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Multidisciplinary approach to functional somatic syndromes

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BMJ Open Multidisciplinary approach to functional somatic syndromes: study protocol for a population-based prospective cohort study

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ABSTRACT

Introduction Isfahan functional disorders (ISFUN) cohort study aims to describe the interplay of genetic and environmental factors in shaping the characteristics of functional somatic syndromes (FSS). This study is primarily intended to investigate the epidemiology, risk factors, course and prognosis of FSSs in a sample of adult Iranian population. The other aim is to develop a new delimitation of FSSs based on an integrated multidisciplinary approach comprising of phenotypic and multiomics data.

Methods and analysis ISFUN is a population-based prospective cohort study designed to follow a population of randomly selected seemingly healthy adults (18–65 years) through annual visits during a 4-year observation period. Structured questionnaires are used for data collection and clinical assessment of the participants. Questionnaire-based diagnosis of FSSs are validated in a medical interview. Human DNA genotyping, microbial amplicon sequencing and urine analysis is under progress for genomics, microbiota and metabolomics profiling, respectively. Enrolment began in September 2017, and study completion is expected in 2022. A total number of 1943 participants were initially recruited.

Ethics and dissemination Ethical approval for data collection was granted by the National Research Ethics Committee of the Iranian Ministry of Health and Medical Education and the Research Ethics Committee of Isfahan University of Medical Sciences (IR.MUI.REC.1395.1.149). Following the description of the study procedure, we obtained written informed consent from all study participants. Study findings will be disseminated through peer-reviewed publications and presentations at scientific meetings.

INTRODUCTION

Among the most common reasons for which people seek medical care are the so-called bodily complaints without an apparent organic origin.^{1 2} It is reported that the main ailments of almost one-third of patients referred to the family physician are non-specific, somatic symptoms with no precise pathology.³ More often than not, these complaints are not attributable to a

Strengths and limitations of this study

- ⇒ This multidisciplinary population-based longitudinal cohort study does not have a disease-oriented approach and a diverse range of data including somatic symptoms, biomarkers, psychological measures and lifestyle information in addition to genomic, faecal microbiota and urine metabolomics profiles of the participants is being collected.
- ⇒ Variations in chronicity and severity of the functional symptoms are checked over a 5-year period in an effort to further our understanding of the course, risk factors and prognosis of functional somatic syndromes (FSSs).
- ⇒ The longitudinal study design coupled with serial collection of clinical data, biological samples and omics profiles will provide a unique platform for personalised medicine and omics-based clinical management of patients suffering from FSSs.
- ⇒ This cohort might lack the power to study rare FSSs.

conventionally defined medical disease or mental disorder and no organic causes can be identified even after complementary diagnostic procedures.⁴ Multiple terms are proposed for such symptoms from which the umbrella concept of functional somatic syndromes (FSSs) is the accepted choice in medical specialties.^{5 6}

The aetiology or underlying mechanisms of FSSs are not yet fully understood. However, various elements like biological, psychological and social factors and possibly the complex interactions among them are all potentially important.^{7 8} Patients frequently meet the diagnostic criteria for more than one syndrome and usually share other non-clinically relevant characteristics.^{9 10} Also, occurrence of a new syndrome could be predicted based on antecedent syndromes which implies a common etiopathogenesis.¹¹ It is suggested that FSSs might be a family



of closely related disorders or expressions of the same underlying illness with various subtypes.¹²

It is difficult to deal with such patients in medical practice because a disease-based explanation cannot be made and the direction of diagnosis mainly hinges on the speciality of the medical consultant rather than the nature of the disorder itself. Experts in each field of medicine have defined and named the syndromes according to their organ of interest without a holistic multiorgan or system view.¹³ Patients may receive diagnoses such as irritable bowel syndrome, functional dyspepsia, fibromyalgia, non-cardiac chest pain, chronic fatigue syndrome, etc depending on the physician's speciality.¹⁴ Hence, a more precise syndrome/symptoms identification system is needed for better patient management.¹⁵ Latent class analysis and cluster analysis of the somatic symptoms have been previously used for creating symptom profiles.^{9 16 17} But we believe the best way to overcome this challenge is through an integrated multidisciplinary approach comprising of both phenotypic and multiomics data.

Therefore, in this cohort study, we are gathering a multifaceted longitudinal dataset including functional symptoms, biomarkers, sociodemographic data, psychological measures and lifestyle information in addition to genomic, faecal microbiota and urine metabolomics profiles of seemingly healthy participants. This will give us the basic requirements for creating a new quantitative definition of FSSs via data modelling and machine learning methods. To the best of our knowledge, this is the first cohort study in the Middle Eastern region aimed at investigating FSSs.

Study aims

The Isfahan functional disorders (ISFUN) cohort study is a population-based longitudinal cohort designed to:

1. Investigate the epidemiology, risk factors, course and prognosis of FSSs in a sample of adult Iranian population. The questionnaire-based diagnoses will be validated against diagnoses made by a personal medical interview as the gold standard method.
2. Challenge the organ/system-oriented view of FSSs by creating a personalised profile according to the clinical, psychological and omics characteristics of each individual. This profile is an effort to plan a tailor-made medical strategy towards personalised medicine.

METHODS AND ANALYSIS

Study population and exclusion criteria

ISFUN study is centred in the Kerdabad neighbourhood of Isfahan, Iran. The main criteria for selecting this location were population diversity of the inhabitants and its generalisability to the main population of Isfahan city according to their mean household income and socioeconomic status. All households from the fourth and fifth district of this area were included using census-based sampling technique. Subsequently, one person per household was randomly selected and if this nominee

did not meet our eligibility criteria, another random individual from the same household was selected and invited to participate in the study. All seemingly healthy adults (aged between 18 and 65) were included except for non-Iranian nationals, women who were pregnant or lactating, close relatives of a previously selected individual (up to the third degree) and a small number who suffered physical or mental disability to the degree that could not participate in providing reliable data on themselves (eg, severe mental retardation or untreated psychosis). Caregivers in the province health centre were responsible for evaluating the selected population using official family and personal health records or a phone call in case of missing data. Cohort management team created the initial participants list, supervised the recruitment process and decided on the new invitations or when to exclude an individual.

Recruitment and follow-up

Recruitment was planned over 6 months beginning on September 2017. First, the objectives of the study were explained by a trained interviewer in a household visit. A custom-made package including introductory brochure, questionnaires, writing paper and matching envelopes, urine and stool specimen containers and guidelines on how to collect biological samples were also offered. The invitee was given a few days to read the educational materials. A direct phone line to an informed caregiver was provided for any questions or concerns remained unanswered. After consenting to join the study, a visit at the local health centre was scheduled during which the participants underwent clinical examination and medical interviews. Questionnaires were completed at home and controlled in different working stations.

There is a natural variance in functional symptoms characteristics over time which affects patient-reported complaints. Thus, the participants are followed through three scheduled annual visits (2019–2021) after baseline data collection to check the chronicity and severity of their symptoms and search for possible responsible factors. Two rounds of annual follow-ups are done and the next is planned to commence in fall 2021. [Figure 1](#) illustrates a flow chart of the ISFUN cohort study.

Outcomes and measurements

Questionnaire data and phenotypic measurements were gathered at baseline and the following annual visits. The cohort management team selected the current list of measurements after a rapid review of existing methods followed by extensive consultation with experts in this field of medicine including psychologists, neurologists, internal medicine specialists and gastroenterologists. Our aim was to use the most reliable, applicable and popular measurements that are currently applied in medical practice for diagnosing FSSs in each body organ. The questionnaire-based data including psychological evaluation, dietary intake and functional symptoms were validated in personal medical visits with a psychologist,

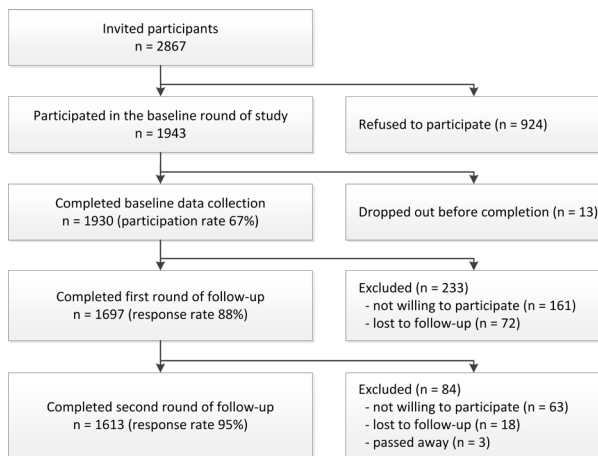


Figure 1 Flow chart of the Isfahan functional disorders cohort study.

a dietician and a physician, respectively, as the gold-standard method. A fixed medical team interviewed all the individuals and were responsible for making sure whether the questions are correctly comprehended and answered. This was done in three separate work stations and could take up to an hour. Incomplete questions were filled during this visit and interview-based diagnosis of the symptoms was also recorded. Phenotype assessment tools and evaluation schedule are described in online supplemental tables 1 and 2.

Physical examination and anthropometric measurements

Clinical examination including measurements of blood pressure, anthropometric parameters (ie, weight, height, neck, chest, waist and hip circumferences), body composition analysis (by bioelectrical impedance), lung function (ie, spirometry), pain sensitivity (using a handheld algometer) and adipose tissue thickness (by skinfold calliper) are performed at baseline and during subsequent follow-ups.

Laboratory methods

Participants were asked to refer to the local health centre early in the morning after 8 hours of fasting. Participants were requested to collect morning midstream urine and a stool specimen in the provided containers at home just before leaving for the health centre. Biological samples were collected on arrival and transferred to the laboratory under cold chain conditions. Stool, urine and fasting blood samples are collected from all the participants. As a quality control indicator, 5% of samples were rechecked for all the metabolic markers. Additional samples of whole blood, serum, plasma, stool, urine and DNA samples are preserved in a biobank for future complementary studies. General laboratory evaluation was performed for all participants in the baseline phase of the study, but only the more important and more variable diagnostic tests were done in the consequent visits due to budget limitations. Laboratory tests and instruments are described in online supplemental table 1.

Biota

DNA has been extracted from blood samples of all participants to be genotyped on Illumina Global Screening Array. Faecal microbial DNA has been extracted for 16S rRNA amplicon sequencing. DNA samples were subjected to spectrophotometric assay for quality assurance.

Dietary intake

Dietary intake assessment is done using a dish-based, semiquantitative Food frequency questionnaire for the Iranian adult population.¹⁸ A qualified dietician assessed the filled questionnaires. Missing or doubtful responses were completed and verified during a medical interview. Participants are reassessed at each annual visit.

Questionnaires

Questionnaires are used to obtain detailed information on functional symptoms, psychological assessment, life-style evaluation, quality of life and sociodemographic information. Considering that some health behaviours or psychological traits (such as eating attitude and coping mechanisms) are fairly stable over time and the high number of questionnaire items for each visit that could cause respondent fatigue, we decided that there was no need to include every questionnaire in all annual visits. However, symptoms profiles, psychological traits and behaviours that are expected to vary over time were checked annually. Four questionnaires were not included in the baseline survey and were added in the first follow-up visit. The list of questionnaires for each phase of the study is mentioned in online supplemental table 2.

Data analysis

Statistical analysis

All data are collected in a central database using SPSS Version 23 software according to a standardised protocol. The results of participants' demographics, questionnaire-based prevalence of functional symptoms and other outcome variables will be summarised using descriptive summary measures, expressed as mean±SD for continuous variables and percentages and frequencies for categorical variables. Student's t-test will be used to assess differences between two means. χ^2 test will be used to assess the degree of association between categorical variables. A two-sided $p < 0.05$ will be considered statistically significant. The diagnostic agreement between questionnaire-based and interview-based diagnosis of syndromes will be assessed using kappa statistic. Exploratory factor analysis and latent class analysis will be performed to detect qualitatively different subgroups inside the study group. Random-effects regression models will be done for time-series analysis. The correlation between genomic and meta-genomic variations with FSSs will be explored in genome wide and meta-genome wide association study analyses, respectively.

Sample size

This is an exploratory observational study and the sample size was based on pragmatic considerations, given time



and facility constraints of the study along with local capacity. Taking the high prevalence of FSSs into account, it was predicted that a total number of 2000 participants would suffice. We estimate that we would have 90% power to detect the hypothetical associations between most of the functional symptoms and the biota/biological data.

Ethics and dissemination

The study was approved by the National Research Ethics Committee of the Iranian Ministry of Health and Medical Education and the Research Ethics Committee of Isfahan University of Medical Sciences (IR.MUI.REC.1395.1.149). All participants agreed to participate and signed a written consent form after receiving written and oral information about the study. Subjects consented to undertake annual investigations as set out in the study schedule and for long-term access to their collected biological samples. Study findings will be published in peer-reviewed scientific journals and will be presented at national and international conferences.

DISCUSSION

Functional somatic symptoms (FSSs) are common and are shown to be a risk factor for poor health status and high healthcare use. Despite the high prevalence of FSSs and the burden they put on public health, very few population-based cohorts, such as the Danish study of Functional Disorders have been carried out to investigate their epidemiology and clinical features.^{19–25} A robust classification system of functional disorders is still lacking and although various approaches are suggested for their delimitation, each has its own strengths and weaknesses and hence, more studies are required for better definition and categorization of patient symptoms.²⁶ A major issue in this field is that symptoms could occur in multiple body organs belonging to various medical specialties which warrants the need for a holistic view when confronting such disorders. Moreover, co-occurrence of symptoms could play an important role in diagnosis and treatment of affected individuals. Symptoms clusters based on functional symptoms spread over body organs have shown promising results for studying the risk factors and prognosis of FSSs.^{10 16} We believe this approach could be further improved when corrected for personalised traits such as psychological, life style and biota characteristics.

This longitudinal population-based cohort study is the first nationwide survey of epidemiological characteristics of FSSs in Iranian adult population. In this study, we collect a validated multidomain dataset containing medical, psychological, lifestyle and multiomics data. This will be used to investigate symptoms associations and to suggest a new delimitation of FSS by identifying similar symptom patterns in combination with personalised omics profile of the individuals.

Availability of omics data, repeated measurements of different phenotypes over time and a biobank of blood, serum, plasma, stool and urine samples are among the

other important strengths of this study. On the other hand, although our sample size is relatively large, it may still not be sufficient for evaluating rare FSSs.

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Contributors PA is the lead investigator of this cohort study. PA, AV and HR contributed to the conception and design of the study. PA and HR were responsible for the construction of the questionnaires and HR handled data entry and primary analyses. AV, FH, AA, HR and HS provided methodological and clinical consults on various aspects of the study design and participant recruitment. AA drafted the manuscript. All authors were involved in critical revision of this cohort profile and approved the final manuscript.

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Competing interests None declared.

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SUPPLEMENTAL MATERIAL

A multidisciplinary approach to functional somatic syndromes: study protocol for a population-based prospective cohort study

Peyman Adibi, Alireza Ani, Ahmad Vaez, Fatemeh Hadizadeh, Harold Snieder, Hamidreza Roohafza

Table 1. Laboratory tests and instruments used in ISFUN study.

Laboratory test	Baseline	First follow-up	Second follow-up	Third follow-up	Equipment [Laboratory kit provider]
Complete blood count	*	*	*	*	XN-1000 Hematology Analyzer, Sysmex
Fasting blood glucose Serum cholesterol Triglycerides LDL/HDL cholesterol cholesterol Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Alkaline phosphatase test (ALP) C-reactive protein (CRP)	*	*	*	*	Cobas c 311 analyzer, Roche [Roche diagnostics]
Blood urea nitrogen Serum creatinine, calcium, magnesium, iron	*				Cobas c 311 analyzer, Roche [Roche diagnostics]
Serum ferritin	*	*	*	*	Cobas e 411 analyzer, Roche [Roche diagnostics]
Thyroid-stimulating hormone (TSH)	*				Cobas e 411 analyzer, Roche [Roche diagnostics]
Serum zinc	*				BS800M chemistry analyzer, Mindray [Greiner diagnostic]
25-hydroxy vitamin D	*				HPLC 3345, Rigol-Shimadzu
Blood DNA extraction	*				PrimePrep Genomic DNA Isolation Kit (from Blood) - GeNet Bio
Stool DNA extraction	*				QIAamp Fast DNA Stool Mini Kit - QIAGEN
Verifying DNA sample quality	*				NanoDrop OneC Spectrophotometer, Thermo Scientific
Gel Documentation Imaging	*				E-BOX CX5 TS-20.M, Vilber Lourmat
Urine metabolome	*	*	*	*	Mass spectrometry (GC-MS)

Table 2. Phenotype assessment tools and evaluation schedule in ISFUN study.

Assessment tools	Baseline	First follow-up	Second follow-up	Third follow-up	Assessed disorders/phenotypes
Functional somatic syndromes					
Screening for somatoform symptoms[1]	*	*	*	*	Somatization
Somatic symptom disorder-B criteria scale[2]	*	*	*	*	Symptom-related thoughts, feelings and behaviors
Functional gastrointestinal disorders (FGID) symptoms checklist[3,4]	*	*	*	*	Functional globus, functional heartburn, functional dyspepsia, irritable bowel syndrome, functional constipation, functional diarrhea, centrally mediated abdominal pain, functional abdominal pain syndrome
Non-cardiac chest pain checklist	*	*	*	*	Non-cardiac chest pain
Low back pain checklist	*	*	*	*	Low back pain
Fibromyalgia diagnostic criteria[5]	*	*	*	*	Fibromyalgia
Pelvic and urinary pain/frequency[6]	*	*	*	*	Interstitial cystitis, chronic pelvic pain syndrome, sexual pain disorder
Sexual function questionnaire[7]	*	*	*	*	Female: sexual interest/arousal disorder, orgasmic disorder, genitopelvic pain/penetration disorder Male: erectile disorder, hypoactive disorder, premature ejaculation, delayed ejaculation
Headache checklist	*	*	*	*	Migraine, tension- type, chronic tension- type headaches
Psychological variables					
Diagnostic criteria for psychosomatic research[8]	*	*	*	*	Disease phobia, thanatophobia, health anxiety, illness denial, persistent somatization, functional somatic symptoms secondary to a psychiatric disorder, conversion symptoms, anniversary reaction, irritable mood, type a behavior, demoralization and alexithymia.
Hospital anxiety and depression scale[9,10]	*	*	*	*	Anxiety, depression
Body shape questionnaire[11]	*				Body image disorder
Eating attitudes test[12,13]	*				Dieting, bulimia and food preoccupation, oral control.
Revised adult attachment scale[14]	*				Adult attachment styles
Neo personality inventory subscales [15,16]	*				Neuroticism, openness to experience

Post-traumatic stress diagnostic scale[17]	*				Trauma, post-traumatic stress disorder
Stressful life event questionnaire[18,19]	*	*	*	*	Homelife, financial problems, social relations, personal conflicts, work conflicts, educational concerns, job security, loss and separation, sexual life, daily life, health concerns
Modified COPE scale[20,21]	*				Positive reinterpretation and growth, problem engagement, acceptance, seeking support, avoidance
Warwick-Edinburgh mental wellbeing scale[22]		*	*	*	Wellbeing
Short-form McGill pain questionnaire[23]		*	*	*	Pain
Sense of coherence questionnaire[24,25]		*			Sense of coherence
Multidimensional scale of perceived social support[26,27]		*			Social support
Lifestyle checklist					
Food frequency questionnaire[28]	*			*	Food frequency
Meal pattern checklist[29]	*				Meal pattern
Quality of life short form-12[30]	*			*	Quality of life
International physical activity questionnaire[31]	*			*	Work time, leisure time, transportation
Pittsburg sleep quality index[32]	*			*	Subjective sleep quality, sleep latency, sleep duration, sleep disturbances, use of sleeping medication
Smoking, addiction and drinking checklist	*	*	*	*	Waterpipe and cigarettes smoking, drug abuse, alcohol drinking
Demographic and socio-economic checklist	*	*	*	*	Health costs, socio-economic status, demographic data
Clinical measurements					
Blood pressure measurement	*	*	*	*	Systolic and diastolic blood pressure (sphygmomanometer)
Anthropometric measurements	*	*	*	*	Weight and height measurement - neck, chest, waist and hip circumferences, skinfold thickness
Pain threshold test	*				Hypersensitivity to pain (Algometer - Somedic Type II, probe of 1.0 cm ² ; Somedic Production AB, Hörby, Sweden)
Pulmonary function testing	*				Lung volumes (Spirometer - MIR spirolab; MIR Co., Roma, Italy)
Bioelectrical impedance analysis	*	*	*	*	Body composition

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