cases.

	Case	Control	
Male	2455 (44.74)	3032 (55.26)	Fisher test p value < 2.2e-16
Female	956 (70.76)	395 (29.24)	
Total	3,411 (49.9%)	3,427 (50.1%).	
Age	33.50 (10.00)	26.05 (6.84)	t = 258.59, df = 6871.1, p-value < 2.2e-16

Table 2 Gender and age of participants

Self reported physical health issues

Two hundred and eighty-seven (8.38%) among controls reported one or more physical health problem. This proportion was higher in cases (N= 516, 15.11%). The adjusted odds ratio for the difference was 1.26 (CI 1.06-1.5) with a p value of 0.01.

Table 3 gives details of the 10 most commonly self-reported health problems. Cholesterol, joint pain, and problems with vision were reported more frequently by controls. The odds rations are adjusted for age and gender. Other problems (an umbrella term for any other problem) were higher in cases.

Problem	Cases N %	Controls N %	OR (CI) Adjusted	Wald's p
Heart disease	12 (0.35)	8 (0.23)	0.35 (0.12,0.99)	0.048
High BP	113 (3.31)	45(1.31)	0.92 (0.6-1.41)	0.71
Digestive system problems	112 (3.28)	59 (1.72)	1.54 (1.08-2.19)	0.017
Liver disease	59 (1.73)	27 (0.78)	1.36 (0.8-2.31)	0.25
Sugar (diabetes)	84 (2.46)	33 (0.96)	0.93 (0.83-1.05)	0.24
High Cholesterol	7 (0.20)	16 (0.46)	0.13 (0.05-0.35)	6.37e-05
Joint pain	14 (0.41)	18 (0.52)	0.18 (0.07-0.44)	0.00022
Epilepsy	11 (0.32)	3 (0.08)	3.96 (1.01-15.53)	0.048
Migraine	29 (0.85)	35 (1.02)	0.64 (0.37-1.11)	0.11
Visual problems	36 (1.05)	101 (2.94)	0.13 (0.08-0.2)	<2e-16
Other	149 (4.37)	30 (0.87)	4.65 (3.01-7.18)	1.43e-11

Table 3 comparison of self reported health problems between cases and controls and results of logistic regression. These are Logistic regression results. Case/Control status is the outcome

measure. 0.003 is the threshold for significance given the multiple testing. The odds ratios are adjusted for age and gender. The significant p values are in bold.

The BMI was significantly higher in patients with schizophrenia (mean 24.12, (SD 5.02)) compared with the control (23.53 mean, (SD 3.96)) (OR 0.98 (CI 0.97-0.99)) p 0.00254).

In table 4 we provide the details of responses to questions about smoking. The smoking was more common in cases.

Questions about smoking	Cases	controls	OR (CI)	p
Over your lifetime, have you smoked more than 100 cigarettes? Include cigars, pipes, and chewing tobacco.	1108/3410 (32.49%)	443/3425 (12.93%)	3.23 (2.86-3.67)	< 2.2e-16
Have you ever had a period of one month or more when you smoked cigarettes every day?	991/3413 (29.03%)	387/3424 (11.30%)	3.21 (2.81-3.66)	< 2.2e-16
Did you usually smoke your first cigarette within one hour after waking up?	619/3407 (18.16%)	206/3425 (6.01%)	3.46 (2.93-4.11)	< 2.2e-16
Have you ever wanted to quit smoking or have tried to quit smoking and found that you couldn't?	449/3408 (13.17%)	253/3424 (7.38%)	1.90 (1.61-2.24)	2.894e-15

Table 4 comparison of cases and controls for smoking

DISCUSSION

The major findings of the study are that people with schizophrenia had significantly higher rates of BMI and smoking. The overall number of any physical health condition was higher in cases. Many specific physical health conditions including cardiovascular system disorders did not differ significantly between those diagnosed with schizophrenia and the control population without diagnosis of schizophrenia. High cholesterol, visual problems and joint pains were higher in the controls. The only category that was higher in cases was "other".

The strengths of this study include a large sample size with a control group a uniform data collection procedures by trained assessors with acceptable interrater reliability from multiple sites and use of a methodology and instruments that have been well established in previous research [37]. One limitation is that the data on physical health was self/family reported, without corroboration from other data sources (e.g., medical records). It was not feasible to conduct the physical examinations for number of multimorbidites and self report for physical health conditions has been used in large health surveys before [13].

Metabolic syndrome

The major risk factors for cardio-metabolic disorders i.e. BMI and cigarette smoking were high but surprisingly the disease conditions such as diabetes, high blood pressure and heart disease were not significantly higher in the people with schizophrenia compared to control. This is in contrast to almost universally reported findings of higher rates of cardio-metabolic disorders in people with schizophrenia [39]. High rates of metabolic syndrome are reported in those suffering from schizophrenia from India and Pakistan. A systematic review of studies of metabolic syndrome from India prevalence of Metabolic syndrome in patients with schizophrenia was

29.83%. The prevalence in community studies was 10.81% and in case control studies the odds ratio of prevalence was 3.03 in cases compared with controls [40]. In a hospital outpatient based study from Pakistan with a sample size of fifty six participants, 55.8% had metabolic syndrome [41].

There are a few possible explanations for this unusual finding including underreporting by participants, under recognition of these conditions by health care providers and a low use of antipsychotics due to poor access to treatment. These explanations are not mutually exclusive.

The most likely explanation is lack of identification of cardio-metabolic health problems in people with schizophrenia. Many studies in Europe and North America found that cardiovascular problems in people with schizophrenia are under recognized, under recorded and under treated [24,27,30,34,42]. Many barriers have been described that can lead to under reporting of the symptoms in schizophrenia. Compared with healthy controls individuals with schizophrenia do not spontaneously report physical symptoms [43]. Symptoms of schizophrenia like cognitive impairment, suspiciousness, disorganization and social isolation can result in lack of help-seeking or lack of compliance with care. When they seek help lack of social skills and stigma of mental illness may pose additional barriers for them to receive appropriate care [44]. The support for under-reporting and under recognition of cardio-metabolic symptoms comes from the finding that the "other" category is reported more frequently in cases. This may be representing symptoms experienced by patients with schizophrenia that have not lead to appropriate help-seeking, diagnosis and treatment.

In LMIC like Pakistan, patients with schizophrenia are primarily supported by their families. Almost all treatment is from out of pocket expenses. Physical health care may be less of a priority, especially if it is not causing acute symptoms. Patients are less likely to ask for

assessment and treatment. Unless the physical health problems are actively screened and managed, recognition of metabolic syndrome and its components will remain low.

Although metabolic syndrome is reported in drug naïve patients with schizophrenia [40] the use of antipsychotics is well known to lead to a significantly higher risk for diabetes and metabolic syndrome [45,46]. Low use of antipsychotics is another possible explanation for low prevalence of metabolic syndrome in our study. In many low and middle income countries the treatment gap for schizophrenia, defined as the absolute difference between the true prevalence of a disorder and the treated proportion of individuals affected by the disorder can be very high [47]. The schizophrenia treatment gap for Pakistan was reported as staggering 96% in one study [47].

Other conditions

A study based on World Health Survey described self reported conditions from 48 LMICs including Pakistan. Nine somatic disorders were examined: arthritis, angina pectoris, asthma, diabetes, chronic back pain, visual impairment, hearing problems, edentulism, and tuberculosis. Multi-morbidity defined as two or more disorders had a significantly higher prevalence in individuals with subclinical psychosis, and psychosis [13]. This is also consistent with higher reported prevalence of these physical health conditions in other literature [48–51].

In case of joint pains the self reported prevalence was higher in the control population, which may reflect widely reported negative association between musculoskeletal conditions and schizophrenia [52]. Additionally, in case of painful musculoskeletal conditions it has been postulated that people with schizophrenia may be less likely to present with painful conditions based on indirect evidence that they may experience hypoanalgesia [53].

A lower rate of problems with vision has not been reported before in people with schizophrenia. There are studies to suggest that visual problems are positively associated with schizophrenia [48,50]. The eye problems associated with schizophrenia include eye movement disorder [54], strabismus [55–58] and visual impairment [59,60]. Certain systemic infections can have eye manifestations and can lead to schizophrenia. These include toxoplasmosis [61] and rubella [62]. The possible explanation for a higher reported rate in controls in this study is lack of awareness among schizophrenia patients about the deficits and so lack of help seeking, investigation and treatment.

Clinical implications

Monitoring of physical health should be an integral part of the care for schizophrenia. This can be encouraged through clinical audit and training of providers.

Research implications

Studies that assess the physical health status of schizophrenia patients rather than relying on self-reports will clarify whether these findings are an artifact of self-reports or the pattern of physical health morbidity is different in patients with schizophrenia in Pakistan than rest of the world.

Limitations

The findings should be interpreted in light of a number of limitations. The main one is that data is based on self-reports. It is possible that there is a difference in reporting pattern between the cases and controls. Secondly, the patients and controls were not selected randomly. Thirdly, we enquired about a limited number of physical conditions.

Conclusions:

We report a large cross sectional study that shows the self reported physical health problems in people with schizophrenia. The overall rate of self reported physical health conditions was higher in schizophrenia mainly because they reported a higher number of problems in the "other" category. Apart from a higher rate of increased cholesterol among controls the cardio-metabolic symptoms were not different between the two groups. However, the major risk factors such as BMI and smoking were found significantly higher in individuals with schizophrenia. Most likely explanation is that people with schizophrenia are less aware of their physical health conditions and less likely to seek health care. The findings are consistent with poor health care both for mental health and physical health for people suffering from schizophrenia in LMIC.

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Competing interest

Authors report no competing interests.

Author's contribution

A patient consent form

Not required.

Data sharing statement

This is an ongoing study and data is not available at this stage.

Patient or public involvement in study

It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research

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STROBE Statement—Checklist of items that should be included in reports of ***case-control studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-7
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8-9
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	8-9
		(*b*) For matched studies, give matching criteria and the number of controls per case	11
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8-10
Bias	9	Describe any efforts to address potential sources of bias	11
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how matching of cases and controls was addressed	NA
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	12
		(b) Indicate number of participants with missing data for each variable of interest	12-13
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	NA

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12-14
		(*b*) Report category boundaries when continuous variables were categorized	13-14
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

*Give information separately for cases and controls.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Self-reported health and smoking status, and Body Mass Index: a case-control comparison based on GEN SCRIP (Genetics of Schizophrenia in Pakistan) data

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Self-reported health and smoking status, and Body Mass Index: a case-control comparison based on GEN SCRIP (Genetics of Schizophrenia in Pakistan) data

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Abstract

Introduction: Individuals with schizophrenia are at a high risk of physical health co-morbidities and premature mortality. Cardiovascular and metabolic causes are an important contributor. There are gaps in monitoring, documenting, and managing these physical health . Because of their condition, patients themselves may not be aware of these co-morbidities and may not be able to follow a lifestyle that prevents and manages the complications. In many low and middle-income countries including Pakistan, the bulk of the burden of care for those struggling with schizophrenia falls on the families.

Objectives: To determine the rate of self-reported physical health disorders and risk factors, like Body Mass Index (BMI) and smoking, associated with cardiovascular and metabolic disorders in cases of schizophrenia compared with a group of healthy controls.

Design: A case-controlled, cross-sectional multicenter study of patients with schizophrenia in Pakistan.

Settings: Multiple data collection sites across the country for patients i.e. public and private psychiatric OPDs (Out Patient Departments), specialized psychiatric care facilities, and psychiatric wards of Teaching and District level hospitals. Healthy controls were enrolled from the community.

Participants: We report a total of 6838 participants' data with (N 3,411 [49.9%]) cases of schizophrenia compared with a group of healthy controls (N 3,427 [50.1%]).

Results: Body mass index (BMI; OR 0.98 [CI 0.97-0.99], p = 0.0025), and the rate of smoking is higher in patients with schizophrenia than in controls. Problems with vision (OR 0.13 [0.08-0.2], joint pain (OR 0.18 [0.07-0.44]) and high cholesterol (OR 0.13 [0.05-0.35]) have higher reported

prevalence in controls. The cases describe more physical health disorders in the category "other" (OR 4.65 [3.01-7.18]). This captures residual disorders not listed in the questionnaire.

Conclusions: Participants with schizophrenia in comparison with controls report more disorders. The access in the "other" category may be a reflection of undiagnosed disorders.

Keywords

Physical health, schizophrenia, mental health, low and middle income-countries, Pakistan, self-report, metabolic syndrome, antipsychotics

Strengths of this study

- It is a multicentre study, including individuals from different geographical locations, ethnicities, and socioeconomic class, and uses a strict quality control mechanism for data collection.
- It is, to our knowledge, the biggest study on physical health in schizophrenia in the Pakistani population.

Limitations of this study

- Non-random sampling technique.
- Results are based on subjective self-reports which can be affected by the variation in the pattern of reporting among individuals.

INTRODUCTION

Individuals suffering from schizophrenia are at an increased risk of developing co-morbid non-psychiatric physical health disorders. This includes infections like tuberculosis, HIV, Hepatitis B and C [1,2], osteoporosis [3], digestive system disorders [4,5], respiratory system disorders [6–8], neurological diseases like movement disorders [9,10], and epilepsy [11,12]. A World Health Survey assessed the prevalence of nine different physical health disorders through a large cross-sectional general population study of 242,952 individuals utilizing random sampling from 48 Low- and Middle-Income Countries (LMICs), including Pakistan. Self-reported disorders included arthritis, angina pectoris, asthma, diabetes, chronic back pain, visual impairment, hearing problems, edentulism, and tuberculosis. Twenty-two hundred and twenty-four participants (1.1 %) reported that they had been diagnosed with schizophrenia/psychosis. The adjusted odds ratio for individuals with psychosis was 4.05 (95% CI, 3.25-5.04) for multimorbidity defined as two or more of these disorders [13].

Currently, the most widely studied physical health disorders are cardiovascular and metabolic disease. Several systematic reviews and meta-analyses show clear evidence of an increase in the risk of 1.4-2 times across all cardiovascular and metabolic diseases in individuals suffering from schizophrenia [14], resulting in significantly higher premature mortality [15]. About 60% of the excess mortality due to physical health disorders in severe mental illness [16,17]. The evidence from High-Income Countries (HICs) shows that the mortality gap between schizophrenia and the general population is increasing, mainly due to cardiovascular disease [18]. Evidence from LMICs also suggests that the average potential years of life lost for persons with severe mental illness is about 28 years [19]. In a study from Ethiopia people with severe

mental illness died 30 years prematurely and half of these deaths were because of infectious diseases [19].

Excess morbidity and mortality is a result of some, potentially, modifiable risk factors including smoking [20], obesity [21], and sedentary lifestyle [22]. Lack of access to appropriate health care is another contributor [23,24]. Patients with severe mental illness are less likely to seek help for their physical health disorders [25,26] and the quality of care they receive is inferior to the people without mental illness [27–29]. In individuals with schizophrenia, chronic diseases like diabetes mellitus, dyslipidemia, hypertension are under-diagnosed and under-treated [30], blood pressure and cholesterol are less likely to be recorded by GPs [31]. Consequences of mental illness like cognitive impairment, social isolation and, suspiciousness may deter patients from seeking help [29]. Individuals with schizophrenia have a higher Body Mass Index (BMI) compared with the general population. The etiology includes but is not limited to adverse effects of antipsychotics. Other factors involved are pretreatment/premorbid genetic vulnerabilities, psychosocial and socioeconomic risk factors, and an unhealthy lifestyle [32].

Most studies from well-developed health care systems have focussed on cardiovascular diseases or metabolic disorders in individuals with schizophrenia [33–35]. Individuals with psychosis are generally at high risk of multimorbidity, including physical health disorders, such as arthritis, chronic back pain which may not increase the risk of premature mortality, but will have a significant negative impact on the quality of life [36]. Despite the increased knowledge of heightened mortality from high-risk conditions such as diabetes, the research on multimorbidity (i.e., two or more physical health comorbidities) in people with psychosis is still limited. The

prevalence of and risk factors for developing disorders of physical health are well established, but the data from LMIC is sparse [14].

Many studies of physical health disorders in schizophrenia have relied on self-reports [13,37–39]. The prevalence of smoking has also been assessed with self-reports[40]. In a US study, there was a consistency between the information from Medicaid, Medicare, and primary data from self-reports, testifying to the validity of patient self-report [39]. In absence of electronic patient records and variation in the quality of case-records self-report is a viable approach to gathering information about physical health disorders in schizophrenia patients in Pakistan.

This study is based on self-reported data on physical health disorders and smoking from a case-control study of individuals with schizophrenia. Additionally, we measured weight and height to assess the Body Mass Index (BMI). As part of a large, ongoing, multicenter, case-control study of the genetics of schizophrenia (GEN-SCRIP: GENetics of SChizophRenia In Pakistan), we have assessed co-morbidity of different physical health disorders, BMI, and history of smoking. We aim to compare the self-reported physical health status of participants with schizophrenia with those without this illness.

METHODS

Data presented here was generated from an ongoing, genetic case-control study initiated in 2018. The study aims to collect 10,000 each of unrelated cases and controls from multiple sites in all the regions of Pakistan. Given the diversity of the population, we aimed to represent all the major racial groups in our data. Cases were recruited from clinics across sites in the country. The

clinics were both public (i.e., government institutions) and private sector. Clinicians referred previously diagnosed patients to the research team. Comparable controls were recruited from the local communities by advertising in educational institutions, vocational training centers, local malls. Study participants were asked to self-report physical health disorders and risk factors for cardiovascular and metabolic disease including smoking. We also measured the weight and height of the participants to calculate BMI. The data was collected between August 2018 and September 2019.

Sites

We collected data from 24 sites in the country. Data collection sites were spread across the country. Table 1 provides the provincial details of centers sampled.

Province	Cities	Total clinics
Khyber Pakhtunkhwa	Dadar, Peshawar, Mardan	7
Punjab	Faisalabad, Gujranwala, Khushab, Sargodha, Lahore, Multan, Sahiwal, Rahim Yar Khan, Sialkot	13
Sindh	Hyderabad, Karachi	3
Capital area	Islamabad	1

Table 1 Summary of data collection sites by province

Centers were spread across the country, included public sector hospitals and clinics and private sector clinics, to reach as many ethnic and racial groups as possible. Patients were recruited both from outpatients and inpatient departments. Ethics approval was taken from the Institutional Research Ethics Board of teaching hospitals and the National Bioethics Committee of Pakistan.

Interviewers

Study interviewers had a graduate-level education in psychology or pharmacy. Interviewers received training in the administration of the study instruments (Screening Questionnaire and Diagnostic Interview for Psychosis and Affective Disorders (DI-PAD)[41]. We selected these instruments to align with our collaborating team in the United States who have successfully employed these tools for over a decade and in order to make our data comparable to theirs. The questions for the Screening Questionnaire are from validated instruments and DI-PAD is based on questions from Diagnostic Interview for Genetic Studies (DIGS) [42], a well-validated interview. Our senior diagnosticians were trained in New York City by our collaborating team. Senior diagnosticians who took part in initial training are three fully trained psychiatrists and one Ph.D. scholar. These individuals trained study interviewers. Interviews were supervised until inter-rater reliability was achieved, measured as Fleiss' kappa of 0.8 or more. Thus, training typically lasted approximately four days. We use the same stringent quality control system for data collection as used by our New York City collaborating team.

Physical health assessment

The physical health assessment consisted of the following three aspects.

1. Body Mass Index (BMI)

Both for cases and controls we measured the height and weight and used that for calculation of BMI.

2. Assessments of physical health disorders

We used a Screening Questionnaire that has been developed for this purpose by our collaborating group, the Genomic Psychiatry Cohort Consortium (GPC) in the United States. The consortium was established in 2008 and they have collected nearly 65,000 participants for various studies. They have used the Screening Questionnaire in these studies. The Screening Questionnaire includes 32 questions and screens for mania, psychosis, depression, anxiety disorder, alcohol, nicotine, and other substance use history. It is based on questions from well-validated interviews. The Screening Questionnaire also collects demographic information (i.e., age, gender, and self-identifying race and ethnicity), medical conditions and disorders. The section on medical conditions starts with the question "Have you ever been diagnosed with any of these medical conditions or disorders?" and then provides a list of disorders e.g. Heart problems (Examples: coronary heart disease, myocardial infarction), High cholesterol (hypercholesterolemia). The participants can answer yes or no. The last question reads "Any other medical or health problem. If yes, please describe:"

During the adaptation of the Screening Questionnaire, we used colloquial language for different disorders. For example, instead of diabetes, we used the word "sugar" which is widely understood by laypeople.

3. Smoking status

The Screening Questionnaire has a section on smoking that we used for the collection of information about smoking.

Psychiatric assessment

For detailed psychopathological assessment of the cases, a semi-structured interview was conducted using DI-PAD i.e. Diagnostic Interview for Psychosis and Affective Disorders - an 83

items interview schedule. It contains questions about psychopathology for psychotic and affective disturbances, premorbid adjustments of the patient, family history, treatment history, and a section for interviewer ratings based on observations during the process. The screener and DI-PAD were developed by collaborators in the United States [41]. The questions for the DI-PAD are from Diagnostic Interview for Genetic Studies (DIGS) [42]. We translated and back-translated the DI-PAD and the screener.

The process of translation was managed by a committee of bilingual researchers and linguists (AA, AN, MS, FN, FH, TN, MA). The instruments were in English and we translated them into Urdu. We initially commissioned three independent forward translations. These were reviewed by the committee and one consensus draft was provided to a separate group for back-translation. The back-translation was compared with the original draft and discrepancies identified were addressed through the second iteration of translation. The translation was then reviewed by five bilingual researchers in the field and their feedback was incorporated in the translated version. We then field-tested the translated version in fifty participants. The feedback from interviewers was incorporated in the translation for further improvement. The final translated version was approved by the committee.

The information was gathered through an interview with the patients, their accompanying caregiver when available, clinical records from the clinic where the patient was seen, and information from the treating clinical team.

Participants and Data collection

Informed consent was taken from all participants. Patients fulfilling the DSM-V criterion for schizophrenia or schizoaffective disorder depressed type were enrolled. Exclusion criteria for the

cases were (1) Poly-substance or any other abuse except cannabis before the onset of psychosis (2) acute toxic psychosis (3) patients with a history of severe head injury (4) onset of schizophrenia after the age of 50 (5) neurological disorder before the onset of psychotic symptoms (6) psychotic depression (7) psychotic symptoms secondary to any medical conditions (8) schizophrenia Co-occurring with intellectual disability (9) schizoaffective manic type. A record of the excluded patients was also maintained.

Controls

We aimed to enroll controls who did not have a personal or family history (in first degree relatives), of schizophrenia, Major Depression, or Bipolar Disorder. We administered the Screening Questionnaire to these subjects. We used purposive sampling to recruit controls from matched communities. The controls had to be unrelated biologically to each other and the cases. We identified controls by advertising in educational institutions, professional training institutes, and in the community. The lower limit for the age in controls was 23.

Quality control

A stepwise standard operating procedure was designed and followed to make the process of enrollment uniform and alike among all sites. The data entered by interviewers was checked by a trainer/supervisor on daily basis and any issues were resolved by a face-to-face or telephone conversation. Ten percent of patients from each center were randomly selected and recalled for a repeat, independent interview by another trainer/supervisor. If a center enrolled less than one hundred patients, then we recalled a minimum of ten patients for a second interview. If we identified any issues with an interviewer in a center, we provided them additional training.

Data analysis

We used R version 3.6.1 (https://cran.r-project.org/bin/windows/base/old/3.6.1/) for data analysis. For categorical variables we provide percentages. We performed Fisher exact test or t-test as appropriate. We report frequencies of various physical health disorders. We performed logistic regression with case-control status as outcome measure and age and gender as covariates. We report odds ratios and p values for Wald's test. The other category in health issues covers anything not included in the list. We calculated body mass index (BMI) from height and weight. We used logistic regression with age and gender as covariates to examine the differences between cases and controls. In the screening questionnaire, there are four questions about smoking. We report the difference between cases and controls and use logistic regression with age and gender as covariates. We selected age and gender as covariates for these analyses because of prior evidence of their effect on physical health disorders, smoking, and BMI.

Patient or public involvement in study

It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research

RESULTS

The schizophrenia cases are diagnosed using DSM V criteria. The total number of cases was 3,411 (49.9%) and the total number of controls was 3,427 (50.1%). The mean age of cases was 33.50 (SD 10.0) years and of controls, it was 26.04 (SD 6.86) years.

Participants

There were 3,411 (49.9%) and 3,427 (50.1%) controls. Among cases, there were 2455 males and 956 females. In controls, 3032 were males and 395 females. There are more males in the control

group and more females in cases. The cases were older in age (mean 33.50 years [SD10.00]) than controls (mean 26.05 years [SD 6.84]) p-value < 2.2e-16.

Self-reported physical health disorders

Two hundred and eighty-seven (8.38%) among controls reported one or more physical health disorders. This proportion was higher in cases (N= 516, 15.11%). The adjusted odds ratio for the difference was 1.26 (CI 1.06-1.5) with a p-value of 0.01.

Table 2 gives details of the 10 most commonly self-reported health problems. Case/Control status is the outcome measure. To control for multiple comparisons, alpha was set at 0.003 as the threshold for significance. The odds ratios are adjusted for age and gender. Cholesterol, joint pain, and problems with vision were reported more frequently by controls. The numbers represent the participants who reported that they have been diagnosed with the condition e.g. for heart problems 12 participants in the case group and 8 participants in the control group said that they have been diagnosed with a heart condition. The odds ratios are adjusted for age and gender. Other problems (an umbrella term for any other problem) were higher in cases.

Disorders (N missing)	Cases N %	Controls N %	OR (CI) Adjusted	Wald's p
Heart disease (0)	12 (0.35)	8 (0.23)	0.35 (0.12,0.99)	0.048
High BP (0)	113 (3.31)	45(1.31)	0.92 (0.6-1.41)	0.71
Digestive system disorders (4)	112 (3.28)	59 (1.72)	1.54 (1.08-2.19)	0.017
Liver disease (3)	59 (1.73)	27 (0.78)	1.36 (0.8-2.31)	0.25
Sugar (diabetes) (1)	84 (2.46)	33 (0.96)	0.93 (0.83-1.05)	0.24
High Cholesterol (2)	7 (0.20)	16 (0.46)	0.13 (0.05-0.35)	**6.37e-05**

Joint pain (3)	14 (0.41)	18 (0.52)	0.18 (0.07-0.44)	**0.00022**
Epilepsy (1)	11 (0.32)	3 (0.08)	3.96 (1.01-15.53)	0.048
Migraine (20)	29 (0.85)	35 (1.02)	0.64 (0.37-1.11)	0.11
Visual problems (0)	36 (1.05)	101 (2.94)	0.13 (0.08-0.2)	**<2e-16**
Other (6)	149 (4.37)	30 (0.87)	4.65 (3.01-7.18)	**1.43e-11**

Table 2 Comparison of self-reported health problems between cases and controls and results of logistic regression. The significant p-values are in bold.

In figure 1 we show the percentage of self-reported physical health disorders in cases and controls. Apparent access of reported percentage in heart disease, high blood pressure, diabetes, digestive system disorders, and liver disease is not significant after adjustment for age and gender.

Figure 1 about here.

The BMI was significantly higher in patients with schizophrenia (mean 24.12, [SD 5.02]) compared with the control (23.53 mean, [SD 3.96]; OR 0.98 [CI 0.97-0.99], p = 0.00254).

In table 3 we provide the details of responses to questions about smoking. Smoking was more common in cases than in controls.

Questions about smoking	Cases	controls	OR (CI)	p
Over your lifetime, have you smoked more than 100 cigarettes? Include cigars, pipes, and chewing tobacco.	1108/3410 (32.49%)	443/3425 (12.93%)	3.23 (2.86-3.67)	< 2.2e-16

Have you ever had a period of one month or more when you smoked cigarettes every day?	991/3413 (29.03%)	387/3424 (11.30%)	3.21 (2.81-3.66)	< 2.2e-16
Did you usually smoke your first cigarette within one hour after waking up?	619/3407 (18.16%)	206/3425 (6.01%)	3.46 (2.93-4.11)	< 2.2e-16
Have you ever wanted to quit smoking or have tried to quit smoking and found that you couldn't?	449/3408 (13.17%)	253/3424 (7.38%)	1.90 (1.61-2.24)	2.894e-15

Table 3 comparison of cases and controls for smoking

DISCUSSION

The major findings of the study are that people with schizophrenia had significantly higher BMIs and reported rates of smoking. The overall number of any physical health disorders was higher in cases. Many specific physical health disorders including cardiovascular system disorders did not differ significantly between those diagnosed with schizophrenia and the control population without a diagnosis of schizophrenia. The adjusted odds ratios of individuals reporting high cholesterol, visual problems and joint pains favoured controls. The only category that was higher in cases was "other". The question in the screening questionnaire about the "other" category enquired about "any other medical or health problem". The "other" category gives the participants a chance to describe any other physical health disorder that was not listed

in the screening questionnaire e.g. Heart problems (Examples: coronary heart disease, myocardial infarction), High blood pressure (hypertension), and Digestive problems (Examples: gastrointestinal, celiac disease). As expected, response to this question resulted in a description of a large number of conditions in colloquial language that are difficult to summarize. We present this as one category as we suspect that this large number of "other" represent unexplored and undiagnosed physical health disorders.

Metabolic syndrome

The term metabolic syndrome has been used historically to describe a group of health conditions leading to increased risk of heart diseases and related problems. Physically, metabolic syndrome can manifest as increased waistline, high blood pressure, increased blood sugar, and obesity. The major risk factors for cardio-metabolic disorders i.e., high BMI and cigarette smoking were present but surprisingly, disease conditions such as diabetes, high blood pressure, and heart disease were not significantly higher in the individuals with schizophrenia compared to control. This is in contrast to almost universally reported findings of higher rates of cardiometabolic disorders in individuals with schizophrenia [14,43]. High rates of metabolic syndrome are reported in those suffering from schizophrenia from India and Pakistan. In a systematic review of studies of metabolic syndrome from India prevalence of Metabolic syndrome in patients with schizophrenia was 29.83%. The prevalence in community studies was 10.81% and in case-control studies, the odds ratio of prevalence was 3.03 in cases compared with controls [44]. In a hospital outpatient-based study from Pakistan with a sample size of fifty-six participants, 55.8% had metabolic syndrome [45].

There are a few possible explanations for this unusual finding including underreporting by participants, and under-recognition of these conditions by health care providers. These explanations are not mutually exclusive. The most likely explanation is the lack of identification of cardio-metabolic health problems in individuals with schizophrenia. Many studies in Europe and North America found that cardiovascular problems in individuals with schizophrenia are under-recognized, under-recorded and under-treated [24,27,30,35,46]. Many barriers have been described that can lead to under-reporting of the symptoms in schizophrenia. Compared with healthy controls individuals with schizophrenia do not spontaneously report physical symptoms [47]. Symptoms of schizophrenia, like cognitive impairment, suspiciousness, disorganization, and social isolation can result in lack of help-seeking or lack of compliance with care. When they seek help lack of social skills and stigma of mental illness may pose additional barriers for them to receive appropriate care [48]. The support for under-reporting and under-recognition of cardio-metabolic symptoms comes from the finding that the "other" category is reported more frequently in cases. This may be representing symptoms experienced by patients with schizophrenia that have not led to appropriate help-seeking, diagnosis, and treatment.

In LMIC like Pakistan, patients with schizophrenia are primarily supported by their families. Almost all treatment costs are covered from out of pocket expenses. Economic reasons are an important factor in non-adherence to treatment for schizophrenia in Pakistan [49,50] and neighbouring India with similar socioeconomic conditions [51–53]. Physical health care may be less of a priority, especially if it is not causing acute symptoms. Patients are less likely to ask for assessment and treatment. Unless the physical health disorders are actively screened and managed, recognition of the metabolic syndrome and its components will remain low.

Other conditions

A study based on the World Health Survey described self-reported conditions from 48 LMICs including Pakistan. Nine somatic disorders were examined: arthritis, angina pectoris, asthma, diabetes, chronic back pain, visual impairment, hearing problems, edentulism, and tuberculosis. Multi-morbidity defined as two or more disorders had a significantly higher prevalence in individuals with subclinical psychosis, and psychosis [13]. This is also consistent with the higher reported prevalence of these physical health disorders in other literature [54–57].

In the case of joint pains the self-reported prevalence was higher in the control population, which may reflect a widely reported negative association between musculoskeletal conditions and schizophrenia [58]. Additionally, in the case of painful musculoskeletal disorders it has been postulated that people with schizophrenia may be less likely to present with painful conditions based on indirect evidence that they may experience hypoanalgesia [59].

A lower rate of problems with vision has not been reported before in people with schizophrenia. There are studies to suggest that visual problems are positively associated with schizophrenia [54,56]. The eye problems associated with schizophrenia include eye movement disorder [60], strabismus [61–64], and visual impairment [65,66]. Certain systemic infections can have eye manifestations and can lead to schizophrenia. These include toxoplasmosis [67] and rubella [68]. The possible explanation for a higher reported rate in controls in this study is lack of awareness among schizophrenia patients about the deficits and so lack of help-seeking, investigation, and treatment.

Clinical implications

Monitoring of physical health should be an integral part of the care for individuals with schizophrenia. This can be encouraged through clinical audit and training of health care providers.

Research implications

Further work that employs assessment of physical health by health professionals rather than self-report will provide a better estimate of comorbidity in patients with schizophrenia in Pakistan.

Limitations

The strengths of this study include a large sample size with a control group a uniform data collection procedures by trained assessors with acceptable interrater reliability from multiple sites and the use of a methodology and instruments that have been well established in previous research [41]. However, the findings should be interpreted in light of a some important limitations. One limitation is that the data on physical health was self/family reported, without corroboration from other data sources (e.g., medical records). It was not feasible to conduct full physical examinations for the number of multi-morbidities reported. We did, however, collect information from family members in addition to participant self-reports, which strengthens our data.

In part due to the diverse, potentially heterogenous nature of our sample, there may be a difference in reporting patterns between and within the cases and controls. However, many factors can influence the reporting of physical symptoms and physical disorders. For instance, because of cognitive deficits individuals with schizophrenia may be unaware of physical symptoms [69,70] and antipsychotics reduce the pain sensitivity [69,70] that would affect the reporting of physical health disorders. Additionally, a lack of social skills [29]and difficulties in communicating physical needs also affect their reporting pattern[71].

Finally, the patients and controls were not selected randomly. For cases, everyone who met the criteria and consented was enrolled in the study. Due to the lack of services, severe and chronic cases are more likely to seek help from psychiatric facilities. This should result in higher levels of morbidity in our cases.

Conclusions:

We report a large cross-sectional study that shows the self-reported physical health disorders in participants with schizophrenia. The overall rate of self reported physical health disorders was higher in schizophrenia mainly because they reported a higher number of problems in the "other" category. Apart from a higher rate of increased cholesterol among controls the cardio-metabolic symptoms were not different between the two groups. However, the major risk factors such as BMI and smoking were found significantly higher in cases with schizophrenia. Prior evidence from the literature suggests that individuals with schizophrenia are less aware of their physical health disorders and less likely to seek health care. Excess of reported disorders in the "other" category may reflect disorders that have not been reported to and investigated by the health care providers.

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Competing interest

Authors report no competing interests.

Author's contribution

A patient consent form

Not required.

Data sharing statement

This is an ongoing study and data is not available at this stage.

Ethics statement

This study was conducted under the ethics approval from National Bioethics Committee, Islamabad, Pakistan, Reference Number .4-87/NBC-367/19/2060.

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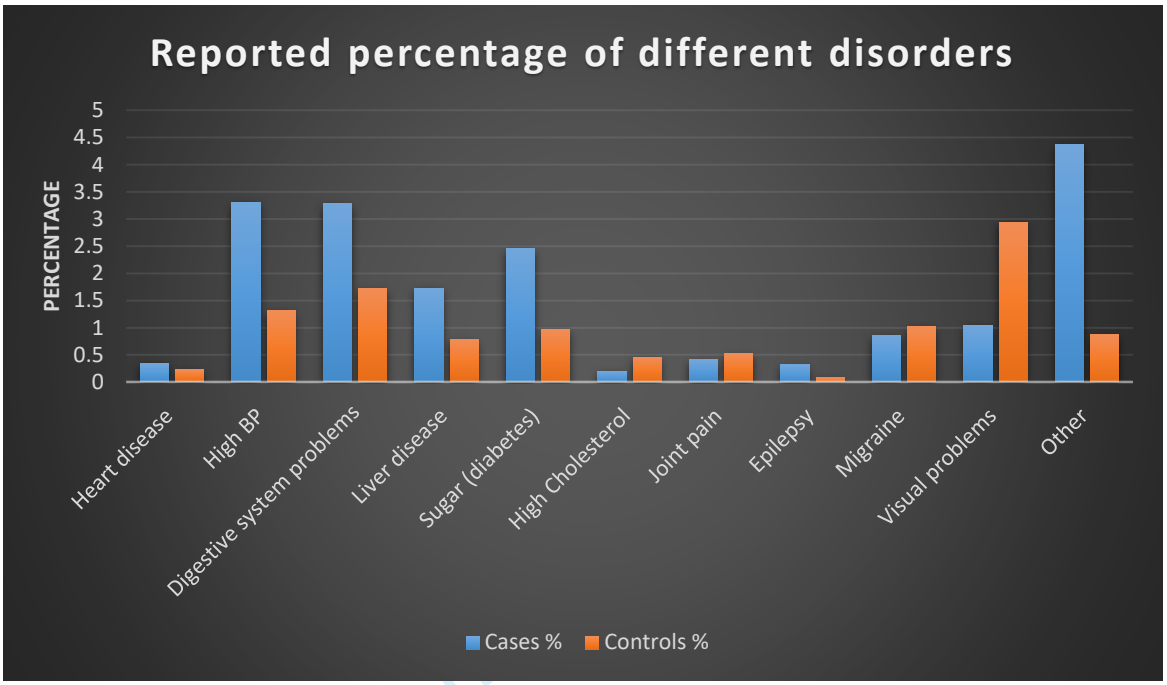
Figure legend

Figure 1 percentage of self-reported physical health disorders in cases and controls.



STROBE Statement—Checklist of items that should be included in reports of ***case-control studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-7
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8-9
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	8-9
		(*b*) For matched studies, give matching criteria and the number of controls per case	11
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8-10
Bias	9	Describe any efforts to address potential sources of bias	11
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how matching of cases and controls was addressed	NA
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	12
		(b) Indicate number of participants with missing data for each variable of interest	12-13
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	NA

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12-14
		(*b*) Report category boundaries when continuous variables were categorized	13-14
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

*Give information separately for cases and controls.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.