

REVIEWS

A review of mother-child and birth cohort studies in the Middle East Area

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ABSTRACT

Mother-Child and Birth cohort studies offer an excellent opportunity to evaluate the effects of 'early life' exposures providing an insight in the etiology of chronic diseases. To our knowledge, this is the first study that aims to provide a comprehensive review of these studies in the Middle East Area (MEA). Authors searched to relevant registries, the Pubmed interface, internet search tools and had personal contact with study PIs. The search revealed 117 mother-child and birth cohort studies from 9 MEA region countries (Iran, Israel, Jordan, Kuwait, Lebanon, Palestine, Saudi Arabia, United Arab Emirates and Qatar). Variability in the identified studies refers to the study design, objectives and the years of recruitment. Biological samples and data on environmental exposures were absent with the exception of limited studies (n = 44). This review revealed a sufficient number of available cohorts, however few have followed up children beyond the age of 2 years. Improved study designs focused on molecular and environmental data acquisition are required in a region that shares a set of unique characteristics in terms of landscape, climate, culture, and lifestyle. This review provides valuable information for planning future studies and set the grounds for collaborations within the MEA region and internationally.

Key Words: Maternal health, Child health, Birth cohorts, Mother-child cohorts, Middle East Area

1. INTRODUCTION

Numerous longitudinal pregnancy, mother-child or birth cohort studies have been established in different countries to aid our understanding of child health and wellbeing and, in the longer terms, the etiology of non-communicable diseases (NCDs) in adulthood. The global burden of NCDs is rapidly growing and according to the NCDs Progress Monitor 2017 released by the World Health Organization (WHO) in 2017 NCDs are responsible for the 70% of deaths worldwide.^[1] Based on a recent report more than 30% of school children (13 to 15 years) in Bahrain, Egypt, Kuwait, Oman, and the United Arab Emirates (UAE) are either overweight or obese.^[2] The Middle East and North Africa (MENA) region has also been identified by the International Diabetes

Federation (IDF) as having the highest prevalence of diabetes in the world. According to the IDF Diabetes Atlas (8th Edition), almost 38.7 million adults (20-79 years) had diabetes in the MENA region in 2017.^[3] However, the leading cause of death not only in the Middle East Area (MEA) region but globally remains the cardiovascular diseases. It is estimated that 1.4 million of CVD deaths occurred in the Eastern Mediterranean region in 2015.^[4]

Although the underline causes of this unobstructed raise of NCDs are not clear, there is substantial epidemiological evidence suggesting that an adverse intrauterine environment alongside with genetic predisposition, may program susceptibility of the fetus to later development of chronic diseases.^[5]

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The concept known today as the Developmental Origin of Health and Disease (DOHaD) was originally proposed by Dorner (first to use the term 'programming'), but received broader recognition by Barker et al. by showing the associations between maternal undernutrition, infant low birth weight and a higher risk for developing cardiovascular disease in later life.^[6-8] Over recent decades, within this model new indicators of altered fetal development have emerged which have far escaped the nutritional aspects.^[9,10] As a result, new generation epidemiological studies have been established with developmental considerations, not being restricted to fetal life but throughout the lifespan.

The study design of pregnancy and birth cohort studies are ideally suited to strengthen causal inference between early life stressors (even before birth during intrauterine development), genetic susceptibility, childhood health and the development of complex and common diseases in adulthood. The life course approach of these studies, with long-term follow ups, enables the timely identification of phenotypic profile at risk. They generate enormous and comprehensive data repositories sufficient to assess or to have the potential to assess the effect of early life stressors along with those accruing in adulthood or transmitted over generations, on health risk.^[7,11-14] Modern birth cohort studies use the recent advantages in biotechnology and exposure assessment technologies with high-throughput, sophisticated molecular platforms (abbreviated as '-omics' encompassing genomics, transcriptomics, proteomics, metabolomics, epigenomics and others) introducing molecular epidemiology and a new era of biomarkers (exposure, susceptibility and early response). More specifically, the study design of these cohorts utilize traditional epidemiological tools (i.e. questionnaires, clinical examinations, etc.) with advanced exposure assessment technologies (i.e. environmental monitoring and modern techniques such as sensors, smartphones and Geographic Information Systems (GIS)), and '-omics' platforms, to capture a wide range of exposures and their associations with disease onset.^[15-18] This is a unique monitoring approach for the processes of the disease development, tracking, at multiple levels and systems (i.e. molecular, environmental, physical, behavioral, mental, etc.), assessing how fast one degenerates from its optimum and its relevance to the occurrence of the disease. Current literature provides a large number of research papers using data from birth cohort studies, highlighting their essential contribution to understanding individual's vulnerability to disease during early stages of life.

In the last twenty years, birth and pregnancy cohort studies have gained high recognition in Europe, United States,

Canada and Australia with numerous cohorts being established in these countries.^[13,19-21] Moreover, a number of web-based networks and inventories (www.micyrn.cainCanada; www.lifecycle-project.eu/for-scientists/the-eu-child-cohort-network, www.chicosproject.eu/cohorts and www.closer.ac.uk in Europe; www.niehs.nih.gov/research/supported/cohort/index.cfm in USA; www.birthcohorts.net) have been created with main objective to provide information on available cohorts and foster collaborations among them. In the MEA region, available evidence in this research field is currently underrepresented in the literature. The identification of completed, ongoing or newly planned cohorts in the MEA region will provide researchers with a valuable source of information of what is currently available and develop the capacity for an attempt to create birth-cohort networks in the Middle East. The full potential of individual cohorts can be fully revealed through these birth cohort networks which will provide a great opportunity for common analysis (data sharing), pooling data across the different studies, increase statistical power and eliminate chance findings via replication of results.^[22-25]

The main aim of present study is to provide an overview of the ongoing or planned mother-child and/or birth cohort studies in the MEA region, currently missing from literature. Given the specific characteristics of the population and the great diversity in, lifestyle, socioeconomic structure and cultural practices, this review intends to offer a broader geographical representation of these studies and facilitate collaboration across the cohorts not only within the MEA region but internationally. Additionally, this review will be a source of information that needs to be considered by researchers with respect to new research hypotheses, to study methodology and to type of data planned for future studies to be collected. To our knowledge, this is the first review in the Middle East Area of the available mother-child and birth cohort studies.

2. METHODS

A structured review was implemented as a search strategy to identify mother-child and birth cohort studies conducted solely in MEA countries or as part of an international initiative. The geographic boundaries of the Middle East Area vary in the literature. In this review, MEA refers to the area that is enclosed by the Eastern Mediterranean and the Red Sea extended over the Arabic Peninsula, including the following countries: Bahrain, Iran, Iraq, Israel, Jordan, Lebanon, Syria, Kuwait, Oman, Palestine, Qatar, Saudi Arabia, UAE and Yemen (see Figure 1).



Figure 1. Geographical representation of the Middle East Area region for the current review. (To develop this map the authors used USGS National Map Viewer, <http://viewer.nationalmap.gov/viewer/>)

Table 1. Search Strategy for Medline: MESH Terms used to identify relevant studies

1. "mothers"		5. "longitudinal studies"
2. "child"		6. "studies"
3. "parturition"	OR	7. "prospective"
4. "birth"		8. "cohort"
AND		
9. "Middle East"		17. "Kuwait"
10. "Bahrain"		18. "Oman"
11. "Iran"		19. "Palestine"
12. "Iraq"		20. "Qatar"
13. "Israel"		21. "Saudi Arabia"
14. "Jordan"		22. "UAE"
15. "Lebanon"		23. "Yemen"
16. "Syria"		

2.1 Identification of MEA Mother-Child and Birth cohort studies

MEA mother-child and birth cohort studies were identified from multiple sources. We first searched the web-based database LINK Registry (<http://www.linkregistry.org/search.aspx>; link currently not available) for the time-period starting October to December 2015. The LINK Registry was a database of pregnancy and birth cohort studies from around the world, designed to promote collaboration among researchers by sharing information on participant population, biospecimens and data collected in different studies and information about planned studies. Additionally, we searched (October 2015 to October 2019) the web-based database <http://birthcohorts.net>. This database is an open registration of cohorts worldwide, which collect

information on specific exposures, outcomes or biological samples of interest. One additional study was identified by searches of Google and Google Scholar (October 2015 to October 2019).

2.2 Literature search strategy

Published peer reviewed papers were identified using Medline (National Library of Medicine) dataset. The literature search was initiated on 17th of October 2015 and completed

on 8th of October 2019 using the PubMed interface. Search terms used were chosen from the USNLM Institute of Health list of Medical Subject Headings (MESH) for 2017 as follows: Mother, Child, Birth, Prospective, Cohort, Middle East, Bahrain, Iran, Iraq, Israel, Jordan, Lebanon, Syria, Kuwait, Oman, Palestine, Qatar, Saudi Arabia, UAE and Yemen. Full details of the research strategy and key terms' combination are provided in Table 1. The authors have chosen a study coding to facilitate the report and discussion of results.

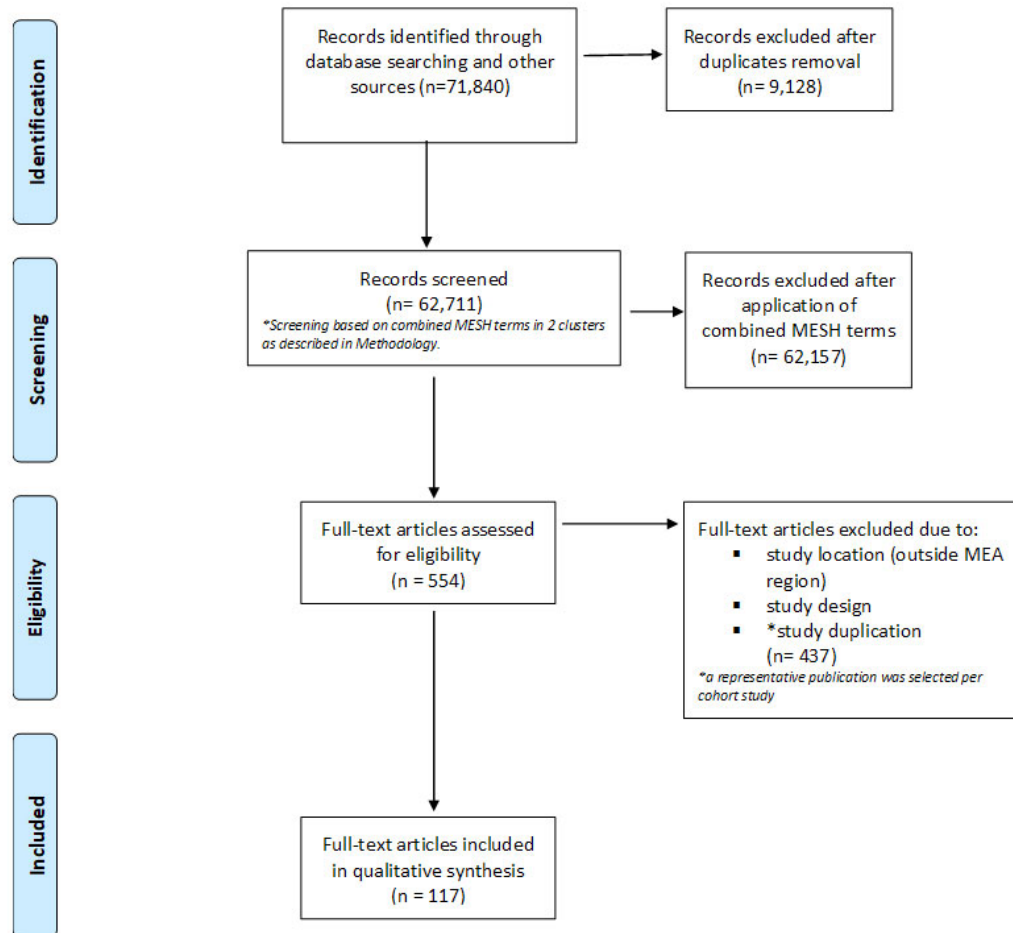


Figure 2. PRISMA flow diagram of the MEA cohort studies selection process

Table 2. Brief description of the different cohort study categorization included in the current review

Category 1: Pregnancy/Birth cohorts	Category 2: Mother-Child cohorts
<ul style="list-style-type: none"> • Birth/mother-child/pregnancy /prospective/longitudinal cohorts or cross-sectional study of longitudinal population or qualitative review of birth cohort • MEA countries or MEA countries participating in international initiatives • Reporting any type of results or insight to methodology or systematic or meta-analysis studies 	<ul style="list-style-type: none"> • Only MEA countries • Enrollment of mothers into the cohort during pregnancy or at birth • Included at least one child follow-up after birth
	Category 3: Registries
	<ul style="list-style-type: none"> • Retrospective and/or surveillance studies

The initial search was done using each of the MESH terms alternatively with each MEA country. Studies were included based on the following: cohort design, study location and follow up status. The publications were saved initially under the country's name in a separate library and the duplicates were removed. As shown in Figure 2, all the publications of each country were compiled together ($n = 71,840$), duplicates were cleared ($n = 9,128$) and a total of 62,711 publications were included in the general MEA library. Filtering this library by using the following combined MESH terms: mother, child, birth, Middle East, prospective, cohort, resulted in 554 papers excluding the duplicates. Titles, abstracts and full text of the studies were revised by two independent reviewers for relevance. Disagreement between the reviewers was solved either by consensus or by including a third reviewer. At this point, 437 papers were excluded resulting to 117 publications (authors have selected a representative publication for each cohort study).

Then studies were divided into three main categories based on the criteria-, described in Table 2. A total of 117 cohort studies were identified of which 42 fall under Category 1 that refers to Pregnancy/Birth cohorts (following women during their pregnancy up to delivery/birth) and 75 under Category 2 for Mother-Child cohorts (following mother-child pairs; women during their pregnancy, at delivery and their child/children after birth). Additionally, from this search 7 Registries (Category 3) were identified supporting mother-child and/or birth cohort studies' research. Information extracted from publications included recruitment period, study population, time points of follow up, data collection and biological samples collected.

3. RESULTS

In total, 42 mother-child cohorts were included through the current literature review. These studies have been conducted solely in MEA countries or as part of an international initiative and included at least one child follow up after birth (see Supplement 1). Most of the studies were identified in Iran ($n = 16$) following Israel ($n = 12$), Kingdom of Saudi Arabia ($n = 5$), Kuwait ($n = 2$), United Arab Emirates ($n = 3$), Jordan ($n = 2$), Qatar ($n = 1$) and a collaboration study between Qatar and Lebanon ($n = 1$). As it is shown in Supplement 1, the number of the mother-child participants varies from 50 (IR1, Iran) to 750,000 (IL33, Israel), the duration of the studies ranged from few months to multiple years (IL27, duration: 1991-2014) and the objectives of the studies mainly included birth outcomes, pregnancy and neonatal complications, maternal mental health, child development, nutrition and infant

feeding practices. The majority of the studies did not have available maternal or child biological samples with the exception of IR8, 10, 35, 49; IL1, 2, 7, 31, 33; J1; KW2; KS1, 2, 3, 4, 9; QA1 and Qatar/ Lebanon collaboration cohort.

Supplement 2 includes 75 pregnancy or birth cohorts as identified from publications review and via web-based registries. In this group, Iran and Israel counted the majority of these studies with 34 and 18 cohorts, respectively; followed by Kingdom of Saudi Arabia with ($n = 5$), Palestine ($n = 4$), Jordan ($n = 2$), Oman ($n = 2$), Kuwait ($n = 2$), Yemen ($n = 2$), Qatar ($n = 2$) and Lebanon, Syria and United Arab Emirates and a collaborative study (between Kuwait, KSA and UAE) with one cohort each. As it is shown in Table 4, the number of the participants varies from 44 (IR28, Iran) to 201,048 (IL29). The duration of the studies ranges from less than a year to decades (IL29) and the objectives of these studies were mainly mortality, birth outcomes, pregnancy complications, environmental exposures and maternal health. OM2, a study from Oman was a part of Intergrowth 21st Project, an international initiative. In 29 studies, Iran ($n = 16$), Israel ($n = 3$), Jordan ($n = 1$), Oman ($n = 2$), Kingdom of Saudi Arabia ($n = 3$), United Arab Emirates ($n = 1$), Qatar ($n = 1$), Yemen ($n = 1$) and in a collaboration study ($n = 1$) were used biological samples.

As shown in Supplements 1 and 2, a total of 16 cohorts have followed women during their pregnancy (Iran, $n = 19$; Israel, $n = 5$; Kingdom of Saudi Arabia, $n = 5$; Palestine, $n = 1$; Kuwait, $n = 1$ and Qatar, $n = 3$). Two of these cohorts (QA1 & Qatar/Lebanon collaboration cohort) are ongoing and currently collecting data on pregnant women. Studies with available information for mothers after delivery focusing on postpartum depression or other stress symptoms (antenatal anxiety, post-traumatic stress, maternal/fetal attachment) during or after pregnancy have been identified in Iran (IR37, 46, 2, 13, 32), Israel (IL4, 10, 12, 14, 26), Palestine (PS2) and Qatar (QA1). MEA Birth registry initiatives have also been covered by this review. Table 3 presents 7 birth registries as identified from the analysis of both manuscripts reviews and the web-based registries. In Israel there are found four registries IL22-25. IL22 is an ongoing registry collecting data on maternal exposure to chemicals and the birth abnormalities based on the Teratogenic Information Service, while the other three registries include longterm follow ups, up of 12 years. In Lebanon, LB2 registry collected data on neonatal mortality for a year for a population of 5,152 and in Qatar, QA2, collected data on perinatal mortality for a year to a total of 20,583 population.

Table 3. Description of Birth Registries in the MEA region

Country	Study Coding	Source	Duration of the study	Population	Pre-natal	Post-natal	Objectives	Data Collection	Biological samples	Follow Up
Israel	IL22	(26, 27) (28-32) (33)	1985-present	Teratology Information Service	✓	✓	Maternal exposure/major anomalies	Q: maternal demographics, medical and obstetric histories, exposure details (dose, duration, route of administration, timing in pregnancy and indication for therapy), concurrent exposures, BO	NA	NA
	IL23	(34)	1964–1976	92 408	–	✓	Registry	Q	–	17 years
	IL24	(35)	1995-2012	3956	–	✓	VLBW Neonatal morbidities	Medical records	NA	11 years
	IL25	(36)	1997-2004	220805	–	✓	Risk for cancer	Israel National Cancer registry	NA	10 years
	Lebanon	LB2	(37)	2002-2003	5152	–	✓	Neonatal mortality	Medical records	–
Palestine	PS4	(38)	2015	34482	–	–	Built a research registry	Medical records	–	NA
Qatar	QA2	(39)	2011	20583	–	✓	Perinatal mortality	Medical Records	–	Birth

4. DISCUSSION

This review provides an insight of the notable efforts from the MEA local institutions and/or research teams to set up longitudinal mother-child and birth cohort studies. The identified studies show a great variability on the study design, the follow up of their population, as well as the data and specimen collection. Some of the studies are general pregnancy cohorts with various aims, while others focus on evaluating specific outcomes (i.e. breastfeeding or nutrition) and others are simple registries. Despite the substantial efforts made in the MEA to initiate birth cohorts, these efforts lack of frequent and long term follow up points after birth, with limited biological samples collection. Given the emergence of advanced technologies and sophisticated genetic analyses, the assessment of biological and environmental factors needs to be further acknowledged. Longitudinal birth cohort studies are essential to understanding the life course, risk, early predictors and protective factor for the development of chronic diseases, as well as the complex interplay between genes and environment. According to the current literature, the majority of the published papers about the DO-HaD concept mainly comes from birth cohort studies from

the West, while as it is shown in this review, the published papers coming from MEA cohorts are limited. This could be attributed to the relative wealth of Western societies and their ability to provide appropriate infrastructure and long-term funding to support these longitudinal birth cohort studies. The role of national and international funding organizations appears to be critical for the initiation and, most important, the maintenance of such studies.^[40] The establishment of long-term birth cohort studies requires a huge investment in time, effort and money. In West, mainly In Europe, for the past two decades, longitudinal studies have been supported by different organizations providing funding schemes suitable for supporting such studies. The economic deficits in some MEA countries could impede funding opportunities for scientific research projects and especially for longitudinal studies where long-term funding is essential.

The importance of national registries or even big data repositories for the surveillance of diseases and population characteristics should also be acknowledged. Well-maintained registries with accumulating data are mainly used to provide information for rare diseases (e.g. cystic fibrosis), evaluate survival predictors and changes in survival, and monitor the

health of the population. However, there is no doubt that the use of registry data need to overcome several challenges such as privacy protection, completeness of patient records, data quality, variable definitions, reference ranges that may vary by country, and data harmonization. Despite the challenges that may encounter, the liaison between birth cohorts and registries is a great opportunity for research especially when focusing on specific health or exposure-related questions. As shown previously, in the MEA region only few registries are currently available with no information for collaborations between cohorts and registries. However, in the recent and following years researchers and policy makers should make better efforts to make sustainable registries that will be able to work more with other parts of the health system. Advances in current research require scientists from a wide range of expertise who will be able to address questions, and use available data, that individual cohorts may not have thought of. The development of new or existing cohorts in combination with other study designs (case-control, clinical trial) and registries is desirable. Well-designed electronic platforms for data collection, automated derivation of required variables, data quality checks and positive attitudes by researchers towards data sharing are some of the actions that will support this endeavor. Although in West (Europe and the US), cohorts are trying to build a network by harmonizing their protocols and pool their data together, it is important to mention that there is no provision for MEA regional and/or global partnerships. Collaborative efforts in Europe such as the ENRIECO (www.enrieco.org), CHICOS (chicosproject.eu) and HELIX (www.projecthelix.eu) projects are important lessons that could help MEA region countries develop this field further. There is clear need for collaboration between the cohorts or the harmonization of new data and biological sample collection that will allow the study of long term outcomes and prevent the overlap of measures among the studies.

Cohort studies are expensive and time-consuming type of studies. Researchers have to address many challenges such as recruitment, retention rates, fund resources and manage logistics, especially in large scale cohorts with long term follow ups. Based on this review, authors observed that many of the studies in the Middle East lack of frequent, long term

or had no follow up points after birth and missed collection of biological samples. Due to the study design and/or the absence of long term follow ups, current studies are not able to provide evidence on the etiology of main health concerns in the region such as diabetes, obesity, cardiovascular diseases. While the setup of a new cohort would be ideal, the design of new follow-ups, including collection of biological samples of the already existing cohorts with harmonized protocols focused of the main burden of diseases in MEA region would much more benefit research. More efficient methods, innovative technologies (smartphones, apps, email, social media) along with the experience of researchers in this specific geographical area can be in favor of research by simplifying logistics and minimizing the cost of current studies. New birth cohorts or the existing ones can only provide novel insight into early predictors of the disease onset through collaborations if researchers are able to promptly respond and shift research in line with scientific changes and infrastructural needs.

AUTHORS' CONTRIBUTION

E.F contributed to the conception and design of the work; literature review, analysis and interpretation of the data, manuscript writing; S.A contributed to literature review, analysis and interpretation of the data, manuscript writing; V.L contributed to literature review, analysis and interpretation of the data, manuscript writing; A.H contributed to literature review, analysis and interpretation of the data; M.K contributed to the ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; E.S contributed to the accuracy or integrity of any part of the work are appropriately investigated and resolved and the final approval of the version to be published.

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The authors developed the map presented in this article (Figure 1) with the use of the United States Geological Survey (USGS), The National Map Viewer, <http://viewer.nationalmap.gov/viewer/>.

CONFLICTS OF INTEREST DISCLOSURE

The authors declare that they have no competing interests.

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