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RESEARCH ARTICLE

Level and trend of total plasma cholesterol in national and subnational of Iran: a systematic review and age-spatio-temporal analysis from 1990 to 2016

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Abstract

Purpose We aimed to estimate the level and trend of plasma cholesterol and raised total cholesterol (TC > 200 mg/dl) prevalence at national and subnational level of Iran.

Methods Nine national surveys and 27 studies, encompassing 3,505 unique points on over 500,000 adults, aged > 25 years with a report of laboratory measurement of TC were found. Age-spatio-temporal model and Gaussian Process Regression were used to estimate mean TC for each sex, 5-year age groups, and 31 provinces from 1990 to 2016.

Results At national level, age-standardized prevalence of TC > 200 mg/dL has decreased from 57·2%(53·3–61·1) to 22·4%(20·5–24·3) in women and 53·2%(49·1–57·3) to 18·0%(16·4–19·6) in men. TC distribution presented a condensation between 170-200 mg/dL. At subnational level, decreasing and converging patterns of raised TC prevalence were detected.

Conclusion The decrease in raised TC is likely the result of statin widespread use, food industry improvements, and the expanded primary health care.

Keywords Cholesterol · Hypercholesterolemia · Prevalence · Iran · Longitudinal studies · Systematic review and meta-analysis

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Introduction

There is a rapid transition from communicable to non-communicable diseases (NCDs) in world especially in the fast developing nations like Iran [1, 2]. The World Health Assembly developed an action plan at global level in 2013 to confront the epidemic of NCDs and to achieve a 25% reduction in risk of premature mortality from cardiovascular diseases, cancers, diabetes, and chronic respiratory diseases till 2020 [3]. This plan can be implemented mainly through a comprehensive primary prevention to control the metabolic risk factors of NCDs. Raised total cholesterol is recognized as one of the main four metabolic risk factors of major NCDs and is amenable to risk modifying preventions [4, 5]. There is compelling evidence on causal relationship between this modifiable risk factor and cardiovascular diseases (CVDs) and some cancers [6]. Previous evidence shows a decreasing trend of raised total cholesterol (TC) and the burden attributable to it globally and in high-income regions, but the trends in a number of developing regions such as east and southeast Asia are increasing and in many other low- and middle-income regions, trends are uncertain [7]. In Iran, based on the Global Burden of Disease estimates, the national trend of raised TC is increasing in the total community while after adjustment for age, it shows as a stagnation, criticizing the ageing pattern of Iranian population [7]. However, due to data scarcity, difficulties of measuring total cholesterol, and various definitions for high TC, the evidence on levels and trends of this risk factor are not consistent, not adequate, and not comparable across regions and nations. Collecting high quality data at global, regional, national, and even sub-national levels is thus a crucial step for evidence-based policy making in low resource settings. To this date, there is no study to comprehensively combine data both from small observational studies and large national surveys to understand the current state of hypercholesterolemia in Iran and evaluate national acts and programs.

In the current study, we aimed to quantify the levels and trends of mean total cholesterol, to estimate the distribution and prevalence and also the number of adults with raised total cholesterol at national and sub-national levels in Iran from 1990 to 2016 through consistent statistical methods.

Methods

This systematic review and meta-analysis has been conducted in accordance with guidelines for the systematic review of observational studies reporting of prevalence and cumulative incidence data and Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA).

Information collection

The mean total cholesterol and prevalence of high TC by sex and age across all provinces of Iran from 1990 to 2016 was assessed based on two sources of data: 1. National-level large surveys and registries 2. Published literature of smaller studies. National large surveys and registries were identified after contacting the officials at Iranian Ministry of Health and Medical Education (MOHME). In this regard, nine national surveys in Iran, constituting two iterations of national health surveys (NHS) in 1991 and 2000, and seven iterations of NCD Risk Factors Surveillance Surveys (STEPs) were defined. In the next step, we performed comprehensive systematic review on available evidence to detect smaller studies. We searched PubMed/MEDLINE, Embase, Web of Science, and Scopus for international databases and Scientific Information Database (SID), IranDoc, IranMedex (Barekat Knowledge Network System), and Magiran for national data bases, with time window of their inception to Jul 2021 and no limitation of document type, language, or publication status. Keywords were collected through experts' opinion, literature review, controlled vocabulary (Medical Subject Headings (MeSH) and Excerpta Medica Tree (EMTREE)), and reviewing the primary search results in accordance to PICO method: 1. Population was defined as Iranian population at risk of metabolic irregularities 2. Intervention of records of assessing the cholesterol level through laboratory measurement, 3. Comparison based on age-groups, sex-groups, geographical stratifications, and year, and 4. Outcome of TC as higher than 200 mg/dL was considered hypercholesterolemia. As the distribution pattern of TC has been substantially changed over 26 years of this study, we used a left-transitioned factitious cut-off of 170 mg/dL (as the theoretical minimal risk) for definition of impaired cholesterol to grab cases of dyslipidemia more sensitively [8, 9]. Two reviewers independently screened titles and abstracts from the search results to find possibly eligible papers and then reviewed the full text of selected papers against the eligibility criteria. The references of the selected articles were also searched for eligible studies. Any disagreement in the screening process was resolved through discussion, or through negotiation by a third review author. More details can be found in the Appendix. Exclusion criteria were placed as of studies without assessing the population that is generalizable and representative of Iranian community as a whole (i.e., hospital-based or healthy-worker-based samples, or sample size of less than 5, or non-randomized study with incorrect sampling frame), not reporting TC, or details of TC detection or using method other than conventional laboratory measurement (i.e., self-report), using secondary data (systematic review or further analysis of already published studies), reports of not being peer reviewed (conference proceedings, preprints) were disputed. In case of overlapping data source, the larger report was used. We assessed the quality of included studies using Critical Appraisal Tool (CASP) in the scale of 1 to 10. The final quality score of an article was calculated as the mean of the quality scores that two reviewers provided. We obtained individual-level data of national surveys and tabulated data from the smaller-scale studies.

Statistical analysis

In order to estimate the log mean total cholesterol by sex (two sexes), age-specific (13 age categories started at 25 to 85 year-old with 5-year age intervals), province (31 provinces), and year (27 years from 1990 to 2016), we used a linear mixed effect model, with variables including wealth index, years of schooling, and urbanization as fixed-effects covariates and province with random effects for the model [8]. We modeled the log transformation of total cholesterol to maintain the normality assumption for the outcome. As data at the individual level were added, no further data cleaning or harmonization was required. The predictions and residuals of our data points were extracted from this model to be used later in the age-spatio-temporal model. We standardized all the estimates with the latest Iran national census population of 2016.

We aimed to consider the variation between sex-age-year-province combinations by socio-economic status measures including years of schooling, wealth index, and urbanization. These variables helped us to improve the final national and sub-national estimates as they have a high correlation with health-related measures and risk factors. Years of schooling was measured according to the level of education attainment for each person extracted from the Statistical Canter of Iran (Household and Income Survey). This variable variated from 0 to 25 years. We calculated wealth index based on the Household and Income Survey data for each household. We did a principal component analysis over all the assets and income of each household. Urbanization was calculated according to the population sizes living in the urban areas over total population size for each age-sex-year-province combination ranging from %0 to %100. We transformed each variable to a logarithm scale to get the normal distribution if it was the case.

We ran an age-spatio-temporal model on the residuals extracted from the linear mixed effect model, in which we borrowed strengths over age groups, provinces, and years by smoothing the residuals [9]. To do this we calculate adjacency matrices over age, province and year. Regarding these matrices, the adjacent provinces, years and similar age groups will be more consistent with each other. Since this model considers the information of neighboring provinces and nearby time points and ages, it can improve estimates compared to the linear mixed effect model. Finally, we used the output of previous models as a mean prior for Gaussian Process Regression (GPR) model [10–12].

To address the various population size of different studies, we consider the sample size of each study as one of the variance components in the GPR model. The variance in GPR model includes two parts for considering the variance within each study and between studies. The sampling variance was calculated as the inverse probability of the study sample size. Uncertainty in the measurements due to non-sampling error was captured in the model for each type of data source. These parameters were estimated based on the degree to which a source tends to disagree with the other sources. The more that a particular source conflicted with other sources, the higher the variance parameter will be and thus the more uncertain the measurements. We considered the Matern function as the covariance function in Gaussian process regression, the Matern function determines the amount of borrowing neighborhood correlation in our timespan. It has three parameters that control the correlation and smoothness of the time trend. We included the extra variation sources in the GPR model using hyperparameters in the Bayesian modeling approach.

In order to estimate the prevalence of elevated and raised TC, we used a cross-walk method to regress prevalence over mean TC, extracted from the GPR model. The final estimates and uncertainty intervals were calculated using the posteriors of the GPR model. RStan package in (Version 2.21.2) R (Version 4.1.1) was used to implement Hamilton Monte Carlo (HMC) method. A total sample of 5000 was retained from 10,000 iterations (4 chains with 2500 iterations) from the posterior distributions. 95% uncertainty intervals were generated for estimates and non-overlapping of estimates was regarded as statistical significance difference. The median, 2·5 percentile, and 97·5 percentile of this distribution were used as point estimates of lower and upper UIs, respectively [13]. The details of statistical methods can be found in the Appendix.

Sensitivity analysis

We conducted a sensitivity analysis to examine the validity of our estimations [14]. We randomly selected 10% of our original data points and dropped them. We reiterated all the models on the remaining 90% and compared the in-sample validity using the following four metrics: root mean square error (RMSE), root median square error, median relative error, and mean relative error of prediction models. Median relative error and mean relative error are defined as median of values TC over its estimates by each model and mean of absolute value of estimates over its estimates, respectively.

In the next stage we examined the proportion of the originally dropped 10% data points that were within the 95% uncertainty interval of our 90% withheld data.

Results

After systematically reviewing the online data repositories, 3100 unique records were retrieved. Of this amount, 304 were withheld for full text assessment. After full text refinement, 27 were included reporting 88 data points that could be admixed with 3417 data points of nine national surveys (Fig. 1). In total, 3,505 data points on over 500,000 adults, aged 25 to over 85 years, recruited in national and provincial population-based surveys in Iran as well as published studies from 1990 to 2016 were pooled (Table 1 for summary of included published studies). These studies were commonly running over the large cohort/cross-sectional studies at subnational levels (i.e., 1. Golestan Cohort Study (GCS) 2. Pars Cohort Study (PCS) 3. Isfahan Healthy Heart Program (IHHP) 4. Tehran Lipid and Glucose Study (TLGS) 5. Kerman Cohort Study (KERCADR) 6. Mashhad Cardiovascular Cohort Study 7. Persian Gulf Healthy Heart Study). The number of data sources for each province and year is demonstrated in the heat map in the Appendix. For sensitivity analysis, we calculated the proportion of data points in our masked data set that were located in the uncertainty interval of our 90% withheld data. For TC, 82·7% of ten percent withheld data hold in 90% prediction of model and its uncertainty, representing accuracy and homogeneity of data and models.

National estimates

From 1990 to 2016, age standardized mean TC in women has significantly decreased from 202·5 mg/dL (191·2 – 214·6) to 174·5 mg/dL (166·6 – 182·8). Similarly, in men,

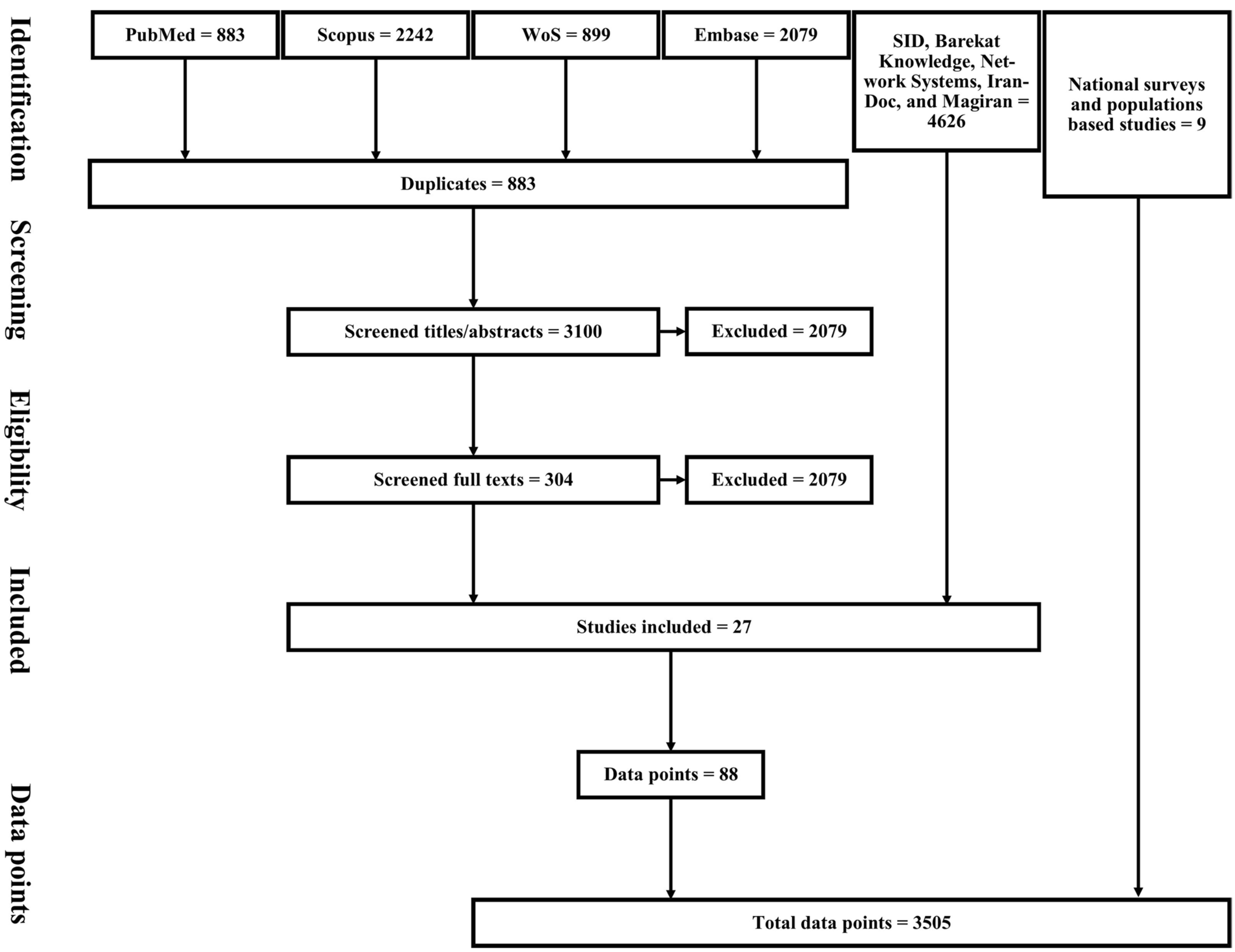


Fig. 1 the flowchart of studies

Table 1 Summary and characteristics of included published studies

Study	Scale	Design	Sample size	Female percentage	Age	Main finding
Rafiei M [15] 1994	Provincial (Isfahan)	Descriptive population-based survey of random clusters	2200	45%	Range: 20—70	59.9% of males and 71.7% of studied female had TG > 200, a signified difference
Izadi N [16] 1994	Provincial (Kermanshah)	Cross-sectional records analysis of outpatient centres	2309	61%	Mean (SD): 54.9 (10.8)	The mean TC of males was 189.1 (SD: 57.3) while in women it was significantly higher 197.8 (54.2)
Amiri M [17] 1997	Provincial (Bushehr)	Cross-sectional	2092	52.6%	25–34 age group: 31.8% 35–44 age group: 30.4% 45–54 age group: 23% 55–66 age group: 14.6%	24% of total population had hypercholesterolemia. 26% of women and 21% of men were hypercholesterolemic
Kharrazi H [18] 1998	Provincial (Kermanshah)	Case–control study	115 CAD (excluded) and 135 control (including)	29.5% of CAD group and 37% of con54trol group	Mean (SD) for CAD: 54.4 (8.9) For control: 55.3 (12.3)	The mean TC of control group was 160 (SD: 26)
Mellati AA [19] 2003	Provincial (Zanjan)	Population-wise cross-sectional	2768	52.6%	Mean (SD) 39.7 (14.4)	31.3% of males and 40% of females had TC more than 200, showcasing a significant difference
Azizi F [20] 2003	Provincial (Tehran)	Population-wise cross-sectional	6246	63%	20–24 age group: 12% 25–34 age group: 26% 35–44 age group: 26% 45–54 age group: 20% 55–64 age group: 16%	The mean (SD) TC in total sample was 173 (123). In males it was 190 (142) compared to 162 (109) in females
Karam GA [21] 2004	Provincial (Kerman)	Case–control study	49 cases and 49 controls	53%	Range: 35—65	The mean TC (SD) among control group was 235.8 (10.6)
Chehrei A [22] 2005	Provincial (Markazi)	Cross-sectional population-based study	750	77.3%	41.1 (16)	High TC was detected in 28.5% of sample. Females with 22.9% and males with 30.2% of hypercholesterolemia
Sadr SM [23] 2005	Provincial (Yazd)	Cross-sectional	2000	50%	Mean (SD): 47.8 (15)	The mean TC (SD) in men was 191 (41) and 205 (46) in females
Marjani A [24] 2009	Provincial (Golestan)	Case–control	50 cases (excluded) and 50 controls (included)	62%	Mean (SD) 49.4 (9.5) for cases abd 50.3 (9.8) for controls	The mean TC (SD) of control groups among females was 160.4 (27) and 159.8 (23.8) for males

Table 1 (continued)

Study	Scale	Design	Sample size	Female percentage	Age	Main finding
Azimiyan J [25] 2007	Provincial (Qazvin)	Cross-sectional	400	100%	Mena (SD): 38.2 (2.5)	22% of participants had TC more than 200
Balali-Mood M [26] 2005	Provincial (Khorasan Razavi)	Cross-sectional	108	-	Mean (SD): 37 (7.8)	The mean TC was 133.9 (104.2) among factory workers
Veghari GH [27] 2011	Provincial (Golestan)	Cross-sectional	1995	50%	Mean (SD): 44.6 (-)	The mean TC among females was 209.4 (42.9) and it was 196.7 (39.5) in males
Marjani A [28] 2011	Provincial (Golestan)	Cross-sectional	100	100%	Mean (SD): 54.3 (5.2)	The mean TC was 210.8 (49.2)
Boshtam M [29] 2012	Provincial (Isfahan)	Cross-sectional	10,151	49.9%	Mean (SD): 35 (16.9)	The mean TC was estimated to be 185.9 (42.1)
Maharlouei N [30] 2013	Provincial (Shiraz)	Cross-sectional	924	100%	Mean (SD): 52.2 (8.4)	The mean TC was estimated to be 209.7 (48.7)
Veghari G [31] 2013	Provincial (Golestan)	Cross-sectional	1995	50%	Range: 25–65	The mean TC was 203.6 (40.7) in total sample and it was 12.7 higher in women
Hajian-Tilaki K [32] 2014	Provincial (Mazandaran)	Cross-sectional	1000	55%	Range: 20–701	TC in men: 191.6 (56.7) TC in women: 198.6 (43.6)
Haghighatdoost F [33] 2014	Provincial (Isfahan)	Cross-sectional	9555	50%	Mean (SD): 38.7 (15.5)	TC in men: 199.6 (39.8) TC in women: 204.5 (39.1)
Janghorbani M [34] 2014	Provincial (Isfahan)	Cross-sectional	9889	57.8%	Mean (SD): 52.0 (10.9)	TC in those without metabolic syndrome: 209.6 (51.8)
Bagheri Lankarani K [35] 2015	Provincial (Shiraz)	Cross-sectional	290 NAFLD and 290 non-NAFLD	55.2%	Mean (SD): 45.4 (12.4)	Total cholesterol was 190.1 (40.5) in sographically non-NAFLD control sample
Motamed N [36] 2009	Provincial (Mazandaran)	Cross-sectional	3273	42.9%	Mean (SD) among males 55.1 (10.4) and 54.0 (9.6) among females	TC in men: 187.2 (41.2) TC in women: 200.1 (42.8)
Fard NR [37] 2015	Provincial (Isfahan)	Cross-sectional	120	11–22% in differed subgroups	Range: 60–85	TC was in range 191–195 in three subgroups of study

Table 1 (continued)

Study	Scale	Design	Sample size	Female percentage	Age	Main finding
Mazidi M [38] 2016	Provincial (Mashhad)	Cross-sectional	8105	60.2%	Mean (SD): 48.3 (8.2)	TC was 190.8 (40.0) in total sample
Ghasemzadeh Z [39] 2016	Provincial (Tehran)	Cross-sectional	5518	54.1%	Mean (SD): 54.2 (10.0)	Mean TC was 221.6 (47.2) in total sample
Meysamie A [40] 2007	Provincial (Tehran)	Cross-sectional	4250	55%	Mean (95%CI): 39.4 (39.2 – 39.6)	TC was measured to be 196.3 (36.7) in total sample
Bakhshayeshkaram M 2016	Provincial (Shiraz)	Cross-sectional	819	58.5%	All age range with even distribution	36.5% of participants had abnormal TC of more than 200

NIDDM Non-insulin dependent diabetes mellitus; *SD* Standard deviation; *TC* Total cholesterol

mean TC significantly decreased from 197·3 mg/dL (186·1 – 209·4) to 168·5 (160·7 – 176·7) (Fig. 2). The decrease was more prominent in men compared to women. Also, there has been detected a shift in the distribution of TC, from 1990 to 2016 (Fig. 3). This pattern shows that the mean of the entire distribution has been shifted to left; however, the standard deviation of distribution has also decreased. Nationally, the number of adults with total cholesterol over 200 mg/dL decreased from 10·5 (9·8 – 11·5) million in 1990 to 9·9 (9·0 – 10·6) million in 2016. Age standardized prevalence of raised TC (TC > 200 mg/dL) at national level has decreased from 57·2% (95% CI: 53·3 – 61·1) to 22·4% (20·5 – 24·3) in women and from 53·2% (49·1 – 57·3) to 18·0% (16·4 – 19·6) in men between 1990 and 2016 (Fig. 2). The percent change in age-standardized prevalence was -61% (-66% to -54%) in women and -66% (-71 to -60) in men from 1990 to 2016 (Appendix Fig. 3). Mean TC, and prevalence of raised TC increased in adults of 25 to 55 years of age and then showed a steady trend till the oldest age group of + 85 (Appendix Fig. 4). The age pattern of prevalence of those with TC > 200 mg/dL similarly increased in the 25 to 55 age groups (young adults) and then it stabilizes for older adults and geriatric community.

Figure 2 (linear trends): Trends in age-standardized mean total cholesterol and prevalence of total cholesterol > 200 mg/dL (solid lines) and > 170 (dashed lines) by sex in people aged 25 years and older at national level from 1990 to 2016. The lines show the posterior mean estimates and the shaded areas show the 95% CI. See Appendix for trends by province·

The number of adults with TC > 170 mg/dL increased from 15·6 (15·0—16·1) million (7·6 million in women) in 1990 to 22·9 (21·6—24·2) million (12·0 million in women) in 2016. Age standardized prevalence of this factitious group at national level has decreased from 82·4% (79·8 – 84·8) to 49·5% (46·8 – 24·4) in women and from 79·7% (76·7 – 82·3) to 43·7% (41·0 – 46·5) in men between 1990 and 2016 (Fig. 2 and Appendix Fig. 2). The percent change in age-standardized prevalence of TC > 170 mg/dL from 1990 to 2016 was -40% (-45 to -35) in women and -45% (-50 to -39) in men (Appendix Table 1).

Subnational estimates

In women across all provinces, the mean age standardized TC in 2016 ranged from 166·4 mg/dL (154·1 – 179·6) to 182·3 mg/dL (171·4 – 193·8). In men, respective measures for TC were as low as 159·0 mg/dL (150·1 – 168·2) to as high as 178·2 mg/dL (168·0 – 189·0) in 2016 (Appendix Figs. 1 and 2). In terms of the trend of mean TC from 1990 to 2016, the percent change ranged from -23·6% (-36·3 – -8·8) to -5% (-20·1 – 13·1) in women. The equivalent results in

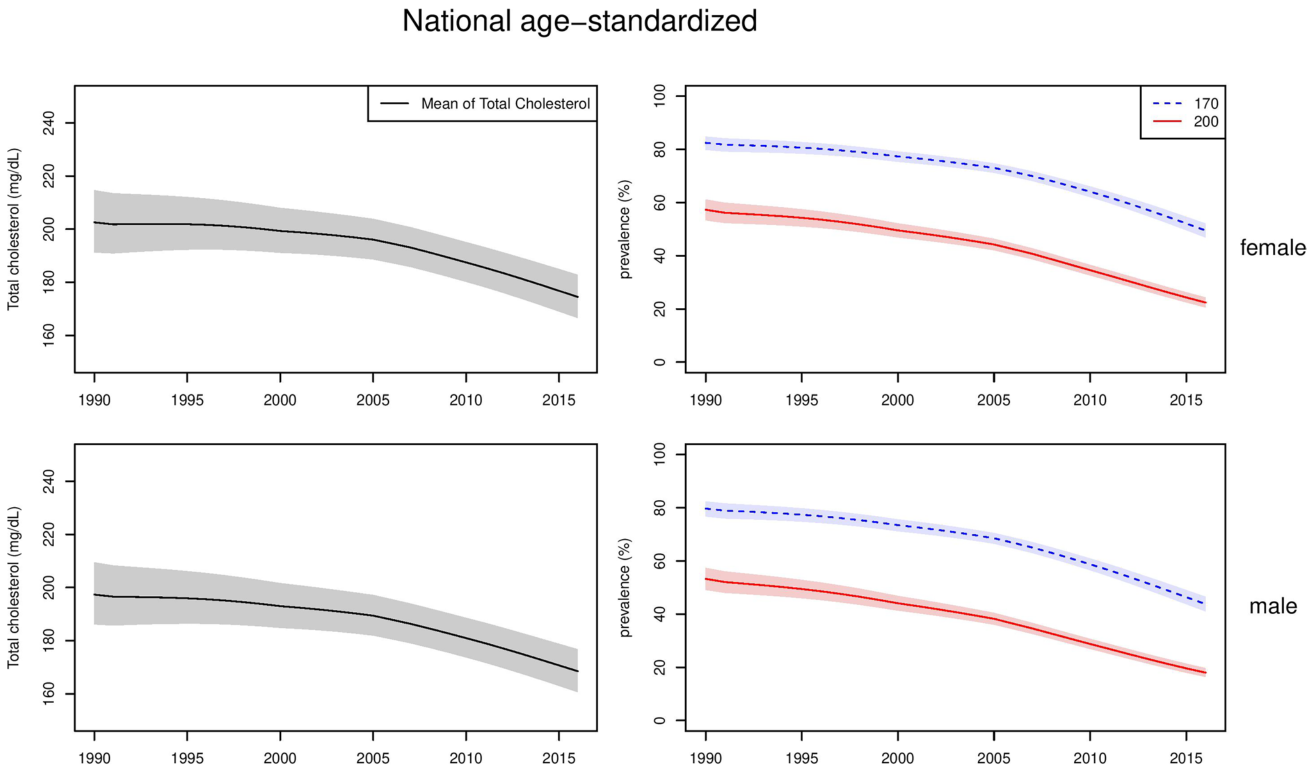
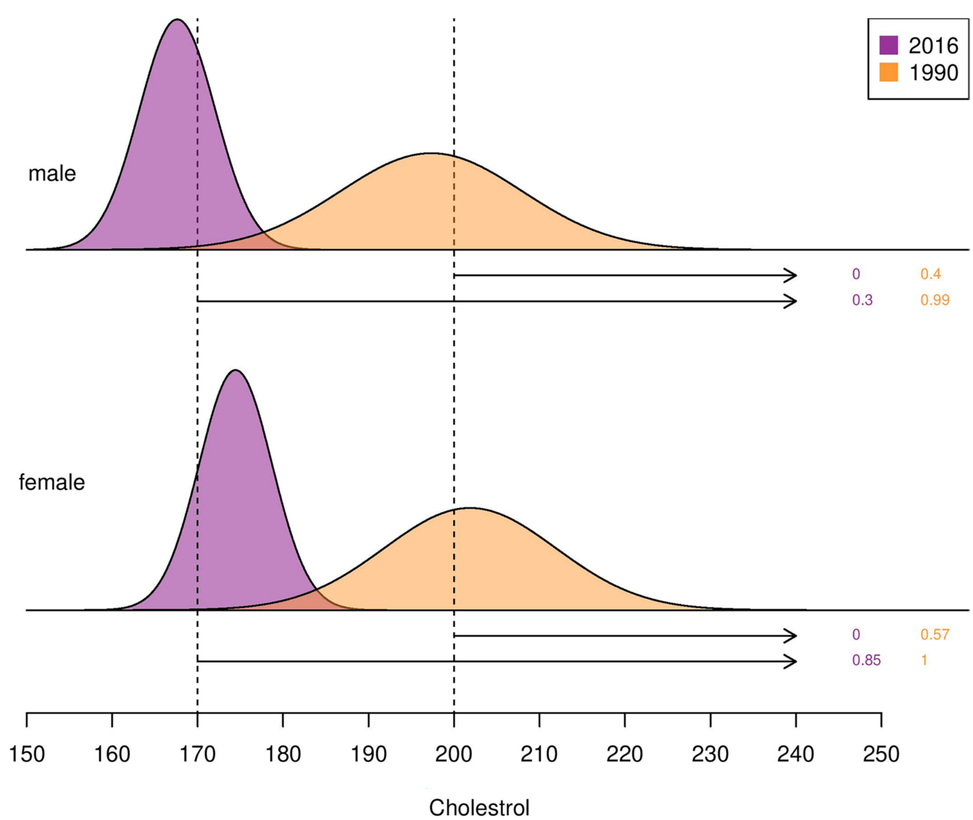


Fig. 2 (Linear trends) Trends in age-standardized mean total cholesterol and prevalence of total cholesterol

Fig. 3 Shift in the distribution of total cholesterol in men and women from 1990 to 2016

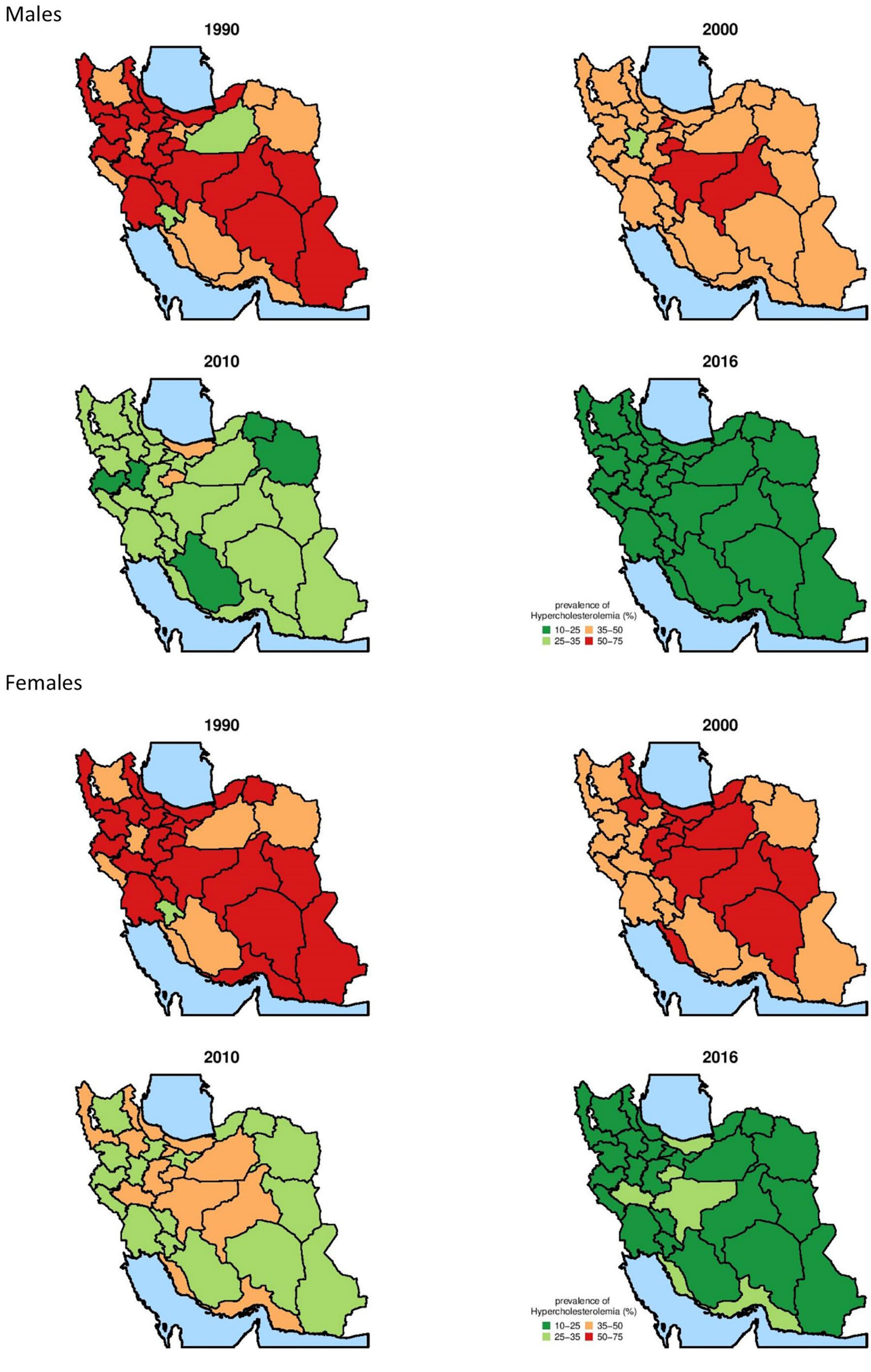


men were -24·8% (-33·5 – -14·9) to -0·6% (-15·3 – 16·3) (Appendix Fig. 2). The prevalence of raised TC has halved in almost all provinces in both sexes from 1990 to 2016, except for one province in men and four provinces in women (Figs. 4 and 5). In 1990, age standardized prevalence for TC equal or greater than 200 in women ranged from 34·0% (28·7% – 39·6%) to 75·5% (70·0% – 78·4%), and in 2016 the range was as low as 17·8% (16·0% – 19·7%) to as high as 27·5% (24·9% – 30·2%). In men, the age standardized prevalence in 1990 ranged from 33·3% (28·6% – 38·4%) to 74·9% (71·4% – 78·2%) and in 2016, from 13·1% (11·8% – 14·6%) to 23·8% (21·4% – 26·4%) (Fig. 2, Appendix Fig. 2). In 1990, there was no province with mean TC less than 170 mg/dL in women, and concerningly, 21 provinces (two-third of all subnational levels) had the mean TC over 200 mg/dL. This condition attenuated in the study period, as in 2016 there was no province with mean TC > 200 mg/dL among females and five provinces had mean TC < 170 mg/dL. In men, in 1990, there was no province with TC < 170 mg/dL, while in 2016 the mean TC was less than 200 mg/dL in all provinces and even less than 170 mg/dL in 22 provinces. Overall, it is indicated that decreasing progress was more rapid in men compared to women (Appendix Fig. 6). Similar age pattern as national trend has been detected in subnational levels of Iran in 2016; an increasing pattern during adulthood and stabilization in elderly. Although, there is an evident convergence in population with TC > 170 mg/dL during adulthood while showcasing a clear divergence in older age groups, a signal for an underlying unequal accessibility to health-care goods (Appendix Fig. 5).

Discussion

The results of our study showed a consistently decreasing trend in mean TC and prevalence of raised TC across both sexes, all age groups, and all provinces in Iran from 1990 to 2016. While the number of adults with TC > 200 mg/dL decreased from 1990 to 2016, we observed an increase in the number of adults with borderline TC estimates (170 – 200 mg/dL) in this period. In other words, the distribution of this risk factor is narrowing over time and most hypercholesterolemic patients are efficiently treated, but, the distribution is towering over the borderline area. Therefore, as the population is growing, although high-risk subgroups are being effectively prevented, there is a critical risk of cardiovascular disorders in this low-risk but crowded subpopulation [6, 41]. This condition was more prominent in females. Across provinces similar pattern has been detected yet with variable intensities.

Generally, our results are compatible with estimates made by Farzadfar et al. on mean TC and its trend from 1980 to 2008 [7]. Both of the results show a rather minimal change till 2008, while our study shows a decreasing trend mainly from 2008 afterwards. They reported that in 2005, 16,000 deaths (14,000 to 18,000) in women and 18,000 deaths (16,000 to 20,000) in men were attributable to high TC [42]. The Global Burden of Disease Study showed that in 1990, 11,100 deaths (8,300 to 14,300) in women were attributable to raised TC while the respective figures were 19,400 (13,700 to 25,800) in 2016. Respective figures for men were 15,000 (11,200 to 19,600) deaths in 1990 and 27,500 (19,600 to 37,000) deaths in 2016 [43]. In comparing our observations to international trends, the observed decrement in the mean TC and also the prevalence of dyslipidemia in our study was among the highest in previously reported time trends [44–46]. This finding shows the probable contribution of effective treatment in decreasing high levels of TC, while there are probably other determinants that have further decreased lower levels of TC. It is mainly prominent when we consider the observation that most of the adults with TC higher than 200 mg/dL have moved to 170 to 200 mg/dL TC levels. It supports the dual impacts of primary and secondary prevention on decreasing TC among Iranians since 1990. Improvement of food industry has had a certain impact. In early 2000s, a transition happened in the food industry of Iran in which, solid hydrogenated and animal fat was largely replaced by liquid vegetable oil with lower trans fatty acids. Based on a report released by the Iranian Ministry of Health and Medical Education, the use of solid hydrogenated oil has been replaced by liquid vegetable oil in Iran since 1990s. This transition can be the main driver of the shift in distribution of TC to left and denotes the success of the health system in improving food industry and implementing public education. Moreover, during the past decade, the prescription of statins in both primary and secondary health care settings has become routine based on most recent guidelines for the prevention of cardiovascular diseases, which are the most important causes of morbidity and mortality attributable to high TC. In the 2016 iteration of STEPs in Iran, it has been estimated that 74.2% of adults with hypercholesterolemia were aware of their condition and in total 6.9% of Iranian population (8.5% for females and 5.1% for males) were receiving statins. In the latter survey it has been pointed out that dyslipidemia patients at rural areas were less likely to be covered (5.6%) compared to urban inhabitants (7.2%). Moreover, the coverage rate differed significantly in wealth categories, with middle-class group of patients more likely receiving fat-lowering medication [47]. Studies demonstrated the negative correlation between statin sales and cholesterol level among Iranian population and uncovered an striking increase in statins sale in last two decades [48–50]. Although there have been programs to reduce the statin therapy expenditure and make it accessible to every patient, there still remains inequity and disparity, yet the cost-effective analyses have revealed that the


Males
1990
2000
2010
2016
prevalence of
Hypercholesterolemia (%)
10–25
35–50
25–35
50–75
Females
1990
2000
2010
2016
prevalence of
Hypercholesterolemia (%)
10–25
35–50
25–35
50–75

◂**Fig. 4** Age-standardized prevalence of total cholesterol > 200 mg/dL by sex and province in people aged 25 years and older in 1990, 2000, 2010, and 2016

current method of providing statins is highly effective and is in accordance to WHO's threshold of annual per capita share [51]. The differential pattern of mean and high TC in men and women may have biologic plausibility as well as other co-existing distal life style and cardio-metabolic risk factors in women such as overweight and obesity, diet, and physical inactivity [52–58].

Our results are of a great importance to policy makers as follows; 1) the success in decreasing the prevalence of raised TC in Iranian population validates the effectiveness of previously implemented policies at public health level. Even though in the healthcare network in Iran statins are available, there is no service package specifically designed for primary and secondary prevention of high serum cholesterol and the capacity of the health system for tackling NCDs and their metabolic risk factors is inadequate [59, 60]. Moreover, the combination of inter-sectoral collaboration between the health systems, food industry, health education, and all organizations that are somehow involved in health and well-being of Iranians can guarantee the continuation of decreasing trend of TC in Iran. This inter-sectoral collaboration can be achieved by health system guided education and awareness by media, edibale oil production refinery, accessibility of statins at primary health centers, decreasing out-of-pocket payment by patients, etc. Also, advantages of healthy diet should be promoted and for those with raised TC, compliance to adjusted diet needs to be encouraged and assessed [61]. These should be in line and in conjunction to management of other metabolic disorders as well [62]. However, 2) the increased number of adults with borderline TC and ageing of population shows a potential threat to the health system and it shows that there are many people that if not efficiently managed or prevented, would have dyslipidemia anytime soon. The establishment of the Iranian Non-Communicable Diseases Committee (INCDC) is the first concerted effort to design a comprehensive service package specific to metabolic risk factors of NCDs and their integration into the health system of Iran [63]. Nevertheless, the implementation and effectiveness are not evaluated yet. 3) The observed disparities among two genders necessitate further investigation of the underlying reasons while enlightens the importance of population-specific policies; what worked for men, might not work for women. And finally, 4) the different statistics of different provinces is a call for subnational designed and implemented programs to be more efficient and effective.

In other areas of the world similar works have been performed to understand the status of TC in their hosted population. Most of these surveys were carried out in nations with higher socioeconomic status and information about developing countries is redundant. In United States, a survey was performed on 18,000 adults and found that unadjusted 53.2% to 56.1% of study sample had hypercholesterolemia. Only 39.1% to 54.4% of their hypercholesterolemia patients were receiving lowering agents and 47.0% to 64.3% of the latter group had a controlled cholesterol after medication [64]. A Finnish experience discovered that the rate of hypercholesterolemia treatment coverage and effectiveness has increased steadily [65]. A pooled analysis of national self-reported surveys in Switzerland indicated an increasing trend of treatment coverage and effective treatment in last decades and reaching to 38.8% and 75.1%, respectively [66]. Based on the estimates of Global Burden of Disease, the deaths attributable to hypercholesterolemia has remained stagnant over the past three decades. This condition has had a decreasing trend in higher sociodemographic areas while increasing in countries with lower index [67]. In Iran, this has been estimated to remain in a same range (62.3 deaths per 100,000 population in 2019 with 95% uncertainty range of 47.5 to 79.4). It is worth to note that the reports of Global Burden of Disease lack the estimates of serum cholesterol level and prevalence of

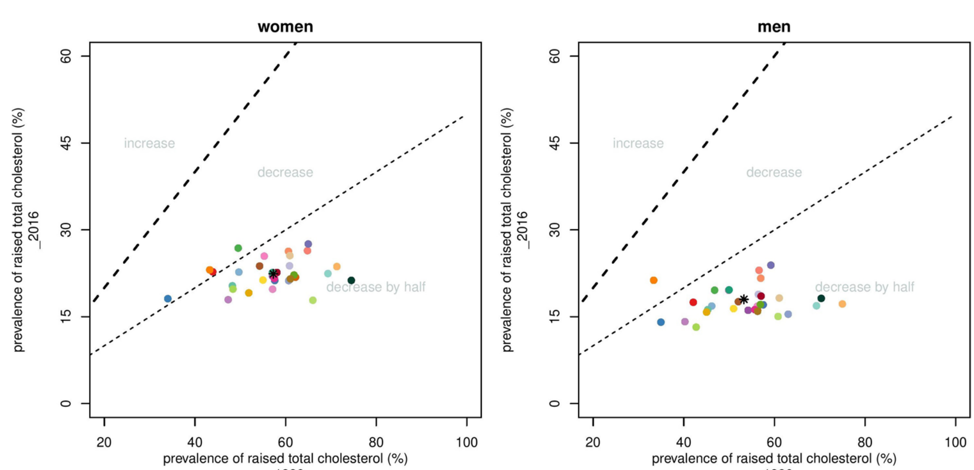


Fig. 5 Comparison of age-standardized prevalence of raised total cholesterol > 200 mg/dL in adults by sex, by province between 1990 and 2016

hypercholesterolemia, a gap that was needed to be filled with proper statistical techniques. Our pooled analysis followed the same trend and pattern seen in other nations that the rate of effective coverage has improved in Iran in last years and current acts, from public health point of view, were effective in lowering the total cholesterol level, while narrowing of the towering of it in lower but borderline ranges can have consequences that needs to be foreseen. It is worth mentioning that COVID-19 pandemic may have changed the pattern of care, access, and even incidence of metabolic conditions [68], a matter that needs to be further evaluated in future works.

Our study has several strengths. It is the first comprehensive systematic review on levels and trends of high TC at subnational scale using advanced statistical methods to overcome the data scarcity in Iran. We investigated all the available data in this regard to report the most comprehensive statistics. We also reported the measures in different subgroups to enlighten the disparities and differences, applicable for further policy making. Yet, our study has certain limitations. We had to overcome data scarcity by statistical methodology, which increased the uncertainty of our estimates. For estimating the prevalence of elevated and raised TC, we used crosswalk on our estimates for mean TC. To make estimates by 5-year age groups among adults older than 65 years, we split age groups based on the data of the last iteration of National NCD Risk Factor Surveillance in 2016 and applied it to previous years. And finally, and most importantly, we could not differentiate Low Density Lipoprotein from High Density Lipoproteins, which imposes bias on our estimates for burden attributable to unfavorable cholesterol.

In conclusion, the trends of TC are improving in Iran across all provinces, both sexes, and all age groups. To continue the current success, policy makers require to maintain the previously implemented effective policies. Moreover, the success should not be taken for granted as there are a considerable number of people just below the cut point of raised cholesterol. Additionally, different provinces and different genders require different approaches that should be addressed in national programs and plans.

Abbreviations TC: Total Cholesterol; GBD: Global Burden of Disease; GPR: Gaussian Process Regression; NCD: Non-Communicable Disease; NHS: National Health Survey; RSME: Root Mean Square Error; SDG: Sustainable Development Goals

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Author contribution FF designed and supervised the study and approved of the final version of the manuscript.

PM did entire data preparation, statistical analysis, prepared results, wrote the manuscript, edited the content of manuscript, and approved of the final version.

EM did the comprehensive systematic review, wrote the manuscript, prepared results of systematic review, edited the content of manuscript, discussed the results, and approved of the final version.

SGS did the comprehensive systematic review, wrote the manuscript, edited the content of manuscript, and discussed the results.

AA did the comprehensive systematic review and did entire data preparation.

SD did data collection through contacting principal investigators of population-based studies.

NP did data collection through contacting principal investigators of population-based studies.

ER did the original data preparation and statistical analysis.

FM did the comprehensive systematic review, prepared results of systematic review, edited the content of manuscript, discussed the results, and approved of the final version.

MS Revised the Manuscript.

YM did data collection through contacting principal investigators of population-based studies.

AK supervised administrative process.

HJ supervised administrative process.

The rest of the co-authors were collaborators in our team.

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Data availability The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

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Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

References

1. Azadnajafabad S, Mohammadi E, Aminorroaya A, Fattahi N, Rezaei S, Haghshenas R, et al. Non-communicable diseases' risk factors in Iran; a review of the present status and action plans. J Diabetes Metabolic Disorders. 2021;1–9.
2. Mohammadi E, Aminorroaya A, Fattahi N, Azadnajafabad S, Rezaei N, Farzi Y, et al. Epidemiologic pattern of cancers in Iran; current knowledge and future perspective. J Diabetes Metabolic Disorders. 2020;1–5.
3. Chestnov O. World Health Organization Global Action Plan for the Prevention and Control of Noncommunicable Diseases. Geneva, Switzerland. 2013.
4. Forouzanfar M, Alexander L, Anderson H, Bachman V, Biryukov S, Brauer M, et al. GBD 2013 Risk Factors Collaborators Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015;386(10010):2287–323.
5. Aminorroaya A, Fattahi N, Azadnajafabad S, Mohammadi E, Jamshidi K, Khalilabad MR, et al. Burden of non-communicable diseases in Iran: past, present, and future. J Diabetes Metabolic Disorders. 2020;1–7.
6. Azadnajafabad S, Karimian M, Roshani S, Rezaei N, Mohammadi E, Moghaddam SS, et al. Population attributable fraction estimates of cardiovascular diseases in different levels of plasma total cholesterol in a large-scale cross-sectional study: a focus on prevention strategies and treatment coverage. J Diabetes Metab Disord. 2020;19(2):1453–63.
7. Farzadfar F, Finucane M, Danaei G, Pelizzari P, Cowan M, Paciorek C, et al. Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group (Cholesterol) National, regional, and global trends in serum total cholesterol since 1980: systematic analysis of health examination surveys and epidemiological studies with 321 country-years and 3.0 million participants. Lancet. 2011;377(9765):578–86.
8. Smith SC, Allen J, Blair SN, Bonow RO, Brass LM, Fonarow GC, et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and Blood Institute. J Am Coll Cardiol. 2006;47(10):2130–9.
9. Detection NCEPEPo, Adults ToHBCi. Third report of the National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III): The Program; 2002.
10. Mohammadi Y, Parsaeian M, Mehdipour P, Khosravi A, Larijani B, Sheidaei A, et al. Measuring Iran's success in achieving Millennium Development Goal 4: a systematic analysis of under-5 mortality at national and subnational levels from 1990 to 2015. Lancet Glob Health. 2017;5(5):e537–44.
11. Foreman KJ, Lozano R, Lopez AD, Murray CJ. Modeling causes of death: an integrated approach using CODEm. Popul Health Metrics. 2012;10(1):1–23.
12. Mehdipour P, Navidi I, Parsaeian M, Mohammadi Y, Moradi LM, Rezaei DE, et al. Application of Gaussian Process Regression (GPR) in estimating under-five mortality levels and trends in Iran 1990–2013, study protocol. 2014.
13. Mohammadi E, Ghasemi E, Azadnajafabad S, Rezaei N, Saeedi-Moghaddam S, EbrahimiMeimand S, et al. A global, regional, and national survey on burden and Quality of Care Index (QCI) of brain and other central nervous system cancers; global burden of disease systematic analysis 1990–2017. PLoS ONE. 2021;16(2): e0247120.
14. Rajaratnam JK, Marcus JR, Flaxman AD, Wang H, Levin-Rector A, Dwyer L, et al. Neonatal, postneonatal, childhood, and under-5 mortality for 187 countries, 1970–2010: a systematic analysis of progress towards Millennium Development Goal 4. The Lancet. 2010;375(9730):1988–2008.
15. Rafiei M, Boshtam M, Sarraf-Zadegan N. Lipid profiles in the Isfahan population: an Isfahan cardiovascular disease risk factor survey, 1994. Eastern Mediterranean health journal = La revue de sante de la Mediterranee orientale = al-Majallah al-sihhiyah li-sharq al-mutawassit. 1999;5(4):766–77.
16. Izadi N, Rahimi MA, Rezvanmadani F, Shetabi HR, Darbandi M. A survey on epidemiology of type II diabetes in patients referring to the diabetes clinic in Kermanshah Province during 2013–14: A short report. J Rafsanjan Univ Med Sci. 2017;16(1):83–90.
17. Amiri M, Emami SR, Nabipour I, Nosrati A, Iranpour D, Soltanian AR, et al. Risk factors of cardiovascular disease in bushehr port on the basis of the who monica project, the persian gulf – heart project. Iranian South Med J. 2004;6(2):151–60.
18. Kharrazi H, Raygani AV, Sabokroh A, Pourmotabbed T. Association between apolipoprotein E polymorphism and coronary artery disease in the Kermanshah population in Iran. Clin Biochem. 2006;39(6):613–6.
19. Mellati A, Mousavinasab S, Sokhanvar S, Kazemi SAN, Esmailli MH, Dinmohamadi H. Correlation of anthropometric indices with common cardiovascular risk factors in an urban adult population of Iran: data from Zanjan Healthy Heart Study. Asia Pac J Clin Nutr. 2009;18(2):217–25.
20. Azizi F, Rahmani M, Ghanbarian A, Emami H, Salehi P, Mirmiran P, et al. Serum lipid levels in an Iranian adults population: Tehran lipid and glucose study. Eur J Epidemiol. 2003;18(4):311–9.
21. Karam GA, Reisi M, Kaseb AA, Khaksari M, Mohammadi A, Mahmoodi M. Effects of opium addiction on some serum factors in addicts with non-insulin-dependent diabetes mellitus. Addict Biol. 2004;9(1):53–8.
22. Chehrei A, Sadrnia S, Keshteli AH, Daneshmand MA, Rezaei J. Correlation of dyslipidemia with waist to height ratio, waist circumference, and body mass index in Iranian adults. Asia Pac J Clin Nutr. 2007;16(2):248–53.
23. Sadr S, Namayandeh S, Moadares M, Rafiei M. Serum uric acid levels and its association with cardiovascular risk factors. Iran J Public Health. 2009;38(1):53–9.

24. Marjani A, Veghari G, Badeleh MT. Serum lipid peroxidation and leptin levels in male and female type 2 diabetic patients in Gorgan (South East of Caspian Sea), Iran. J Chin Clin Med. 2010;5(1).
25. Mahdavi-Mazdeh M, Saeed HashemiNazri S, Hajghasemi E, Nozari B, Zinat Nadia H, Mahdavi A. Screening for decreased renal function in taxi drivers in Tehran, Iran. Renal Failure. 2010;32(1):62–8.
26. Balali-Mood M, Shademanfar S, RastegarMoghadam J, Afshari R, NamaeiGhassemi M, Allah Nemati H, et al. Occupational lead poisoning in workers of traditional tile factories in Mashhad, Northeast of Iran. Int J Occup Environ Med. 2010;1(1):29–38.
27. Veghari G, Joshaghani H, Hoseini S, Sedaghat S, Nik Nezhad F, Angizeh A, et al. The Study of prevalence of Hypercholesterolemia and some relative factors in Golestan province. Payavard Salamat. 2010;3(3):10–24.
28. Marjani A, Moghasemi S. The metabolic syndrome among postmenopausal women in Gorgan. Int J Endocrinol. 2012;2012: 953627.
29. Boshtam M, Ramezani MA, Naderi G, Sarrafzadegan N. Is Friedewald formula a good estimation for low density lipoprotein level in Iranian population? J Res Med Sci. 2012;17(6):519–22.
30. Maharlouei N, Bellissimo N, Ahmadi SM, Lankarani KB. Prevalence of metabolic syndrome in pre- and postmenopausal Iranian women. Climacteric J Int Menopause Soc. 2013;16(5):561–7.
31. Veghari G, Sedaghat M, Joshghani H, Niknezad F, Angizeh A, Tazik E, et al. Plasma total cholesterol level and some related factors in northern Iranian people. J Nat Sci Biol Med. 2013;4(2):359–63.
32. Hajian-Tilaki K, Heidari B, Hajian-Tilaki A, Firouzjahi A, Bagherzadeh M. The discriminatory performance of body mass index, waist circumference, waist-to-hip ratio and waist-to-height ratio for detection of metabolic syndrome and their optimal cutoffs among Iranian adults. J Res Health Sci. 2014;14(4):276–81.
33. Haghighatdoost F, Sarrafzadegan N, Mohammadifard N, Asgary S, Boshtam M, Azadbakht L. Assessing body shape index as a risk predictor for cardiovascular diseases and metabolic syndrome among Iranian adults. Nutrition (Burbank, Los Angeles County, Calif). 2014;30(6):636–44.
34. Janghorbani M, Amini M. Metabolic syndrome in type 2 diabetes mellitus in isfahan, iran: prevalence and risk factors. Metab Syndr Relat Disord. 2007;5(3):243–54.
35. Lankarani KB, Mahmoodi M, Lotfi M, Zamiri N, Heydari ST, Ghaffarpasand F, et al. Common carotid intima-media thickness in patients with non-alcoholic fatty liver disease: a population-based case-control study. Korean J Gastroenterol = Taehan Sohwagi Hakhoe chi. 2013;62(6):344–51.
36. Motamed N, Mardanshahi A, Saravi BM, Siamian H, Maadi M, Zamani F. The 10-year absolute risk of cardiovascular (CV) events in Northern Iran: a population based study. Materia Socio-Medica. 2015;27(3):158–62.
37. Rashidi Pour Fard N, Karimi M, Baghaei MH, Haghighatdoost F, Rouhani MH, Esmaillzadeh A, et al. Dairy consumption, cardiovascular risk factors and inflammation in elderly subjects. ARYA Atherosclerosis. 2015;11(6):323–31.
38. Mazidi M, Heidari-Bakavoli A, Khayyatzadeh SS, Azarpazhooh MR, Nematy M, Safarian M, et al. Serum hs-CRP varies with dietary cholesterol, but not dietary fatty acid intake in individuals free of any history of cardiovascular disease. Eur J Clin Nutr. 2016;70(12):1454–7.
39. Ghasemzadeh Z, Abdi H, Asgari S, Tohidi M, Khalili D, Valizadeh M, et al. Divergent pathway of lipid profile components for cardiovascular disease and mortality events: Results of over a decade follow-up among Iranian population. Nutr Metab. 2016;13(1):43.
40. Meysamie A, Ghodsi S, Ghalehtaki R, Esteghamati A, Asgari F, Gouya MM. Distributions of high-sensitivity C-reactive protein, total cholesterol-HDL ratio and 10-Year cardiovascular risk: national population-based study. Acta Medica Iranica. 2017;218–27.
41. Mohammadi E, Morasa FS, Roshani S, Rezaei N, Azadnajafabad S, Moghaddam SS, et al. Estimating the attributable risk of vascular disorders in different ranges of fasting plasma glucose and assessing the effectiveness of anti-diabetes agents on risk reduction; questioning the current diagnostic criteria. J Diabetes Metab Disord. 2020;19(2):1423–30.
42. Farzadfar F, Danaei G, Namdaritabar H, Rajaratnam JK, Marcus JR, Khosravi A, et al. National and subnational mortality effects of metabolic risk factors and smoking in Iran: a comparative risk assessment. Popul Health Metrics. 2011;9(1):1–11.
43. Vos T, Abajobir AA, Abate KH, Abbafati C, Abbas KM, Abd-Allah F, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. The Lancet. 2017;390(10100):1211–59.
44 Eliasson M, Janlert U, Jansson JH, Stegmayr B. Time trends in population cholesterol levels 1986–2004: influence of lipid-lowering drugs, obesity, smoking and educational level. The northern Sweden MONICA study. J Intern Med. 2006;260(6):551–9.
45. Ford ES, Capewell S. Trends in total and low-density lipoprotein cholesterol among US adults: contributions of changes in dietary fat intake and use of cholesterol-lowering medications. PLoS ONE. 2013;8(5): e65228.
46. Borodulin K, Vartiainen E, Peltonen M, Jousilahti P, Juolevi A, Laatikainen T, et al. Forty-year trends in cardiovascular risk factors in Finland. Eur J Public Health. 2015;25(3):539–46.
47. Aryan Z, Mahmoudi N, Sheidaei A, Rezaei S, Mahmoudi Z, Gohari K, et al. The prevalence, awareness, and treatment of lipid abnormalities in Iranian adults: Surveillance of risk factors of noncommunicable diseases in Iran 2016. J Clin Lipidol. 2018;12(6):1471-81.e4.
48. Ahmadvand A, Farzadfar F, Jamshidi HR, Mohammadi N, Holakouie-Naieni K. Using drug sales data to evaluate the epidemiology of cardiometabolic risk factors and their inequality: an ecological study on atorvastatin and total cholesterol in Iran. Med J Islam Repub Iran. 2015;29:260.
49. Amirsadri M, Hassani A. Cost-effectiveness and cost-utility analysis of OTC use of simvastatin 10 mg for the primary prevention of myocardial infarction in Iranian men. DARU J Pharm Sci. 2015;23(1):56.
50. Jabbari A, Jafari A, Hadian M, Ghasemi M. Model-based cost-effectiveness analysis of atorvastatin drugs for prevention of cardiovascular diseases in Iran. Int J Prevent Med. 2020;11.
51. Tabari-Khomeiran R, Bayazidi Y, Nikfar S, Homaie Rad E, Varmaghani M, Kokabisaghi F. Inequity in Access of Statins in Iran: A Panel Study Using Provincial Data. Caspian J Health Res. 2019;4(2):33–7.
52. Afshin A, Micha R, Khatibzadeh S, Fahimi S, Shi P, Powles J, et al. The impact of dietary habits and metabolic risk factors on cardiovascular and diabetes mortality in countries of the Middle East and North Africa in 2010: a comparative risk assessment analysis. BMJ Open. 2015;5(5): e006385.
53. Collaborators GO. Afshin A, Forouzanfar MH, Reitsma MB, Sur P, Estep K, et al. Health effects of overweight and obesity in.195:13–27.
54. Danaei G, Singh GM, Paciorek CJ, Lin JK, Cowan MJ, Finucane MM, et al. The global cardiovascular risk transition: associations of four metabolic risk factors with national income, urbanization, and Western diet in 1980 and 2008. Circulation. 2013;127(14):1493–502.
55. GHAJARIEH SS, Kamangar F, Poustchi H, Malekzadeh R. Reducing the burden of chronic diseases: a neglected agenda in Iranian health care system, requiring a plan for action. 2010.

56. Aminorroaya A, Yoosefi M, Rezaei N, Shabani M, Mohammadi E, Fattahi N, et al. Global, regional, and national quality of care of ischaemic heart disease from 1990 to 2017: a systematic analysis for the Global Burden of Disease Study 2017. Eur J Prevent Cardiol. 2021.
57. Fattahi N, Azadnajafabad S, Mohammadi E, Aminorroaya A, Rezaei S, Ghasemi E, et al. Geographical, gender and age inequalities in non-communicable diseases both at national and provincial levels in Iran. J Diabetes Metabolic Disorders. 2021;1–7.
58 Aminorroaya A, Ghasemi E, Shabani M, Rezaei N, Mohammadi E, Fattahi N, et al. Global, regional, and national quality of care and burden of ischemic heart disease, 1990 to 2017: results from the GBD study 2017. Eur Heart J. 2020;41(Supplement_2):ehaa946. 3560.
59. Sepanlou SG, Poustchi H, Malekzadeh R, Kamangar F. Effectiveness and feasibility of lifestyle and low-cost pharmacologic interventions in the prevention of chronic diseases: a review. Arch Iran Med. 2011;14(1):46–53.
60. Azadnajafabad S, SaeediMoghaddam S, Mohammadi E, Rezaei N, Rezaei N, Naderimagham S, et al. Importance of population-wide studies in controlling non-communicable diseases: achievements of non-communicable diseases research center, endocrinology and metabolism research institute. Iranian J Diabetes Metab. 2021;20(1):25–33.
61. Wang Z-j, Tian X-z, Li X, Chen Z, Zhao L-c, Zhou B-f, et al. Dietary treatment and success rate of control in hypercholesterolemia patients treated with lipid lowering drugs: a multi-center study of current status on clinical control of hypercholesterolemia in China. Zhonghua Xin Xue Guan Bing Za Zhi. 2005;33(4):372–5.
62. McClaran J, Déry V, Chockalingam A. Lessons from The Healthy Heart Kit. Perspectives. 2002;27.
63. Peykari N, Hashemi H, Dinarvand R, Haji-Aghajani M, Malekzadeh R, Sadrolsadat A, et al. National action plan for non-communicable diseases prevention and control in Iran; a response to emerging epidemic. J Diabetes Metab Disord. 2017;16(1):1–7.
64. Ford ES, Li C, Pearson WS, Zhao G, Mokdad AH. Trends in hypercholesterolemia, treatment and control among United States adults. Int J Cardiol. 2010;140(2):226–35.
65. Kastarinen M, Tuomilehto J, Vartiainen E, Jousilahti P, Sundvall J, Puska P, et al. Trends in lipid levels and hypercholesterolemia in hypertensive and normotensive Finnish adults from 1982 to 1997. J Intern Med. 2000;247(1):53–62.
66. Estoppey D, Paccaud F, Vollenweider P, Marques-Vidal P. Trends in self-reported prevalence and management of hypertension, hypercholesterolemia and diabetes in Swiss adults, 1997–2007. BMC Public Health. 2011;11(1):114.
67. Institute for Health Metrics and Evaluation. Global Burden of Disease 2022 [Available from: https://vizhub.healthdata.org/gbd-compare/.
68. Rezaei N, Montazeri F, Malekpour M-R, Ghanbari A, Azadnajafabad S, Mohammadi E, et al. COVID-19 in patients with diabetes: factors associated with worse outcomes. J Diabetes Metab Disord. 2021;20(2):1605–14.