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RESEARCH ARTICLE

The Prospective Epidemiological Research Studies in IrAN (PERSIAN) Birth Cohort protocol: rationale, design and methodology

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Background: Birth cohorts are essential for developing evidence-based policies and advancing knowledge on different aspects of the concept of developmental origins of health and diseases (DOHaD). The Prospective Epidemiological Research Studies in IrAN (PERSIAN) is a multicentre cohort in Iran. It is one of the pioneers of DOHaD research in the Middle East and North Africa (MENA) region. This profile provides a brief overview of this birth cohort, focusing on the objectives and design of the study. The main objective of this birth cohort is to evaluate the associations of socio-economic characteristics, lifestyle, diet, environmental exposures and epigenetic factors with outcomes of: pregnancy; mother and child mental and physical health and well-being; child neurodevelopment; and the establishment of chronic disease risk factors.
Methods: The enrolment of PERSIAN Birth Cohort participants is currently ongoing in five Iranian cities (Isfahan, Yazd, Semnan, Sari and Rafsanjan). We plan to recruit 15,000 mother–offspring pairs, and to follow them for at least ten years. Data collection consists of three consecutive phases: (1) periconception until birth; (2) infancy (0–2 years); and (3) childhood (3–11 years). We are collecting data on both 'determinants of health' and 'health outcomes'. In addition to questionnaires and physical examination, various biological samples, including blood, urine, hair, nail, cord blood and breastmilk are being collected. Growth and neurodevelopment of children will be monitored. Appropriate data analysis schemes will be employed to assess the role of early life factors in health and disease that would facilitate international comparisons.

Key words birth cohort • epigenetics • lifestyle • environmental exposure • neurodevelopment

Key messages

- This study provides the profile and objectives of the PERSIAN Birth Cohort ongoing in five cities in Iran.
- This cohort is one of the first longitudinal studies on the developmental origins of health and disease in the Middle East and North Africa.
- It aims to evaluate the effects of gene–environment interactions on pregnancy outcomes and on mother and child mental and physical health.
- The cohort aims to assess the life course establishment of risk factors of non-communicable diseases.

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Introduction

The global prevalence of chronic non-communicable diseases (NCDs), and their contribution to the global burden of diseases has increased during recent years (GBD 2016 DALYs and HALE Collaborators, 2017). Low and middle-income countries (LMICs), including those in the Middle East, are experiencing a rapid epidemiological transition from communicable diseases to NCDs, imposing a considerable burden on their societies. The scientific evidence on developmental origins of health and diseases (DOHaD) supports the possibility and urgency of prevention of NCDs in adults by health promotion interventions from early life. According to DOHaD, environmental exposures before conception, *in utero* and during early life may have life course impacts on physiology and metabolism (Gluckman et al, 2008; Vrijheid et al, 2014). In turn, these changes would determine an individual's sensitivity and risk of developing diseases, including NCDs, later in life. In this context, a broad range of socio-environmental factors including socio-economic characteristics, diet, lifestyle and environmental exposures (such as air and noise pollution, ionising and non-ionising radiation exposure, thermal stress, water pollutants and hormonal disruptors) during pregnancy and early life, are considered to be associated with later life risk of NCDs (Godfrey and Barker, 2000; 2001; Kelishadi and Poursafa, 2014a; 2014b; Van den Bergh, 2011).

Birth cohorts play essential roles in advancing the knowledge regarding different aspects of DOHaD. They often rely on a number of sources and methods including hospital records, questionnaires, biological samples, physical examinations, environmental monitoring/modelling, and clinical and laboratory tests. Such studies provide invaluable data on the association between early life exposures and subsequent health outcomes (Keil et al, 2010; Vrijheid et al, 2012).

To date, DOHaD studies have been mostly based on birth cohorts in high-income Western countries with different personal, cultural and environmental characteristics, thus their findings might not be necessarily translatable to LMICs. Life course research provides evidence that shows what happens *in utero*, in childhood and adolescence, and across generations, impacts on adult health and disease and ageing. Life course perspectives show the complex interactions progressing over time between various determinants and outcomes. We suggest that these perspectives can also determine the dynamic mechanisms that are associated with, between and within heterogeneity in later life health trajectories.

Healthcare services in Iran are based on three pillars: the public-governmental system, the private sector and non-governmental organisations. The Ministry of Health and Medical Education has the responsibility of providing and implementing national health policies. It also manages public and private hospitals, with direct management of public hospitals by medical universities.

Rapid urbanisation, changes in lifestyle and an ageing population, as well as increase in the rate of NCDs, are among the most important challenges for Iranian health system, as in the rest of the world. To tackle these problems at national and global

levels, it is necessary to provide policy makers with reliable data on the determinants of health for implementing preventative programmes (Xie et al, 2011).

Since 2013, nationwide cohort studies have been established in Iran under the title of the Prospective Epidemiological Research Studies in IrAN (PERSIAN). The main objective is to create a solid framework to collect reliable data for healthcare policy and decision making (Poustchi et al, 2017). The PERSIAN Birth Cohort, as part of the PERSIAN Cohort, is a multicentre birth cohort aiming to study the DOHaD in Iran's population. As one of the first studies on DOHaD in the Middle East and North Africa, this cohort will provide new information for the field. This paper is a brief overview of the PERSIAN Birth Cohort, with focus on its objectives and design.

Objectives of the PERSIAN Birth Cohort

The main objective of the PERSIAN Birth Cohort is to evaluate the effects of socio-economic characteristics, lifestyle, diet and environmental exposures, as well as genetic and epigenetic factors, on

- different periods of periconception and early life
- pregnancy complications and outcomes
- mother and child mental and physical health and well-being
- child neurodevelopment
- early- and late-onset of risk factors for chronic NCDs.

We also aim to assess how early life stimuli and exposures over the life course would lead to epigenetic variations.

In addition, in the context of the PERSIAN Birth Cohort we will be able to establish a robust framework to conduct world-class cutting-edge research on existing and emerging health challenges. It could also act as a platform for capacity building for young researchers and students to establish an integrated multicentre network for health promotion and disease prevention.

Methods

Participants and public involvement

The enrolment of participants started in 2016–17 and is currently ongoing in five Iranian cities (Isfahan, Yazd, Semnan, Rafsanjan and Sari). The multicentre approach of the PERSIAN Birth Cohort includes diverse groups from Iran's population, in terms of geographical location, culture and lifestyle habits, which increases the generalisability of the study. To reduce the selection bias, the PERSIAN Birth Cohort covered all forms of hospitals, clinics and health delivery centres (private, public, social security hospitals) in its enrolment process.

Study design and setting

Iran, with a land area of 1,648,195 km^2, is the 17th largest country in the world. We tried to select cities from different parts of the country to cover various environmental, demographic and lifestyle characteristics representative of the Iranian population.

However we could not recruit in all regions, and five cities with collaborative researchers and better availability of facilities were all in the central and northern parts of Iran. These cities and their populations differ in many respects. Isfahan city (the third largest city in Iran, population 2,174,172 in 2011) is the principal industrial city in Iran and the capital of Isfahan province, with a moderate and dry climate. It is located in the plain of the Zayanderud River at the foothills of the Zagros Mountains. Yazd city (the 15th largest city in Iran, population 529,673 in 2011) is the capital of Yazd province and has a dry climate. Semnan city (population 153,680 in 2011) is the capital city of Semnan province and located 216 km east of Tehran, in north central Iran. In general, Semnan city has relatively warm and dry weather in summer and cold weather in winter; its southern part is warm and dry while its northern part has a moderate to cold climate (Babaei et al, 2005; Ziari and Ghorbani, 2017). Sari city (population 296,417 in 2011) is the provincial capital of Mazandaran province, in the north of Iran, between the northern slopes of the Alborz Mountains and southern coast of the Caspian Sea. Sari is the largest and most populous city of Mazandaran with a humid subtropical climate. The economy of Sari is based on food and agriculture industries. Rafsanjan city (population 151,420 in 2011) is the capital of Rafsanjan county, Kerman province. Rafsanjan has a moderate semi-arid climate and is Iran's centre of pistachio cultivation (Kashani-Sabet, 1998).

We have planned to recruit 15,000 mother–offspring pairs, and to follow them for at least ten years. The preliminary sample size calculation of the study was calculated as 10,000 based on the study of the events with more than 1% of prevalence in at least two cities. After that, with increase in the support of the funding body, the sample size was increased to 15,000, sufficient to study the events as rare as those with incidence of less than 0.4% in the study population, which is acceptable for most of the outcomes studied in this cohort. We used two catchment processes in all centres including: (1) recruitment among pregnant women by direct approach to prenatal care providers and clinics. We used the mother and child databank from the National Health Service, phoned pregnant women and after describing the study methods and goals, we invited them to participate in the study; and (2) distribution of invitation advertisements in different locations within the cities.

The study objectives and protocol are explained to participants, and they are reassured that their information will be kept confidential.

The assessments of children are conducted at birth, 2, 4, 6, 12 and 24 months; thereafter they will be followed annually.

Inclusion and exclusion criteria

We enrol pregnant women regardless of the pregnancy time within the first trimester, gravidity, parity or use of fertility treatment, with Iranian nationality, who have resided in the catchment area of the study centre for at least one year, plan to give birth in a hospital located in the city where the cohort study is being undertaken, natural pregnancy or with history of using assisted reproductive techniques for treating infertility, who would not have any communication problems, and who do not plan to move from that city for at least the next five years. Those women who intend to migrate from the city of the ongoing cohort and those without confirmed

compliance to follow-ups will be excluded from the study. We ask participants to attend our centres for future phases.

The routine vaccination of children is obligatory and free in Iran. Thus, to reduce the loss of follow-ups and missing data, we arranged for child follow-up sessions at health centres at the time of their vaccination, which is done at 2, 4, 6, 12 months. From 24 months, we have annual follow ups for them. In addition, every four to six months we provided free health check-up visits for children in the clinics of paediatricians collaborating with the study, both to increase the compliance of families and to complete the necessary follow-up data.

Pregnancies ending in both natural vaginal delivery and caesarean section are included in the study. The high rate of caesarean section in Iran, which is reported to be about 48% (Azami-Aghdash et al, 2014), will provide the PERSIAN Birth Cohort with a unique opportunity to evaluate the short- and long-term health effects of this type of delivery.

Conceptual framework

We at the PERSIAN Birth Cohort are collecting data on both 'determinants of health' and 'health outcomes' at pregnancy and after delivery up to ten years. Our evaluation of the 'determinants of health' will encompass all three domains defined by the World Health Organization (socio-economic environment, physical environment, and individual characteristics and behaviours; Solar and Irwin, 2010).

Data collection

The data collection is based on the computerised questionnaires, biological samples, physical examinations, clinical tests and hospital records, as well as household survey and linked geocoded data of living environment (see Tables 1–3). Together these cover multiple aspects of determinants of health and disease.

We use three groups of questionnaires according to the psychometric properties, and/or local and international validation. Standardised questionnaires and protocols have been developed mainly based on pre-existing questionnaires and protocols applied in European birth cohorts for example, INfancia y Medio Ambiente (INMA), Norwegian Mother and Child Cohort Study (MoBa), Born in Bradford (BiB), Generation R and the Avon Longitudinal Study of Parents and Children (ALSPAC) that have been tailored and validated for the Iranian population. At first, some questionnaires, such as mobile phone use, type of lighting and access to green space, were translated as they do not measure specific components. Some questionnaires like sleep and food frequency are validated in the PERSIAN Birth Cohort (12). Some other questionnaires such as the SF-8 Health Survey and the International Physical Activity Questionnaire (IPAQ) have a Farsi language validated form, which we used. In our cohort centres, questionnaires are administered in face-to-face interviews. Questionnaires are divided into five subdomains, namely: (1) registration and general information, (2) mental health and general lifestyle, (3) environmental and occupational exposures, (4) nutrition and diet and (5) medical information. Interviewers are separately trained for each of these sections, and complete the questions in each part. To arrange the follow-up visits, and informing participants about the upcoming follow-up and its content (such as topics of questionnaires,

Table 1: Tasks during phase 1 of the PERSIAN Birth Cohort

Questionnaire	Enrolment	Trimester 1	Trimester 2	Trimester 3	Delivery
Informed consent	●				
Contact details	●				
Background information	●				
Lifestyle		●	●	●	
General health		●		●	
Domestic violence		●	●	●	
antenatal care		●		●	
Diet		●	●	●	
Environmental exposures		●	●	●	
Medical history		●	●	●	
Psychopathology		●			
Quality of life		●			
Sleep			●		
Family function			●		
Attitude toward pregnancy				●	
Mental health				●	
Anthropometric measures		●	●	●	
Skinfold thickness		●			
Blood pressure		●	●	●	
Ultrasound examination		●	●	●	
Fasting blood glucose		●		●	
Results of laboratory tests		●	●	●	
Blood		●	●	●	
Hair		●	●	●	
Nail		●	●	●	
Urine		●	●	●	
Cord blood					●
Geocoding (using GPS)		●	●	●	
Placental problems					●
Mode of delivery					●
Gestational age					●
APGAR score					●
Premature rupture of membranes					●
Length of delivery					●
Newborn anthropometry					●
Foetal distress					●

types of biological samples, clinical exams and so on) two weeks prior to the next visit, the participants will be contacted over the phone and will be asked about their availability to make an appointment for the visit. One week and one day before the visit, the participants will receive reminder text messages or phone calls.

Table 2: Description of questionnaires used in phase 1

Topic	Description	Source(s)
Mother: background information		
Demographic	Age, sex, ethnicity, religion, marital status, place of birth, lifetime residential addresses	PERSIAN
Socio-economic	Education, employment status, current and past occupational history, income, healthcare access, ownerships and household condition (housing tenure, housing conditions, overcrowding and household amenities), deprivation, social capital, domestic violence	PERSIAN
Family history	Family environment, childhood experiences, medical and psychiatric history of parents, siblings, grandparents, aunts/uncles, familial marriage of the subject, parents, and grandparents	
Occupational history	Current and previous job titles, working during pregnancy, maternity leave, job satisfaction, relationship with colleagues, shift working, manual material handling, occupational exposures to chemicals, pesticides, radiation, noise and heat	INMA, IRAS
Medical history	Obstetric and gynaecologic history, contraceptive history, medication use and vaccination history, visual problems, pre-pregnancy anthropometric measures, history of chronic diseases (cardiovascular conditions, diabetes, allergic conditions, respiratory conditions, neurologic conditions and so on)	
Home environment	Number of inhabitants and their relation to the newborn, heating system, biomass burning, ventilation, natural light, flooring (carpet, rug, ceramic and so forth), type of windows, pet and livestock, presence of insects (cockroaches, flies and the like), use of chemicals	INMA, HELIX
Mother: during pregnancy		
Lifestyle	Physical activity, time-activity pattern, health risky behaviours, active and passive smoking, alcohol consumption, substance abuse, transportation mode, cosmetics use and hair dye, phthalate questionnaire	HELIX
General and mental health	Perceived general mental and physical health and well-being, psychological conditions, general and pregnancy-related problems (emotional, depression, anxiety), attitude towards pregnancy, domestic violence, quality of life, sleep, family functioning	
Antenatal care	Date of the first visit for pregnancy cares, type of care (private vs public), perceived quality of care	
Diet	Food frequency questionnaire, use of supplements including micronutrients and vitamins	PERSIAN
Environmental exposures	Indoor and outdoor air pollution, noise (annoyance and sensitivity and exposure), temperature (indoor and outdoor), mobile phone use, Wi-Fi use, ultraviolet, medical diagnostic radiation, water pollution and consumption, green spaces, chemicals (cleaning products, insecticides, pesticides)	INMA, HELIX
Medical conditions	Medication use during pregnancy, obstetrics problems including vaginal bleeding, oral health, pregnancy-related complications including gestational hypertensive disorders, gestational diabetes, hyperemesis gravidarum, low back pain, gastroesophageal reflux, constipation, pelvic pain, incontinence, sleep disturbance, pregnancy itch, oedema, infections, fever, exacerbation of pre-existing chronic conditions, use of assisted reproductive techniques	INMA, Generation R
Father: before pregnancy		
Medical and occupational history	Identification and contact details, anthropometric, past and current living address, social capitals, perceived social support, food supplement before pregnancy, occupation history, commuting to the workplace, shift working, medical radiation, medical history, history of asthma and allergy, history of trauma, visual acuity, auditory function, dental hygiene, familial history of disease	

Table 3: Assessment of exposure to environmental factors

Exposure topic	Description
Outdoor air pollution	Monitor-based methods for cohorts with available air pollution monitoring data. Using land use regression techniques for a number of cohorts. These methods will be complemented by data on time-activity patterns obtained via questionnaires
Indoor air pollution	Questionnaire-based data on indoor sources and home characteristics. Potentials for validation of estimates by means of monitoring in a small number of subjects will be explored
Water contamination	Exposure assessment will be based on a combination of questionnaires and routinely collected measurement data by local water companies. Potentials for validation of estimates by means of biomonitoring in a small number of subjects will be explored
Allergens & microbial agents	Exposure to pet allergens will be assessed by means of questionnaires. Settled dust sampling to assess allergens, bacteria/endotoxins, and environmental microbiota using wipe samples will be performed at subsample of cohort
Microbiota	Will be assessed by means of biological samples: skin swab, vaginal swab, faecal sample
Pesticides	Exposures via household use, occupational exposure and diet, will be assessed by means of questionnaires. Potentials for assessing exposure based on geographic information system (GIS) techniques will be explored
Microbiota	Will be assessed in a subsample by means of biological samples: skin swab and faecal samples
Greenness	Residential surrounding greenness will be assessed by means of satellite data. Use of green spaces will be assessed by means of questionnaires. Indoor plant ownership will be assessed by means of questionnaires. Access to green spaces will be assessed by means of GIS techniques
Built environment	Built environment characteristics including walkability, connectivity, land use diversity and residential density will be measured via questionnaires and collection of geographical data
Temperature	Outdoor temperature will be assessed based on the measurements made by the closest weather station to the residential address and the remote sensing data (identification of the city heat islands). Indoor temperature will be assessed for a subsample of cohort participants by means of temperature logger
Radiation	Exposure to ionising radiation sources will be assessed by means of questionnaires. UV exposure will be assessed by a combination of questionnaires collecting data on: time spent under the sun, sun risky behaviours (use of solarium or sunbathing), sun protective behaviours (sunscreen use and clothing) and modelling techniques. Exposure to other non-ionising radiation (including radio frequency) will be assessed by means of questionnaires
Noise	Will be assessed by means of questionnaires characterising noise sensitivity and annoyance and exposure. A land use regression model for developing noise maps for a number of cohorts will be explored
Metals	Will be assessed in blood, cord blood, hair, nail and urine. The focus will be on measuring lead (Pb), mercury (Hg) and arsenic (As)
Persistent organic pollutants	Urine samples will be analysed by high-performance liquid chromatography (HPLC) (adjustment for lipid content will be considered). The focus will be on polychlorinated biphenyls (PCBs) and dichlorodiphenyltrichloroethane (DDT)
Occupational exposures	Reconstruction of past exposures using a job exposure matrix, by elucidating job titles, tasks and durations. All jobs coded according to International Standard Classification of Occupations (ISCO)

Health determinants and outcomes

We are collecting data on health determinants including:

1 Socio-demographic background (details in Table 2).
2 Physical environment. Air pollution exposure is assessed through linkage between residential address of participants and land use regression models for the city. Additionally, we also ask the participants about relevant factors associated with indoor and outdoor air pollution exposures. Thermal stress is covered by a detailed questionnaire including participants' behaviour at warm temperatures, frequency of exposure to hot environments and water intake during such days. Environmental noise exposure and noise annoyance from different sources is assessed through detailed questions regarding traffic, neighbourhood, in-home appliance noise, construction and industrial noise. The use of detergents, glosses and waxes, naphthalene or similar materials, electric air fresheners and insecticide/pesticide sprays are considered as exposure to chemicals. Mobile and Wi-Fi usage (wireless internet) are considered for their non-ionising radiation.
3 Personal characteristics and lifestyle includes such issues as: genetic background, diet, physical activity, sleep pattern, domestic violence, personality, medical history, breastfeeding, risky behaviours such as smoking, alcohol consumption, recreational drug use (occasional drug use for pleasure) and substance abuse or addiction, occupational exposures, feeding practices and feeding habits, accidents/intoxications, cosmetics use and hair dye.
4 Delivery conditions including delivery place, delivery presentation, delivery method, medications used during delivery. The Domestic Violence Questionnaire is a short, simple and self-administered instrument. It is designed to capture the major dimensions of the concept of domestic violence, including physical and psychological violence.

We also collect data on outcomes including:

1 Pregnancy-related complications such as ectopic/molar pregnancy, pregnancy-induced hypertensive disorders, gestational diabetes, infections, hyperemesis gravidarum, placental abnormalities, hip and abdominal pains, anaemia, maternal mortality, oligohydramnios/polyhydramnios, gestational and postpartum mental health, sleep disturbance and psychological stress.
2 Pregnancy outcomes such as abortion, delivery complications, stillbirth, placental weight, APGAR score (1 and 5 minutes), length of gestation, foetal growth and congenital anomalies, as well as neonatal anthropometric measures and anogenital distance.
3 Child's growth and development including mental development, physical development and growth spurt.
4 Child health, for example respiratory infections, gastroenteritis, parasitic infections, asthma, allergy/rhinitis/eczema, metabolic syndrome, diabetes, hypertension, epilepsy, anaemia, vitamin D deficiency and sleep disturbance.

Study phases

Data collection involves at three consecutive phases: phase 1: periconception until birth, phase 2: infancy (0–2 years), and phase 3: childhood (3–11 years).

Phase 1

Participants in phase 1 are pregnant women and their husbands. During their first pregnancy visit to the cohort centres, they are provided with written and oral information about the study, its aims and its impact on the local and national healthcare system, as well as measurements to be conducted, and possible risks. Those mothers who agree to participate are asked to sign the informed consent form before the examinations start. The child's biological father is also invited to participate in the study at the first pregnancy visit (directly if attending the visit and indirectly through letters or phone calls if they did not attend the visit). Questions related to the medical history and occupational exposures are asked of fathers to assess their effects on the future health of their children. Phase 1 includes baseline, first trimester, second trimester (24th–27th week of pregnancy) and third trimester (one week before estimated date of delivery) visits. Baseline visits are planned for the identification and enrolment of pregnant women before the tenth week of pregnancy. At the baseline visit, after verbal and written approval by eligible women, the participants will be asked about their lifetime exposures and also their general demographic characteristics. At first trimester visit (week 13–15 of pregnancy), participants are asked about their exposure, lifestyle, history of previous pregnancies/abortion, pregnancy interval and perceptions from the start of conception. Blood, urine, hair and nail samples are collected from the mothers at this time. Cord blood is also collected at the time of delivery.

Tables 1 and 2 show the detailed information about tasks, and methods used for data collection at phase 1. In addition to data collection through questionnaires, bio banking, blood pressure and anthropometric measurements, mothers undergo the routine para-clinical tests of pregnancy in Iran, including fasting blood sugar and ultrasound examination at the first and third trimesters to assess foetal growth and gestational age. We are using standardised and calibrated equipment for measuring anthropometric indexes and blood pressure. Environmental health technicians document geocoding residential addresses using Global Positioning System (GPS) equipment and characterising the home environment by questionnaires.

Phase 2

In phase 2, participants are mothers who were enrolled in the first phase along with their live-born infant. We collect data using questionnaires, biological samples, physical examinations, clinical tests, hospital records and a survey of the living environment. The tasks planned for each visit of phase 2 and the information being collected through questionnaires in Tables 4 and 5.

Phase 3

In this phase, annual data will be collected for the children born at the first phase of this cohort. In addition to physical examination, questionnaires regarding lifestyle

behaviours and school performance will be completed. Dental and eye examinations are also considered for this phase.

Biobank

The PERSIAN Birth Cohort collects a wide range of biological samples, including blood, urine, hair, nail, cord blood and breastmilk depending on the phase of study. In future years, children's saliva and a lost baby tooth will also be stored. The most challenging part of this procedure is collection of blood and urine samples from

Table 4: Tasks during phase 2 of the PERSIAN Birth Cohort

Questionnaire	2 months	6 months	12 months	24 months
Brain development (N)	●			
Anthropometric measures (N)	●	●	●	●
Anogenital distance (N)	●			
Eye refraction (N)			●	●
Blood pressure (N)			●	●
Infections (N)		●	●	●
Sleep (N)		●	●	●
Food frequency questionnaire (N)		●	●	●
Breastfeeding (N)		●	●	
Medication (N)		●	●	●
Hospital admission (N)		●	●	●
Passive smoking (N)		●	●	●
Neonatal jaundice (N)		●		
Respiratory and allergic conditions (N)		●	●	●
Pacifier dummy use / thumb sucking (N)		●	●	●
Household pesticide use (N)		●	●	●
Time-activity (N)			●	●
Home move (M)		●	●	●
Home characteristics (M)		●		●
Antibiotic use (M)		●	●	●
Noise exposure (M)		●		●
Change in marital status (M)		●	●	●
Social support (M)		●		
RF/ELF exposure (M)		●		●
Sleep disturbance (M)		●		●
Occupational status (M)			●	
Urine, faeces, and hair (N)	●	●		
Milk (M)	●	●		
Settled dust	●			●
Nail (N)		●		
Growth curve (N)		●		
Vaccination history (N)		●	●	●
Auditory test (N)		●		

Note: N = neonate; M = mother; RF/ELF = radiofrequency and extremely low frequency.

Table 5: Description of questionnaires used in Phase 2 of the PERSIAN Birth Cohort

Topic	Description	Questionnaire
Newborn		
Infections	Respiratory infections, gastrointestinal infections	INMA
Sleep	Sleep frequency, sleep duration, sleep problems	CBCL
Diet	Breastfeeding, complimentary feeding, multivitamin/supplement use, food frequency questionnaire	INMA
Medication	Antibiotic use, allergy/asthma	INMA
Hospital admission	Frequency and duration of admission, admission reason	
Neonatal jaundice	Duration and treatment	
Time-activity	Home-indoor, home-outdoor, nursery, other-indoor, other-outdoor	INMA
Asthma/wheezing	Symptoms, physician diagnosis, medicine uses	INMA
Allergy, eczema and food allergy	Symptoms, physician diagnosis, medicine uses	INMA
Pacifier dummy use / thumb sucking	Starting and ending age, frequency	
Household pesticide use	Frequency, type, house pets	
BPA/Phthalates	Sources (canned food, plastic food containers and packages), frequency of use	INMA
ELF/RF	Frequency, duration, device type (mobile, tablet, cordless phone, Wi-Fi)	GERONIMO/ REM-BRANDT/ MobiKids
Mother		
Mental health	General perceived health, depression, anxiety/stress, life events	
Occupation/employment	Employment status, job title	INMA
Mobility	New address, new contact details	
Medication use	Antibiotic use, iron, vitamins, anti-depressants, painkillers, sleeping pills, cough medicines, contraceptives, herbal remedies	ALSPAC
Noise	Sensitivity, annoyance	
RF/ELF	Frequency, duration, device type (mobile, tablet, cordless phone, Wi-Fi)	INTER-PHONE/ MobiKids
Sleep	Sleep frequency, sleep duration, sleep problems	PSQI
Home characteristics	Pets/animals, floor type (carpet, stone, cement and so on), ventilation (air conditioning, windows opening time), new decoration/painting	INMA
Father		
Mental health	General perceived health, depression, anxiety/stress, life events	

pregnant women, as well as the cord blood. We prepared a multistage system for maximum success in the collection of these samples. As a first step, laboratory experts take a blood sample from mothers in each hospital or clinic that they visit. In the case of missing the opportunity to take samples at the interview session, biological samples including blood, urine, hair and nail during pregnancy are obtained from pregnant women during their referral for routine national medical laboratory tests. The blood, urine, nail and hair samples will undergo the necessary processes, and then be transferred to the biobank of each cohort to be stored according to the biobanking protocol of the PERSIAN Cohort (Poustchi et al, 2017).

At delivery time, we collect cord blood. At the last visit by the pregnant women (in the third trimester), we ask them about the hospital in which they plan to deliver; and again we follow them by phone calls. We have arranged with all hospitals to allow our expert staff to attend the delivery room or operating theatre to obtain the cord blood.

Assessment of neurodevelopment

The neurodevelopment status of children is assessed at different age groups and by standardised questionnaires that are validated for the Iranian population. These questionnaires include:

- Ages and Stages Questionnaire (ASQ; www.agesandstages.com)
- Early Childhood Behavior Questionnaire (ECBQ; https://research.bowdoin.edu)
- Child Behavior Checklist (CBCL; www.aseba.org)
- Modified Checklist for Autism in Toddlers-Revised, with Follow-Up Interview (M-CHAT-R/F; www.mchatscreen.com).

When necessary, children are referred for more specific tests and further evaluations.

Assessment of epigenetic process

Epigenetic features can change in response to internal and external factors. Mechanisms of interaction between the genome and the environment can be provided by epigenome.

In the current birth cohort, we will perform prospective analysis of longitudinal data to explore the epigenetic variations, such as DNA methylation, in order to determine the epigenetic changes of early life experience and exposure to social, environmental and biological stimuli over the life course. In addition, we will assess whether there are differences between epigenetic patterns in the populations of the five Iranian cities. We will also explore whether epigenetic variations of early life experiences can be correlated with pregnancy complications and later outcomes in the offspring.

Quality control and data management

High-quality data are of crucial importance, especially for a longitudinal study. The web-based intelligent data entry platform of the study minimises data entry typos. For identification and linkage of mother, father and child data to each other,

we defined an 11-digit Birth Cohort ID (BCID). The first two digits identify the enrolment city. The third and fourth digits show the enrolment centre of pregnant woman in each city. The last digit of the BCID identifies the group for example XXXXXXXXXX1 means mother; XXXXXXXXXX2 means corresponding father and XXXXXXXXXX3 means their child. The PERSIAN Birth Cohort software development team defined lower and upper bands for most of numerical fields to limit outlier responses due to typos. For instance, systolic blood pressure of 3 is not acceptable, which will inform the user of an error. We also uploaded pharmacopoeia and ISCO codes to the platform. The user can readily select the desired drug name or occupational title. This minimises errors and the need for data cleansing. Moreover, all interviewers undergo systematic training sessions by the members of the central steering committee. A web-based portal is provided for interviewers to direct their questions and problems to the principal investigators. In addition to the system design and training, quality control is being conducted in three consecutive stages by the interviewers, field supervisors and quality controllers at each centre. After participants have answered the questionnaires, all the information is entered into the platform. When the interviewers enter the data, the questionnaires are rechecked. Where information is missing, the interviewer will contact the participants to obtain it. Daily and weekly summary reports regarding questionnaires and visits, such as mean daily number enrolled, rate of missing data and questionnaires are available. The field supervisor will assess the relevant statistics and the feedback used in order to fix possible problems. At a third level, the quality controller observes the possible outliers and missing values in the filled data. He/she also checks the accuracy of the data entered, compared to the accepted norms. The coefficient of intra-assay and inter-assay variations is also calculated to assess measurement error.

Statistical analysis

Logistic regression (for binary outcomes) or linear regression for continuous outcome measures will be used as basic statistical analysis. Other techniques such as multilevel modelling or path analysis will be used according to hypothesis of study. Principal component analysis will be used for dietary pattern explanatory analysis. Proportional hazard from Cox regression models will be used for relevant data. Use of Poisson models for count data, such as the number of preterm deliveries per day, will be advisable. However, most of the statistical plans and models applicable for the derived data will be confirmed after completion of each phase and after hypothesis generation. In the case of missing data, the first approach in the PERSIAN Birth Cohort is to collect the data again from the sources such as hospital and insurance documents or for questioners to phone mothers again, asking the missed questions and completing the missing data. If this first approach fails we will use statistical imputations for missing values.

For assessment of environmental exposures, we will use data from available and future models such as land use regression models to fill in the missed data. Land use regression modelling is currently one of the most used methods in epidemiological studies for assessing environmental exposures. This method uses the least-squares regression models for predicting environmental exposures levels based on the available data at a small number of locations and predictor variables. These models are relatively inexpensive and their performance in detecting the small-scale variations

in environmental exposures is as applicable as complex and costly techniques. In our study, land use regression models will be developed by incorporating available point measurements across the five cities and geographical variables collected via different resources including remote sensing. We will validate the land use regression models according to on-site measurements. As the temperature and climatic parameters fluctuate across the year in the study cities, we will include the measurements for different seasons.

Study ethics

Participation in the surveys is voluntary, and participants have the right to withdraw from the study at any time. Potential participants will be provided with information in written and oral formats about the study protocol, measurements to be conducted and possible risks they may pose. Those who decide to participate will sign the informed consent form before beginning the interviews. Depending on the requirements of National Ethics Committee, the informed consent includes separate points for questionnaires, physical measurements and biological sample collection; it provides general consent for all included measures. All PERSIAN Birth Cohort activities will be conducted according to existing guidance in ethics as indicated in the Universal Declaration on Bioethics and Human Rights adopted by UNESCO on 19 October 2005.

This project concerns the collection of personal information and biological samples from participants. Standardised protocols will be used for the collection of biological samples. This collection of biological samples is justified by the contribution of the research to be conducted on them to the improved understanding of an emerging risk of major public health interest: the role of early life exposures in functional health in later life. The amount of biological samples to be collected is designed so as not to constitute any significant burden on the donors. Ethics approval is required from the local ethics committees prior to starting the fieldwork. The PERSIAN Birth Cohort has a withdrawal policy in two distinct sections. For questionnaires and the measurements, and not biological samples, participants can withdraw the study at any time. However, their collected data will be used for further analysis in this case. Participants withdrawing from the study can also ask for their biological samples to be excluded.

Discussion

Because of the importance of the *in utero* environment on later life health outcomes, there is an increase in the number of birth cohorts since the late twentieth century. Birth cohorts can examine the patterning of exposures over the life course, and would allow differentiation between direct associations and confounding factors. Life course studies supply evidence that can show the impact of various factors from the foetal period through childhood and on to adolescence, as well as across generations, on adult health and disease. We suggest that these perspectives can also determine the dynamic mechanisms that are related to the heterogeneity in later life health trajectories.

Half of the world's children are in Asian countries, which are the most rapidly industrialising nations in the world (Kishi et al, 2017b). This rapid urbanisation

together with the cultural and lifestyle changes and weak enforcement on environmental regulations in most of these countries, have imposed considerable health risks for children growing up in this region, which could also affect their health status later in life (Grandjean and Landrigan, 2014; Kishi et al, 2017a). Therefore, there is a need to establish birth cohort studies in these dynamic environments to document the life course effects of health risks and accordingly to develop effective and targeted interventions to tackle the problems.

Birth cohort studies have generated valuable knowledge on how interaction between genetic factors, environmental exposures and lifestyle in early life can have long-term consequences for physical and mental health across the life span, a body of evidence reflected in DOHaD (Campbell and Rudan, 2011; Robinson et al, 2011; Kent, 2012; Dahlen et al, 2013). Chronic stress during the foetal, infancy and childhood periods is associated with weaker physical and mental adaptation and weaker socio-economic and educational outcomes during the life course (Kelly-Irving et al, 2013; Li et al, 2013; Feng et al, 2015; Townsend et al, 2016).

We are looking for the possible effect of environmental factors such as noise, air and light pollution, as well as green space exposure and the thermal environment on pregnancy and birth outcomes, specifically on neurodevelopment. We also evaluate the role of different dietary patterns and the use of supplements and additives on mother and child health outcomes. Considering the huge collection of biologic materials in this study, we will also evaluate a possible association between exposure to selected pollutants with health outcomes and epigenetic variations through measuring their values in the biologic specimens or their effect in the collected samples.

In spite of growing evidence in life course effects of early life factors, some gaps remain in the scientific understanding of the mechanisms influencing these formative phases, especially from populations of LMICs. Recent researches have shown that DOHaD risk varies in relation to different factors including culture, climate and ethnicity. Some of these differences can be related to variations in body composition and nutrient intake. Part of the difference is accounted to be because of greater direct effects of culture on individual behaviour and physiology. Race and ethnicity might affect health through complex and dynamic interactions of related factors (Hanson and Gluckman, 2008). To consider this variation, in the current cohort we included a spread of locations in Iran to understand regional influences on the aforementioned effects. Widely spread geographical data are often costly for recruitment and recall; conducting a study in different geographic clusters by region provides the most cost-efficient and effective strategy for cohort recruitment and retention for future data collections (Morton et al, 2013).

Cohort design is not routinely a feasible choice for the study of rare diseases, as they require very large sample sizes, which are often not achievable. International consortia of several birth cohorts could be a solution to study such outcomes. However, some differences between studies such as variations in timing of follow-ups, outcome definitions and questionnaires, limitations of culture or language-specific assessment tools, heterogeneity of exposure sources, differences in methods for measuring biomarkers and environmental pollutants in air, water and food are among the challenges for pooling data from different birth cohorts.

We developed the study protocols and questionnaires as well as a comprehensive data catalogue with the prospect of participating in such collaborations in future. Moreover, the PERSIAN Birth Cohort is registered in the Birth Cohort Consortium of Asia

(BiCCA; www.bicca.org) and in the inventory of birth cohorts (www.birthcohorts.net). This would help sharing data in the future and making international comparisons in the fields of epidemiology and epigenetics. The cohort steering and scientific committees will make decisions on national and international requests for data sharing.

Study limitations

The selected cities do not represent the whole Iranian population. It would have been better if we could include more regions to cover a wider sample of the different environmental, demographic and lifestyle characteristics of Iran's population. According to aim of the study, only pregnant women were recruited. Other health aspects of Iranian women of different age groups are being assessed in other nationwide studies of the PERSIAN Cohort (12). Another limitation concerns face-to-face interviews with fathers, who are usually at work in the mornings. To overcome this limitation, we mainly invited them to the clinics working in the afternoons. Moreover, each four to six months we organised meetings for families and specialists in different health topics, presenting scientific talks for parents, at which time our staff completed the questionnaires with fathers. For those fathers who could not attend the afternoon clinics and training sessions, our staff filled in the questionnaires by phone call as much as possible.

The other limitation is that cord blood could not be obtained in cases of emergency and/or unexpected deliveries.

Longitudinal studies require sustainable financial support for long-term follow-ups. In our study, the main budget is used for the first phase and as the follow-up phase mainly consists of filling annual questionnaires and anthropometric measurements, it would not incur large costs. The analyses that would need laboratory equipment and other instruments in the future will be considered as sub-studies, which will apply to receive separate grants.

In order to increase the compliance of families for follow-up phases of the cohort, every four to six months, besides free health check-up visits and two or three meetings per year with presentations on general health issues for families, as already mentioned, we have also created social media groups to have interactive conversations with families.

Conclusion

DOHaD proposes that exposures during early life could affect not only foetal and child health, but can also determine susceptibility and risk of future diseases, including NCDs, later in life. This birth cohort can assess the pattern of exposures over the life course, and would help in distinguishing the direct associations and confounding variables in this regard. To date, much of evidence for DOHaD is generated by birth cohorts in Western high-income countries while the majority of the global burden of disease associated with NCDs occurs in LMICs. We address the urgent need to establish birth cohorts in LMICs to generate the knowledge necessary to develop tailored and effective interventions for tackling NCDs early in life. In this context, the PERSIAN Birth Cohort will contribute to the body of evidence on DOHaD for the MENA population, which will have not only local implications but also regional and international relevance.

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Authors contribution

MJZS, ND, PD, AHM, MHB, ShN, HN, ShD, ES, MN, MMA, MM, MHL, AV, SJM, EZ, MM, MH, OY, MSR, AE, AF, HH, MRN, HOE, HP, RM, RK contributed to the design of the questionnaire. All authors read and approved the final version of the manuscript.

Conflict of interest

The authors declare that there is no conflict of interest.

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