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Cohort Profile

The PERSIAN Guilan Cohort Study (PGCS)

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Abstract

The Guilan cohort study was conducted on 10520 men and women between 35-70 years of age in Guilan province and Some'e Sara county, northern Iran, from October 8, 2014 to January 20, 2017 as part of the Prospective Epidemiological Research Studies in Iran (PERSIAN). Eligible participants were contacted over the phone and were invited to refer to the cohort center. Demographic information was inquired during the phone call. Upon arrival of participants at the cohort center, consent forms were filled out and additional data on demographic characteristics, socio-economic status, employment, fuel status and location, lifestyle habits, and sleep and food habits were obtained. Blood pressure and anthropometric indices were measured. Finally, biological samples were collected. There was a participation rate of 83.2%, and a 15-year active follow-up was planned for all of the participants.

The results showed that 53.5% of the participants were female and 56.1% of the participants were rural residents. A total of 1738 participants (16.5%) were illiterate. Of the total cohort participants, 4543 (43.2%) were hypertensive. Hypertension was defined as a systolic blood pressure ≥140 mm Hg or a diastolic blood pressure ≥90 mm Hg, or a prior diagnosis of hypertension by a health professional, or taking antihypertensive medications. Approximately one-third of participants (n=3435 or 32.7%) were obese, and most were females (n=2647, 77.1%). Prevalence of diabetes (defined as fasting blood sugar equal or higher than 126 mg/dL or history of diagnosis with diabetes or taking glucose lowering medication) was 24.1% (20.2 % in males and 27.3% in females). We also obtained laboratory samples for basic and genetic scientific research. According to laboratory evaluations, 3,585 (34.1%) of the participants had hematuria, and most of them were women (n=2151 or 60%).

The preliminary results of our study demonstrate a high prevalence of metabolic risk factors for Non-Communicable Diseases and mainly cardiovascular diseases in Guilan province, which merit detailed investigation of their intricate relationships. The population-based design of the study as well as its large sample size were the main strengths of our cohort study that makes these investigations feasible. Researchers interested in using the information are invited to visit the following websites: http://www.gums.ac.ir/cohort and http://persiancohort.com/.

Keywords: Cohort profile, Iran, Non-communicable diseases

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Introduction

Following the long-term health system reform in Iran, it seems that the incidence of communicable diseases has been considerably decreasing while the prevalence of non-communicable diseases (NCDs) is still increasing.[1] Among NCDs, cardiovascular disease (including ischemic heart disease and stroke) has been reported as the leading cause of death with a prevalence of 42% in Iran.[2] Cancer is the third main cause of mortality in Iran with ascending rise in Guilan over the past decade.[2,3]

Metabolic disorders including diabetes, overweight, obesity, and hypertension are the main risk factors for most of the NCDs. In 2011 in Iran there were just 4.5 million people with diabetes among whom over a quarter were not previously diagnosed.[4] It is predicted that by the year 2030, 9.2 million Iranians will be diabetic.[5] The global study by Ezzati et al reported a prevalence of 11.4% for diabetes in men and 12.9% in women aged 18 years and older in Iran in 2014.[6]

As for hypertension, which is the main risk factor for stroke and ischemic heart disease, different prevalence rates are reported. The results of survey of risk factors of NCDs show that in 2011, 25.6% of the population aged 25 to 70 years had hypertension.[7] Ezzati et al reported a prevalence of around 20% in both men and women aged 18 years or older in 2015.[8]

Finally, there is large diversity in terms of prevalence of obesity and overweight among different Iranian age and sex groups. Nationally in Iran, a prevalence of 40% and 30% for overweight and obesity were reported respectively in

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women in 2016. In men, the prevalence of overweight and obesity were 40% and 20% respectively. [9]

These reports demonstrate the gravity of the upcoming epidemic of NCDs and their metabolic risk factors in Iran. To reduce the heavy financial burden of NCDs, implementation of efficient prevention and treatment plans is warranted. The WHO has considered NCDs as one of the main constraints to poverty reduction and sustainable development.[10] The health economic analysis has suggested that prevention of disease is a cost-effective approach to improve general public health. Effective prevention strategies for NCDs require detailed information about their causes and risk factors. Large population-based prospective cohorts are ideal research studies on the effects of lifestyle, genetic susceptibility, socioeconomic, occupational, and psychological factors on the occurrence of NCDs.[11] Novel information can be collected on these risk factors and their impact on the natural history and causal pathways of disease development.[12] Particularly in the elderly, there should be a program for early disease diagnosis and prevention of NCDs that could lead to reduction in health expenditures and increased quality of life.

Considering the high and rising prevalence of NCDs and their risk factors in Iran, implementation of a prospective cohort study on these diseases and their main modifiable risk factors in the Iranian population seems to be indispensable. Accordingly, the Prospective Epidemiological Research Studies in Iran (PERSIAN) study was designed in 2014 and launched including various geographic, climatic, and ethnic groups in eighteen provinces.[13,14] One of these provinces was Guilan, which is located in northern Iran in the vicinity of the Caspian Sea. The region is characterized by plains and forested mountains. The region's climate is humid and rainy. Also, the main ethnicity of the area is Gilak. Similar to the entire country, NCDs are the main causes of morbidity and mortality in this province.

To comply with the PERSIAN cohort, the Guilan cohort was designed and launched with the following objectives: (*i*) to study the prevalence and incidence of NCDs, (*ii*) to determine the roles and the interaction of genes and lifestyle risk factors in development of various chronic diseases through a large-scale project (*iii*) to establish a biobank for basic and genetic scientific research, and (*iv*) to produce a platform for population based clinical trials to explore cost effective interventions.

Materials and Methods

Some'e Sara county has 3 distinct districts, including Tulemat, central "Some'e Sara", and Mirza Kūchak. Thus, this study was conducted on men and women between 35 and 70 years old in Tulemat (including urban areas and 32 villages) and also a small section of the central part (containing urban areas and 7 villages) that is located in North of Iran. This area was selected due to its high population density, long-term population stability, a relative similarity in demographic and behavioral characteristics between residents of the province, and ease of access to residents due to its proximity to the center of the province. This study was nested within the Iranian Primary healthcare (PHC) system in which community health workers (or Behvarz) serve the residents and provide basic health care. Behvarz are usually selected from local people to act as an interface between people and the health system. The current study largely benefitted from the Behvarz in the health system of Tulemat. Behvarz have very good reputation and credibility among the local population, which increased the effectiveness of this study by encouraging and inviting the residents to participate.

Residents were informed of the objectives of the study process. At baseline, trained health workers walked door-to-door in rural and urban areas to inform individuals of the study and its objectives. Accurate local demographic information was obtained using census data. Behvarz and research interviewers selected individuals, registered their contact information, and determined their geographical location using Garmin GPSMAP 78s (Figure 1).

According to the provided lists, about 27 to 30 eligible participants were contacted over the phone on daily basis during the period from October 8, 2014 to January 20, 2017. The interviewers were able to fluently speak the native language of the region, and participants were invited to participate in an interview. Also, participants were requested to bring their ID cards and medications to the interview. They were asked to fast for 12 hours, have unclipped nails, ensure that they were not in their menstruation phase, and were asked to refer any eligible partner from their relatives to the study. The exclusion criteria included inability to attend the clinic for a physical examination, mental retardation, and unwillingness to participate in the study. During the phone interview, the demographic information of all interview invitees including age, gender, educational and marital status, place of residence, and reasons for lack of interest were recorded. The aims of the study were explained to the participants in detail upon arrival at the cohort center, and consent forms were completed.

Follow-up Evaluations

After the enrollment phase, all participants were actively followed annually according to the PERSIAN cohort protocol for 15 years.[13] In order to optimize the follow-up, the contact number and the household location map (as determined by geographical positioning system [GPS]) were registered. All participants were asked to notify the cohort team of any change in their address. In case participants were reluctant to be followed, they were contacted and encouraged to participate in the study by telephone, mail, or referral of the health workers to participants' residence.

During the follow-up visits, participants were asked about serious health problems including new major diseases as well as causes and durations of any hospitalizations in the past year. Diagnoses of new diseases were evaluated and approved for each participant by 2 trained internists of the cohort

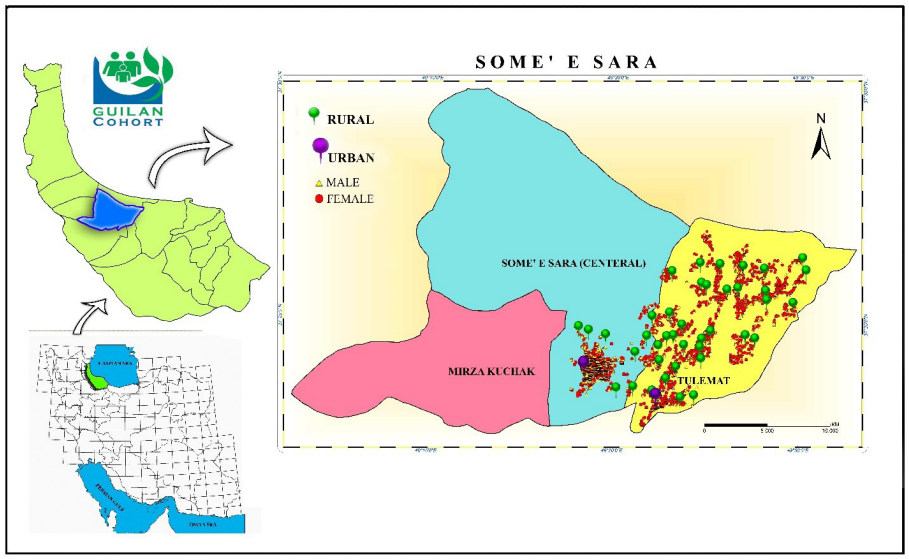

Figure 1. Map With Location of Greater Guilan Area in Iran.

team. Moreover, participants were asked to inform the cohort team in case of new major disease presentations or any intent to migrate. Causes of deaths, which were confirmed by relatives and friends, were collected and recorded from the Some'e Sara county health center mortality registration system. Afterwards, further confirmation was carried out by the cohort mortality registration team.

Obtained Data

A wide range of data in the PERSIAN Guilan Cohort Study (PGCS) was collected using the PERSIAN cohort inventory. Questionnaires were completed using online software specific to this study. The PERSIAN Cohort questionnaire consists of 482 items completed in a face-to-face interview format and a physical examination accomplished by 3 teams of trained interviewers: general, medical, and nutritional.

In the general sector, an eleven-digit code was allocated to each participant. In this phase, the following data were collected: demographic characteristics, socio-economic status, employment status, fuel status and location, lifestyle habits, and sleep and food habits. Anthropometric indices including weight (in kg), height, and hip, waist, and wrist circumference (in cm) were measured according to National Health and Nutrition Examination Survey Manual.[15] Participants were classified into the following body mass index (BMI) groups: underweight (BMI <18.5 kg/m^2), normal weight (BMI = 18.5–24.99 kg/m^2), overweight (BMI = 25–29.9 kg/m^2) and obese (BMI ≥30 kg/m^2).[16] In the medical sector, reproductive history and history of chronic diseases were inquired. History of medication use was assessed by inquiring and exploring the medication that they brought to the interview. Blood pressure was measured twice in each arm after ten-minute intervals in sitting position using Richter auscultatory sphygmomanometers (MTM Munich, Germany). One-minute pulse rates were evaluated as well. The nutrition team filled out a 24-hour food frequency questionnaire (FFQ).

Additionally, alopecia, facial hirsutism, iris color, limb disabilities, and oral hygiene were examined. Eye health was examined. This included a questionnaire regarding eye-specific medical history and a visit by a trained optometrist to assess refractive errors. Individuals who met certain screening criteria (those with diabetic retinopathy, visually significant cataract, glaucoma, glaucoma suspect, lid/orbit lesions, strabismus and other) received a complete ophthalmologic exam.

For each participant, samples of fasting blood (25 mL), urine (at least 10 mL), hair (1-3 cm from the base of the scalp), and nail (10 fingernails or toenails) were collected by trained technicians and labeled. Blood and urine samples were transferred in a cold box to the laboratory of the cohort center. Eighteen milliliters of whole blood in a tube was used with ethylenediaminetetraacetic acid (EDTA) in order to conduct hematology tests. Two 1.5-mL and one 1-mL cryotubes of whole blood, two 1.5-mL and five 1-mL cryotubes of plasma, three 0.5-1-mL cryotubes of buffy coat and two 1-mL cryotubes of serum was separated. All of these tubes were stored in freezers at -70°C. After microscopic and macroscopic testing, 1.5 mL samples of urine were kept at -70°C. Nail and hair samples were placed inside foil wraps and were then placed in individual zipped bags where dehumidifiers were placed inside the bags. Then, the bags were labeled with participant codes and were kept at room temperature. In addition to storing the samples, biochemistry tests and urinalysis were conducted. [13]

All completed questionnaires were re-examined by 2 cohort observers on a daily basis. In case of coding error or any defect in the questionnaire, the participants were contacted again to correct the mistakes. To improve the quality of completed questionnaires, several workshops were held for all team members.

Results

Figure 2 shows a flow chart of the recruitment process. In

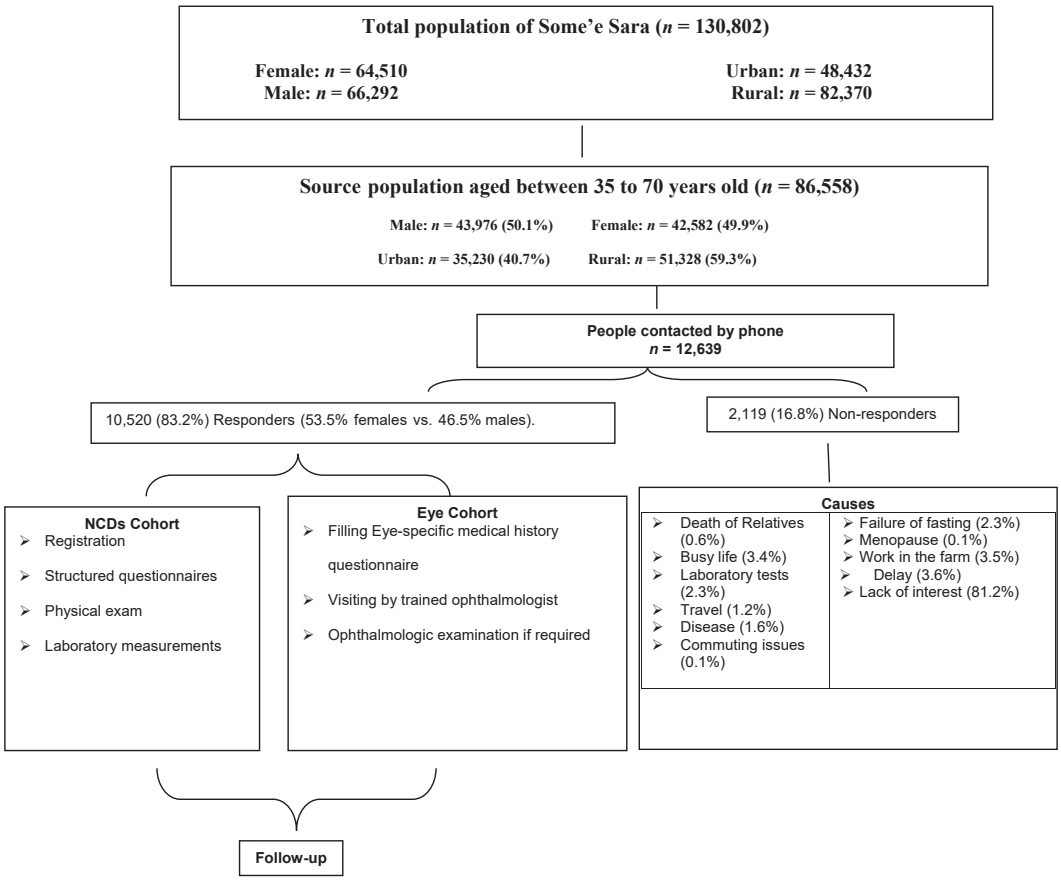

Figure 2. Flowchart of the Data Collection Process in the PERSIAN Guilan Cohort Study From 2014–2017.

summary, a total of 10 520 people were recruited through 12 639 phone invitations corresponding to a participation rate of 83.2%. The most prevalent reason among non-responders was lack of interest (81.2%).

The source population was between 35 to 70 years old and consisted of 42 582(49.9%) women and 43 976(50.1%) men. The population of this study consisted of slightly more females (53.5% females vs. 46.5% males). Also, the majority of the source population lived in rural areas (51 328 or 59.3%), and similarly the participants in our study were mostly recruited from rural regions (56.1% vs 43.9%) (Figure 2). The age pattern of the study participants was similar to the source population. The proportion of participants in each age group were as follows: 29.9% between 35–44 years old, 36.6% between 45–54 years old, 25.9% between 55–64 years old, and 7.6% older than 65 years old). Illiteracy rate was 16.5%, with a male illiteracy rate of 10.4% and a female illiteracy rate of 21.9%. Prevalence of current daily smoking was dramatically higher among men than among women (32.9% vs 0.4%). Hypertension was defined as a systolic blood pressure ≥140 mm Hg or a diastolic blood pressure ≥90 mm Hg, or a prior diagnosis of hypertension by a health professional, or taking antihypertensive medications.[17] The overall prevalence of hypertension was 43.2%. The prevalence was higher in women than men (46.8% vs 38.9%). Diabetes was defined as fasting blood sugar equal or higher than 126 mg/dL or history of diagnosis with diabetes or taking glucose lowering medication.[18] Prevalence of diabetes was 24.1% (20.2% in males and 27.3% in females) (Table 1).

Based on anthropometric measurements, about 7633 (72.6%) of the individuals were overweight and obese (59% of men and 84.3% of women) (Table 1). In addition, based on laboratory data, prevalence of hematuria was 34.1%, which was dominant among women (60%) (Table 2). As the eye cohort was established a few months after the adult cohort, the expert optometrists assessed fewer participants. About 2324 out of 5807 were recommended to be checked by an eye specialist.

Discussion

It is already very well known that Iran is witnessing an evident epidemiological transition. The transition can even be considered as an epidemic of NCDs and their risk factors.[19] Public awareness has increased during the past decade and the attitude of policy makers is favorable towards integrating specific health care packages into the health system that are designed to efficiently control risk factors and to prevent the actual NCDs. Yet, there are main challenges on this route. The main challenge is lack of data at sub-national levels in Iran to reveal the exact impact of risk factors on development of NCDs and the efficient ways to prevent them. Facing diversity in ethnicities, cultures, socio-economic status, life style, nutritional, occupational,

Table 1. Baseline Characteristics of the PERSIAN Guilan Cohort Study (PGCS) Participants From 2014-2017[a]

Baseline Characteristics	Total (n = 10520)	Male (n = 4887)	Female (n = 5633)
Age at baseline, No. (%)			
35–44	3142 (29.9)	1430 (29.3)	1712 (30.4)
45–54	3852 (36.6)	1789 (36.6)	2063 (36.6)
55–65	2730 (25.9)	1279 (26.2)	1451 (25.8)
<65	796 (7.6)	389 (8)	407 (7.2)
Habitat, No. (%)			
Urban	4613 (43.9)	2062 (42.2)	2551 (45.3)
Rural	5907 (56.1)	2825 (57.8)	3082 (54.7)
Marriage, No. (%)			
Single (no partner)	305 (2.9)	78 (1.6)	227 (4)
Married	9527 (90.6)	4733 (96.8)	4794 (85.1)
Widow (er)	566 (5.4)	48 (1)	518 (9.2)
Divorce	122 (1.2)	28 (0.6)	94 (1.7)
Education, No. (%)			
Illiterate	1738 (16.5)	506 (10.4)	1232 (21.9)
1–5 years of schooling	3312 (31.5)	1335 (27.3)	1977 (35.1)
6–12 years of schooling	4832 (45.9)	2590 (53)	2242 (39.8)
University/college	638 (6.1)	456 (9.3)	182 (3.2)
Employment status, No. (%)			
Unemployed	4781 (45.4)	562 (11.3)	4219 (75.1)
Employed	5739 (54.6)	4325 (88.7)	1414 (24.9)
House, No. (%)			
Owner,	8141 (87.0)	4221 (86.5)	4920 (87.5)
Tenant	803 (7.6)	410 (8.3)	393 (6.9)
Organizational	48 (0.5)	21 (0.4)	27 (0.5)
Relatives	522 (5)	233 (4.8)	289 (5.1)
Smoking more than 100 cigarettes in lifetime, No. (%)	2584 (24.5)	2522 (51.6)	62 (1.1)
Current cigarette smoking, No. (%)			
Yes (daily)	1633 (15.5)	1611 (32.9)	22 (0.4)
Yes (sometimes)	194 (1.8)	184 (3.8)	10 (0.2)
No	7866 (74.8)	2298 (47.1)	5568 (98.8)
Past smoking	827 (7.9)	794 (16.2)	33 (0.6)
Age started smoking (mean ± SD)	19.6 ± 7.7	19.4 ± 7.7	27.3 ± 12.3
Hypertension,[b] No. (%)	4543 (43.2)	1904 (38.9)	2639 (46.8)
Diabetes,[c] No. (%)	2531 (24.1)	989 (20.2)	1542 (27.3)
Self-reported co-morbidities at baseline, No. n (%)			
Cardiac ischemia	755 (7.2)	332 (6.8)	423 (7.5)
Myocardial infarction	132 (1.3)	91 (1.9)	41 (0.7)
Stroke	120 (1.1)	46 (0.9)	74 (1.3)
Renal failure	63 (0.6)	29 (0.6)	34 (0.6)
Fatty liver	696 (6.6)	234 (4.8)	462 (8.2)
Hepatitis B	9 (0.1)	6 (0.1)	3 (0.1)
Hepatitis C	10 (0.1)	8 (0.2)	2 (0.01)
Chronic lung disease	386 (3.7)	155 (3.2)	231 (4.1)
Rheumatic disease	309 (2.9)	77 (1.6)	232 (4.1)
Epilepsy	77 (0.7)	38 (0.8)	39 (0.7)
Depression	549 (5.2)	136 (2.8)	413 (7.3)
Psychiatric disorder	1629 (15.5)	482 (9.9)	1147 (20.4)
Cancer	94 (0.9)	29 (0.6)	65 (1.2)
BMI, kg/m^2, No. (%)			
Underweight: <18.50	141 (1.4)	110 (2.3)	31 (0.6)
Normal: 18.50–24.99	2746 (26.0)	1894 (38.7)	852 (15.1)
Overweight: 25–30	4198 (39.9)	2095 (42.8)	2103 (37.3)
Obesity: >30	3435 (32.7)	788 (16.1)	2647 (47.0)
Weight (mean ± SD)	73.9 ± 13.6	75.3 ± 13.8	72.8 ± 13.4
Height (mean ± SD)	162.3 ± 9.5	169.8 ± 6.8	155.9 ± 6.1
Hip circumference (mean ± SD)	104.3 ± 103.2	99.5 ± 16.3	108.4 ± 140.3
Wrist (mean ± SD)	16.7 ± 1.3	17.3 ± 1.1	16.2 ± 1.3
Waist circumference (mean ± SD)	98.8 ± 12.4	93.6 ± 10.9	103.3 ±11.9
Heart rate, bpm (mean ± SD)	78.7 ± 8.6	77.1 ± 8.6	80.2 ± 8.4
Systolic blood pressure, mm Hg (mean ± SD)	118.24 ± 16.75	118.31 ± 16.67	118.19 ± 16.82
Diastolic blood pressure, mm Hg (mean ± SD)	76.97 ± 11.01	77.12 ± 11.12	76.84 ± 10.91

[a] No. (%) = 4887 (46.5) men, and No. (%) = 5633 (53.5) women.
[b] Hypertension was defined as a systolic blood pressure (SBP) ≥140 mm Hg, and /or a diastolic blood pressure (DBP) ≥90 mm Hg, a prior diagnosis of hypertension by a health professional indicating that one had high BP or used antihypertensive drugs.[19]
[c] Diabetes was defined as fasting blood glucose equal to or higher than 126 mmol/L, or was on medication for raised blood glucose, or had a history with diagnosis of diabetes.[20]

Table 2. Laboratory Assessments in the PERSIAN Guilan Cohort Study (PGCS) in 2014–2017[a]

Laboratory test	Total n = 10520(%)	Male n = 4887(%)	Female n = 5633(%)
FBS 100–126 mg/dL	2396 (22.8)	1105 (22.6)	1291 (22.9)
FBS >126 mg/dL	1269 (12.1)	542 (11.1)	727 (12.9)
TG >150 mg/dL	4538 (43.1)	2226 (45.5)	2312 (41.0)
HDL <40 mg/dL	2188 (20.8)	1292 (26.4)	896 (15.9)
LDL >100 mg/dL	6779 (64.4)	3123 (63.9)	3656 (64.9)
AST >30 U/L	743 (7.1)	361 (7.4)	382 (6.7)
ALT (≥45 for male and ≥ 30 for female) U/L	797 (7.6)	295 (6.0)	502 (8.9)
BUN >21 mg/dL	323 (3.1)	179 (3.7)	144 (2.6)
Creatinine >1.41 mg/dL	58 (0.6)	43 (0.9)	15 (0.3)
Vitamin D <10 ng/mL	1529 (14.5)	576 (11.8)	953 (16.9)
Hematuria (>3 red blood cells per high power field on microscopic urinalysis)	3585 (34.1)	1434 (29.3)	2151 (38.1)

Abbreviations: FBS, Fasting blood sugar; TG, Triglycerides; HDL, High-density lipoprotein; LDL, Low-density lipoprotein; AST, Aspartate transaminase; ALT, Alanine transaminase; BUN, Blood urea nitrogen.

[a] No. (%) = 4887 (46.5) men, and No. (%) = 5633 (53.5) women.

educational, and environmental risk factors and crucial role of genetic risk factors across provinces in Iran, studies at sub-national levels are mandatory for collecting high quality data required for cost-effective policy making tailored to specific needs and priorities of communities.[20] The aim of the current study was to evaluate the burden of NCDs attributable to a wide array of risk factors, with the ultimate goal of designing interventions in the setting of this study; interventions that can target modifiable risk factors for the prevention of NCDs.

The preliminary results of this study demonstrate the high prevalence of metabolic risk factors (high BMI, high blood pressure, high FBS, and high cholesterol) in this area of Guilan province. The results also demonstrate the high prevalence of NCDs despite the fact that a large proportion of participants inhabit rural areas. These findings are in accordance with national studies and sub-national estimates in other provinces of Iran. Numerous interventions can be designed to study their cost-effectiveness in controlling the risk factors. Although genetic risk factors are not modifiable, their interaction with other modifiable risks can be a valuable evidence base for effective policies. Vulnerable sub-groups will be identified for targeted interventions. Finally, the trends in NCDs and their risk factors and the effectiveness of interventions will be monitored and evaluated through long term follow-up of the current study.

This study has several strengths and advantages associated with its design and implementation. The prospective design of this study is its most important advantage. This prospective, population-based study provides a favorable context for training researchers in the field of NCDs in northern Iran. All data has been collected through valid tools and instruments. All questionnaires were completed electronically and data recording was conducted online using personal computers. This approach facilitated the whole process of data entry, ensured quality of the data, and provided direct access of principal investigators for monitoring performance of the interviewers. The geographical locations of participants were recorded using a GPS. Subsequently, the locations were mapped using a geographic information system. In accordance with international standards, a bio-bank was established for this study. Therefore, conducting nested case-control and genetic studies will be facilitated in future. In addition, public awareness through cohort executives' lectures and notifications by the local health workers successfully increased public participation. Finally, the study was representative of the entire population of the area and had a large sample size.

Despite its advantages, this study also suffers from several limitations. Until now, we have recruited half of the systematic exposure updates according to follow-ups. As most of the recruited residents are mainly engaged in agricultural activities during specific seasons, there were some difficulties in follow-up of these participants. In addition, there is currently lack of funding for genetic studies.

In conclusion, the Guilan cohort study is among the first steps towards controlling the epidemic of NCDs in Iran. Along with other cohorts nested in PERSIAN, Iran will be a pioneer in investigating NCDs and their risk factors on such large scale among countries in Middle East and North Africa and other countries with similar socio-economic status and determinants of health.

Authors' Contribution

FMG, HP, RM conducted and managed the entire study. FJ and MRN helped in the design of the study. FJ and SGS drafted the manuscript. HAB, KM, AH, MRN, and FJ helped in data collection, analysis, and critical revision of the manuscript. FMG and FJ supervised the entire processes of the study.

Conflict of Interest Disclosures

None declared.

Ethical Statement

The PGCS design was approved by the ethics committees at the Ministry of Health and Medical Education, the Digestive Diseases

Research Institute (Tehran University of Medical Sciences), and also Guilan University of Medical Sciences (P/3/132/215). Informed consent was obtained from all individual participants included in this study. This manuscript has not been published in whole or in part and is not under consideration elsewhere. All authors have read the manuscript and have agreed that the work is ready for submission and accept responsibility for its contents.

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