

Original Article

Burden of Hemoglobinopathies (Thalassemia, Sickle Cell Disorders and G6PD Deficiency) in Iran, 1990–2010: findings from the Global Burden of Disease Study 2010

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Abstract

Background: Hemoglobinopathies are known as the most common genetic disorders in Iran. The paper aims to provide global estimates of deaths and disability adjusted life years (DALYs) due to hemoglobinopathies in Iran by sex and age during 1990 to 2010 and describe the challenges due to limitations of the Global Burden of Disease study 2010 (the GBD study 2010).

Methods: The GBD study 2010 estimates of the numbers of deaths and years of life lost (YLLs) due to premature mortality were calculated using the Cause of Death Ensemble model (CODEm). Years of life lost due to disability (YLDs) were computed by multiplication of prevalence, the disability weight for occurrence of sequelae, and the duration of symptoms. Prevalence was estimated through a systematic search of published and available unpublished data sources, with a Bayesian meta-regression model developed for GBD study 2010. Disability weights were produced using collected data from population-based surveys. Uncertainty from all inputs was incorporated into the computations of DALYs using simulation methods. We aim to prepare and criticize the results of the GBD study 2010 and provide some recommendations for reaching better conclusions about the burden of hemoglobinopathies in Iran.

Results: Between 1990 and 2010, the overall deaths attributed to hemoglobinopathies decreased from 0.51% to 0.36% of total deaths, with the corresponding burden declining from 1% to 0.82% of total DALYs. There was a reduction in deaths and DALYs rates for all ages and the rates attributed to all ages followed the same pattern in Iranian men and women. The highest DALYs for hemoglobinopathies, thalassemia, sickle cell disorder, and glucose-6-phosphate dehydrogenase deficiency (G6PD-D) were found in those aged less than 5 years. The collective burden of all of these hemoglobin disorder was lower in 2010 than in 1990.

Conclusion: Although the screening programs in Iran have been very successful in reducing the number of thalassemia patients between 1990 to 2010, in order to provide a better estimation of the burden of hemoglobin disorders, it is necessary to perform a national and sub-national study of hemoglobinopathies using multiple national and sub-national surveys.

Keywords: Global Burden of Disease, Iran, Hemoglobinopathies

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Introduction

Hemoglobinopathies are classified into two groups according to the type of change in the hemoglobin molecule; sickle cell disease is a qualitative change and thalassemia is a quantitative change.¹ One third of a million people have one of these genetic disorders worldwide. Sickle cell disease (SCD) is the most common monogenic disease in the world. Moreover,

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about 4.5% of all people carry one gene that may confer these abnormalities.²

The prevalence of hemoglobinopathies differs between countries. Hemoglobin disorders are endemic in 71% of 229 countries and affect 89% of births.³ Although no valid data exist for many regions of the world, recent data suggest that about 7% of the world's population are carriers of a hemoglobin disorder, and 300,000-500,000 children are born each year with a hemoglobin disorder of a severe homozygous type.⁴ About 1.1% of couples all around the world are at risk of having a child with a hemoglobin disorder; 2.7 per 1000 conceptions are affected, with 0.46 per 1000 having thalassemia and 2.28 per 1000 having sickle cell disorder.³ Hemoglobinopathies were uncommon in central European countries and in the industrialized countries of northern Europe, yet recently have become more common in these areas due to immigration from endemic areas.⁵

Thalassemia is the second most common disease in a diverse set of areas including the Mediterranean, the Middle East, Central Asia, the Indian sub-Continent, and Southern China (β thalassemia).⁶ Iran is geographically located in the "thalassemia belt" from the Mediterranean basin through the Middle East, Indian subcontinent, and Southeast Asia.⁷ There are about 2–3 million

carriers, and about 800 infants are born each year with thalassemia. The reported incidence rates of gene carriers ranges from 4% to 10%.^{7,8} Iran, with 26,000 people having thalassemia, is one of the most affected countries.⁷ Iran's average annual incidence rate of major thalassemia is 19.8 cases per 100,000, with the highest rate being 28 cases per 100,000 live births during 2003. The incidence rate of disease declined from 43.7 cases in 1997 to 1.5 cases per 100,000 live births in 2010.⁷

Sickle cell disease (SCD) is an inherited hemoglobinopathy that is prevalent in sub-Saharan Africa, the Middle East, India, and also among those of African origin living in Europe and in the Americas. The prevalence of sickle cell disease is high in the southern part of Iran, especially in the Khuzestan province that is at the border of Iraq, the Persian Gulf, and the Omansea.⁷

Glucose 6-phosphate dehydrogenase deficiency (G6PD-D) is prevalent in people of African, Asian, Middle Eastern, and Mediterranean descent and is one of the most common inherited disorders, with more than 400 million people affected by this deficiency globally.⁹ The frequency of G6PD-D in the Middle East varies greatly, ranging from 1% in Egypt to 11.5% in some ethnic groups of Iran. The prevalence of G6PD-D among different Iranian populations is between 10% and 14.9% according to a World Health Organization report.⁴

The Institute for Health Metrics and Evaluation (IHME) conducted the Global Burden of Disease study 2010 (the GBD study 2010), which is the most comprehensive and consistent set of estimates of morbidity and mortality by age, sex, cause, and country. The main objective of the GBD study 2010 was to calculate comparative risk assessments that could compute the burdens of disease and deaths caused by specific risk factors. In the present study, we aim to utilize specific methods to derive the attributed risk factors of hemoglobinopathies in Iran. In addition, this paper aims to present the global estimations of death and Disability Adjusted Life Years (DALYs) due to hemoglobinopathies (thalassemia, sickle cell disorders, G6PD-D) in Iran by sex and age in the years 1990, 2005 and 2010. We also discuss the data, methods, and limitations of the GBD study 2010.

Materials and Methods

The Global Burden of Disease study from 2010 (the GBD study 2010) represents a systematic effort to estimate the magnitude of health loss due to diseases, injuries, and risk factors, with unique data collection and methods that have been explained elsewhere.¹⁰⁻¹⁷ The results for the years 1990, 2005, and 2010 are available on the website of the Institute for Health Metrics and Evaluation (IHME).

Through use of a comprehensive database of death registration systems, vital registration, verbal autopsy, mortality surveillance, and other sources covering 187 countries from 1980 to 2010, the numbers of deaths and years of life lost (YLLs) due to premature mortality were estimated. Furthermore, since the deaths caused by hemoglobinopathies such as thalassemia, sickle cell disorder, and G6PD deficiency are rare, the results were analyzed using the Cause of Death Ensemble model (CODEm) and fixed proportion. Uncertainty intervals were obtained using simulation methods.¹² Years lost due to disability (YLDs) were measured by taking prevalence (frequency) multiplied by the disability weight for sequelae (that is, further severe symptoms) and symptom duration. The severity for different conditions is determined through surveys

of the general public and a systematic search on published and available unpublished data sources for prevalence, incidence, remission, and excess mortality. Prevalence was estimated by using the database for all ages, sexes, sorted by country and year, with a Bayesian meta-regression developed for the GBD study 2010 (DisMod-MR). DisMod-MR used available epidemiological and clinical information to generate sex/age specific prevalence, incidence, and remission. DisMod-MR provides epidemiological estimates for regions with no available data and with known sources of variability in data.¹⁸

Ranks across causes and percentage changes were computed from 1990 to 2010 at the draw level with 95% Uncertainty Intervals (UIs). For percentage changes from 1990 to 2010 that had been calculated at the level of each draw, the median percentage change was reported because the median is less sensitive to extreme values than the mean percentage change.¹⁶

In this study, we describe and criticize the GBD study 2010 results depicting the burden of hemoglobinopathies in Iran from 1990 to 2010 by producing different figures and tables, and close by reviewing the limitations of the GBD study 2010 in the context of our study and its findings.

Results

All types of hemoglobinopathies and hemolytic anemia in Iran contributed to 0.51% (95% UI: 0.26–0.76) of total deaths and 1% (95% UI: 0.69–1.37) of total DALYs in 1990 compared with 0.36% (95% UI: 0.25–0.51) and 0.82% (95% UI: 0.61–1.09), respectively, in 2010.

The number of deaths at all ages due to hemoglobinopathies, thalassemia, sickle cell disorders, and G6PD-D were respectively estimated in 1990 as 1272.15 (95% UI: 895.04–1760.26), 420.719 (95% UI: 291.25–589.49), 488.34 (95% UI: 310.14–727.6) and 46.63 (95% UI: 30.05–72.43) and in 2010 as 1647.54 (95% UI: 830.92–2441.69), 325.37 (95% UI: 231.55–425.8), 261.07 (95% UI: 200.83–323.75), and 41.72 (95% UI: 30.57–58.37).

The corresponding DALYs at all ages in 1990 were 220,179 (95% UI: 149,175–301,925), 103,339 (95% UI: 73,875–144,282), 51,129 (95% UI: 35,101–71,759.7), and 3692 (95% UI: 2371–5732) for hemoglobinopathies, thalassemia, sickle cell disorders, and G6PD-D, respectively; and in 2010 were 159,829 (95% UI: 117,410–217,039), 89,132 (95% UI: 63,545–127,247), 30,501 (95% UI: 23668.7–40455.8), and 2441 (95% UI: 1803–3253.85), respectively.

The attributed age-standardized rates for each hemoglobinopathy and for G6PD-D decreased in 2010 in comparison with 1990. Time trends of age-standardized death and DALYs rates caused by thalassemia, sickle cell disorders, and G6PD-D between 1990 and 2010 are presented in Figure 1; the rates of YLL and YLDs are shown in Figure 2. These estimations are for the entire 20-year time period and based on sex and divisions into various age groups (under 5, 5–14, 15–49, 50–69, and ≥70 years) (Tables 1 and 2).

The findings show that the attributed deaths and DALYs rates at all ages followed the same trend in Iranian men and women, with approximately equal rates. The highest rates of death from thalassemia and sickle cell disorder were observed in Iranian children less than 5 years old. Meanwhile, hemoglobinopathies and G6PD-D were mainly observed in Iranian people over the age of 70 years. The highest level of DALYs for hemoglobinopathies, thalassemia, sickle cell disorder, and G6PD were in the age group

Table 1. DALYs rate (per 100000 population) attributed to hemoglobinopathies by sex and age in 1990 and 2010.

	Year	1990	2010	1990	2010	1990	2010
	Sex						
	Age	Men		Women		Both	
Hemoglobinopathies	Under 5	1090(-)	672	1130	672	1110	672
	5–14 years	382	330.5	302	233	344	283
	15–49 years	207	123	212	167	210	145
	50–69 years	218	155	203	153	211	154
	70+ years	367	331	365	296	367	315
	All ages	411	211	391	221	402	216
Thalassemia	Under 5	412	320	427	322	419	321.5
	5–14 years	229	215	170	146	200	181
	15–49 years	92	59	138	117	115	87.5
	50–69 years	89	76	104	86	96	81
	70+ years	102	121	94	85	98	104
	All ages	186	108	191	133	188.5	120.5
Sickle cell disorder	Under 5	272	140	301	149	286	145
	5–14 years	88	69	78	48	83	59
	15–49 years	45	27	40	29	43	28
	50–69 years	28	22	26.5	21	27	21
	70+ years	19	20	16.5	13	18	17
	All ages	94	42	92	40	93	41
G6PD deficiency	Under 5	17	7.62	15	8.5	16	8
	5–14 years	8	5.1	5	3.3	7	4
	15–49 years	5	2.8	3	2	4	2
	50–69 years	4	2.9	3	2	3.5	2
	70+ years	9	8.2	6	5	8	7
	All ages	8	3.8	6	3	7	3

Table 2. Death rates (per 100000 population) attributed to hemoglobinopathies by sex and age in 1990 and 2010.

	Year	1990	2010	1990	2010	1990	2010
	Sex						
	Age	Men		Women		Both	
Hemoglobinopathies	Under 5	7.8	3	8.2	3	8	3
	5–14 years	1.2	0.6	1.2	0.6	1.2	0.6
	15–49 years	2	1.3	1.5	0.9	1.8	1
	50–69 years	3.6	2.2	2.7	1.7	3.15	2
	70+ years	14.5	14	15	13	15	14
	All ages	3.1	2	2.9	1.5	3	2
Thalassemia	Under 5	1.5	0.6	1.7	0.6	1.6	0.6
	5–14 years	0.3	0.1	0.3	0.1	0.3	0.1
	15–49 years	0.9	0.6	0.7	0.4	0.8	0.5
	50–69 years	0.8	0.6	0.75	0.5	0.8	0.5
	70+ years	0.2	0.1	0.2	0.1	0.2	0.1
	All ages	0.8	0.5	0.7	0.4	0.8	0.4
Sickle cell disorder	Under 5	2	0.8	2.6	0.8	2.5	0.8
	5–14 years	0.7	0.35	0.7	0.3	0.7	0.35
	15–49 years	0.6	0.34	0.4	0.2	0.5	0.3
	50–69 years	0.6	0.4	0.5	0.3	0.6	0.4
	70+ years	0.4	0.3	0.45	0.3	0.4	0.3
	All ages	0.9	0.4	0.9	0.33	0.9	0.35
G6PD deficiency	Under 5	0.15	0.05	0.1	0.04	0.1	0.04
	5–14 years	0.08	0.04	0.05	0.02	0.07	0.03
	15–49 years	0.08	0.04	0.03	0.02	0.05	0.03
	50–69 years	0.14	0.09	0.07	0.05	0.1	0.07
	70+ years	0.7	0.7	0.45	0.38	0.6	0.56
	All ages	0.1	0.08	0.06	0.04	0.08	0.06

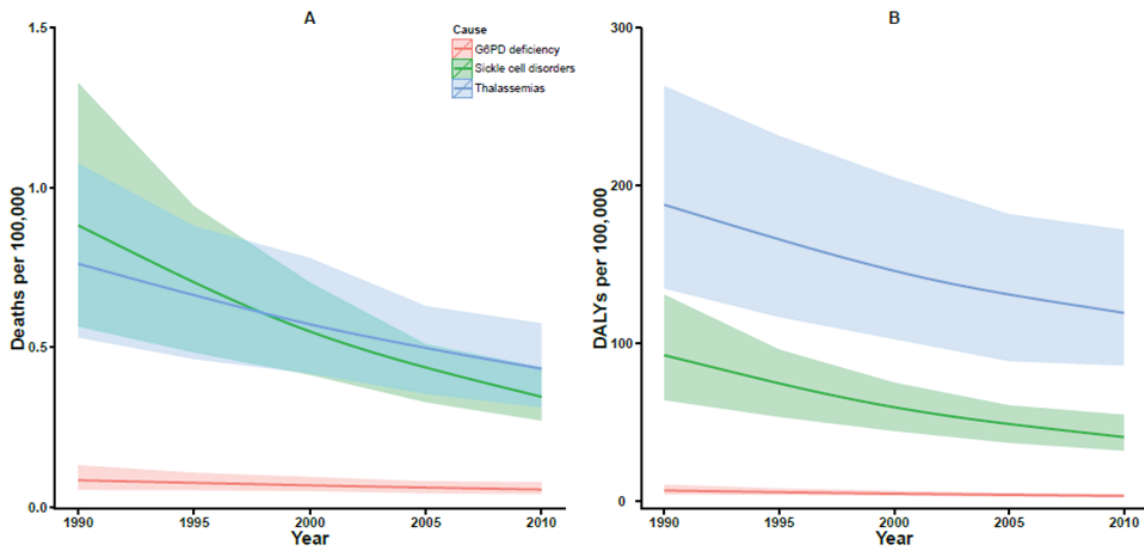


Figure 1. Time trends attributed to Thalassemia, Sickle cell disorders and G6PD deficiency for both sexes.

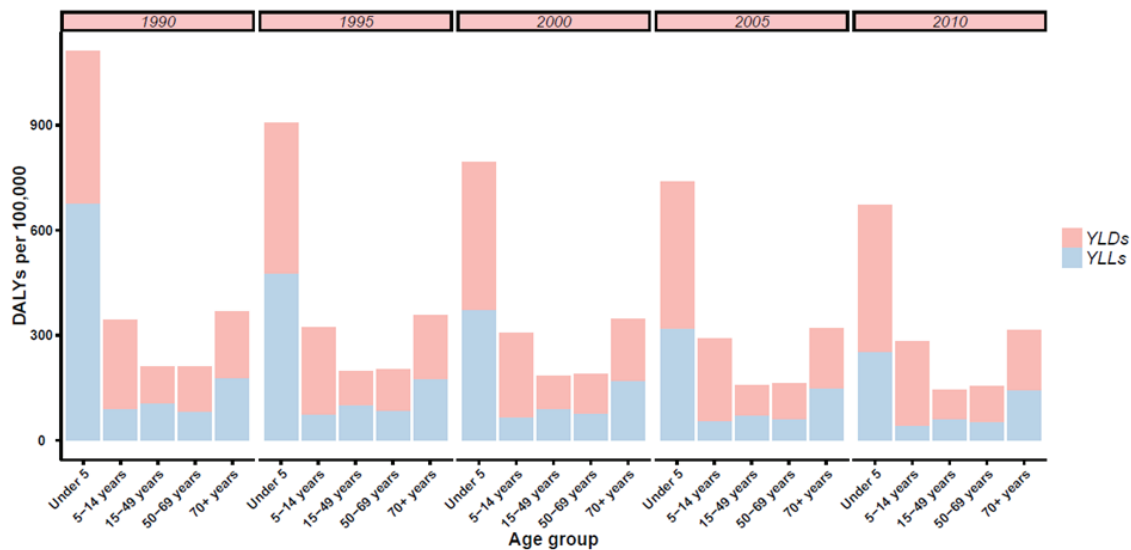


Figure 2. Time trends of DALYs rate attributed to hemoglobinopathies and hemolytic anemia for both sexes by age from 1990 to 2010 in Iran.

of <5 years.

The trend of deaths and the rate of DALYs caused by thalassemia, sickle cell disorders, and G6PD-D in the 5 age groups for 1990 and 2010 are shown in Figure 3. In addition, time trends and rates of death and DALYs attributed to hemoglobinopathies for children younger than one year (as the main affected age group) are illustrated in Figure 4.

Between 1990 and 2010, the rank of DALYs for thalassemia among all of the disorders measured by the GBD study 2010 declined from 35th to 42nd, reflecting a 52% reduction in DALYs (95% UI: -32 to 9). Furthermore, the DALYs rank for sickle cell disease changed from 57th to 74th, signifying a 40% reduction (95% UI: -58 to -12); the rank for G6PD-D shifted from 139th to 149th, reflecting a 33% decrease in DALYs (95% UI: -56 to -1).

Discussion

The results of the GBD study 2010 indicate that the rate of

deaths and DALYs for hemoglobinopathies in Iran decreased between the years 1990 and 2010. This shifting pattern across time, regions, and age groups is consistent with the rising total population, the rising average age of the world's population, and the broad epidemiological transition. Hemoglobinopathy has a regional pattern that is not directly related to broader worldwide transitions in disease epidemiology.⁴

An important policy that led to a decrease in the attributed rate of thalassemia was the National Thalassemia Screening program implemented in 1997. This program included pre-marital screening, counseling for parents with thalassaemic children, and evaluation of the rate of thalassemia in individuals who married before implementation of the program. Another protective element of the program that led to a nearly 80% decrease in the incidence of major beta-thalassemia within the first 8 years was prohibiting marriage in couples whose parents were the carriers of the thalassaemic trait. In 2003, genetic counseling during pregnancy for at-risk couples was added to the program.¹⁹

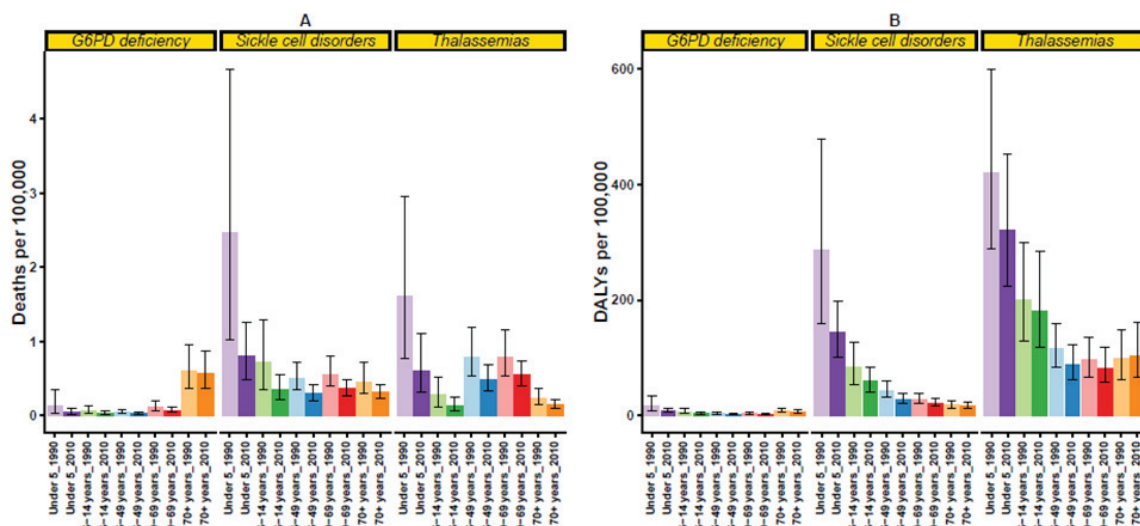


Figure 3. Time trends attributed to Thalassemia, Sickle cell disorders and G6PD deficiency for both sexes by age from 1990 to 2010 in Iran: (A) Death rate, (B) DALYs rate.

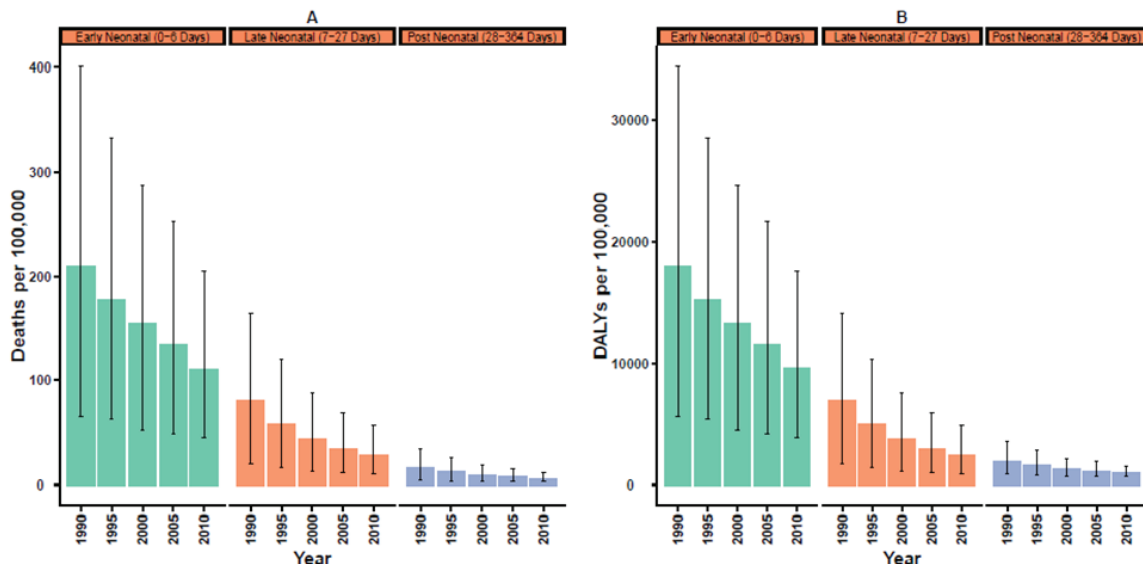


Figure 4. Time trends of DALYs and Death rates attributed to hemoglobinopathies and hemolytic anemia for children younger than 1 year (both sexes) from 1990 to 2010 in Iran.

The highest number of deaths and DALYs attributed to thalassemia and sickle cell disorders in Iran was in children <5 years of age. Improvement in areas such as appropriate nutrition, hygiene, and public health in many countries such as Iran have resulted in an epidemiological transition characterized by a fall in the mortality rate in children less than 5 years of age.²⁰ Accordingly, many children with thalassemia or sickle cell disorders that would have previously died in infancy period now survive due to proper diagnosis and management. Such a trend is now occurring throughout the Middle East, the Indian subcontinent, and in many parts of Asia (including Iran).²¹ The more treatment options improve, the more patients experience adulthood with increasing complications.

Limitations of the GBD study 2010 have been explained elsewhere.^{16,18-24} Here, we mention some limitations of the GBD study 2010 that led to limitations being present in our own study. The

estimation of many diseases such as hemoglobinopathies in Iran by the GBD study 2010 team has been affected by the lack of data sources; meanwhile; several Iranian data sources were not used for estimating the burden of these diseases. A number of published and unpublished epidemiological studies, as well as multiple national and subnational surveys and the data collected by the Center for Disease Control and Prevention (CDC) surveillance system of Iran, are among these unused data sources.

Another limitation is that, while the GBD data are often model-driven, data-driven studies are more reliable. Since the GBD study 2010 findings are at a national level, they are not appropriate for designing interventions and allocating resources at the subnational level; information at a greater level of detail is necessary. By determining the burden of hemoglobinopathies at the subnational level, health policymakers could design and implement more efficient health programs in this field. In this regard, to provide a

better assessment of the burden of hemoglobin disorders, it would be necessary to perform a comprehensive study at the national and subnational level. Reflecting this need for data, the National and Subnational Burden Of Diseases (NASBOD) study in Iran is using a standardized protocol of data collection and statistical methods to compute the burden of diseases, injuries, and risk factors at both the national and subnational levels from 1990 to 2013.²² Two advanced statistical methods are being used to review the data in this study.^{23,24} The national and subnational burden of hemoglobinopathies being reviewed as a sub-component of the NASBOD study and aims to quantify the prevalence and burden of hemoglobinopathies at the national and subnational levels for the 1990 to 2013 time period.

Significant hemoglobinopathies such as thalassemia and sickle cell disorders have not yet been considered an important health burden by governments or non-governmental organizations (NGOs), especially when compared with other major health burdens of developing countries.¹⁹ Therefore, training programs about the nature of genetic diseases and the results of screening programs should be developed. Programs related to advancing screening for genetic disorders and prenatal diagnosis have been very successful in Mediterranean countries; meanwhile, these programs are just beginning in some of the less-developed countries in Asia.²⁰

Immigration, familial marriage, and some cultural beliefs among the different ethnic groups of Iran could generate variations in the prevalence of thalassemia, G6PD-D, and other hemoglobinopathies. Since the development of national prevention programs is at the center of health authorities' activities, collecting national and sub-national data will assist in the prevention of hemoglobinopathies.²¹

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Competing interests

The authors declare that they have no conflicts of interest.

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