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The cost-effectiveness analysis of a nationwide vitamin D supplementation program among Iranian adolescents for adulthood cardiovascular diseases prevention

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ABSTRACT

Objective: This study aimed to evaluate a national vitamin D supplementation program's cost-effectiveness among Iranian adolescents to prevent cardiovascular diseases (CVDs) in adulthood.
Study design: A cost-effectiveness analytical study.
Methods: A decision tree model was adopted to evaluate the cost per quality-adjusted life-year (QALY) of monthly intake of nine pearls of 50,000 IU vitamin D for nine months to prevent CVD a one-year horizon compared to no intervention. The analysis was conducted in Iranian adolescents in first or second high school grades of 47 climatically different Iran regions.
Results: Our analytical analysis estimated the 1090$ cost per QALY gained of the monthly intake of 50,000 IU vitamin D for nine months among adolescents over a one-year horizon. Based on the incremental cost-effectiveness ratio (ICER) threshold of 1032–2666, vitamin D supplementation was cost-effective for adolescents to prevent adulthood CVD. It means that vitamin D supplementation costs were substantially less than the costs of CVD treatments compared to the no intervention.
Conclusions: Based on these findings, the national program of vitamin D supplementation in adolescents would be cost effective to prevent CVD development in adulthood. From an economic perspective, vitamin D supplementation, especially in adolescents with vitamin D deficiency, would be administrated.

Introduction

Cardiovascular diseases (CVD) are the number-one health problem worldwide, accounting for more than 17 million deaths up to 2017, and it will grow up to 22 million by 2030.[1] Based on the world health organization (WHO) reports 2017, more patients annually die from CVD events than from other mortality causes,[2] and CVD events are the leading causes of the disability-adjusted life years (DALYs).[3] Apart from the high rate of early death and disabilities after the CVD events, it imposes an increased burden on the economy and health systems. It was estimated that about 14% of all the total medical expenses in 2015 were accounted for CVD events.[1] Thus, there is a consensus for managing CVD to reduce the adverse effects on patients and health care systems around the world.[4] Although there is a great medical evolution in CVD treatment, CVD prevention's importance in reducing disease burden is inevitable, especially in low-income or developing countries.[5] There is strong evidence suggesting a negative association between the serum concentrations of vitamin D and CVD incidence.[6,7] There is a substantial discrepancy in recently conducted studies to support the useful role of vitamin D supplementation in preventing CVD[8–12] due to the heterogeneity in the supplemented-doses or follow-up duration or the assessed-CVD outcomes. Because vitamin D deficiency is usually associated with traditional CVD risk factors,[13,14] prophylactic supplementation with vitamin D seems to be

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a strategy to reduce the risk of different chronic diseases such as CVD. These days, having a physically inactive lifestyle in children and adolescents also increases the risk of vitamin D deficiency.[15] A recent cross-sectional study conducted among 2596 Iranian adolescents revealed that about 60% of the studied population was vitamin D–deficient, associated with higher cardiovascular risk factors and higher prevalence of metabolic syndrome (MetS).[15]

The MetS is a metabolic disorder that can directly raise the risk of CVD development.[16] By considering the high prevalence of both vitamin D deficiency[15] and CVD events in Iran,[17] the Iran Ministry of Health and Medical Education (MOHME) performed a national vitamin D supplementation program in Iranian population to reduce the CVD developments in adulthood through correcting adolescents' serum concentration of vitamin D.[18] Because adopting a national supplementation program can impose a heavy burden on the economy especially in a developing country, performing an economic evaluation such as the cost-effectiveness analysis (CEA) is a rational approach for the decision-makers to set the interventional health priorities and allocating the resource in the health care system.[19,20] To perform a CEA analysis, the costs and the effects of the various interventional approaches would be compared with each other.[21] Based on the ratio of the differences in costs and outcomes, the incremental cost-effectiveness ratio (ICER) is usually used to report the results.[21] In this way, to reporting ICER, quality-adjusted life years (QALYs) would be a more reliable outcome, which includes the quantity and quality of life improvement and make it easier to compare the various interventions.[22] Based on our knowledge, only one study was conducted to assess a vitamin D supplementation program's cost-effectiveness on CVD prevention through the Markov modeling. It reported that vitamin D supplementation is a cost-effective strategy to reduce the risk of non-fatal and fatal cardiovascular outcomes among Australian adult migrants. Still, they used the data about the relationship of serum vitamin D and hypertension (HTN) incidents among young women to assess the effects of supplementation.[23] Due to the scantiness of economic evaluations supporting the cost-effectiveness strategies for CVD prevention, this paper will focus on the cost-effectiveness of a national vitamin D supplementation program among Iranian adolescents to reduce CVD prevalence in adulthood.

Methods

National program's characteristics

Target population and setting

The Ministry of Health in Iran has adopted a national policy and program for vitamin D supplementation (50,000 IU/month) for all age groups all over the country. Because the adolescent group was the only group, which provided us with the complete data from the Nutrition Improvement Office of the Ministry of Health, we performed this cost-effectiveness study among the Iranian adolescent's population. It is also important to note that the sample of adolescents were not selected randomly, while we selected the provinces or cities randomly.

The current study was conducted on the data of first or second grades of high school students of 47 climatically different Iran regions who participated in the national vitamin D supplementation program in 2016. The Office of Community Nutrition Improvement of Iran Ministry of Health provided crude data about the program population covered by this intervention program in 2018. The data of 1,519,762 students (733,657 females and 786,105 males) were obtained. Because girls are more Vitamin D–deficient than boys, 87.5% of girls and 69.5% of boys were covered by this national vitamin D supplementation program. A total of 1,185,211 students (78.5% of the total population) were supplemented with vitamin D.

Supplementation strategy

According to the national vitamin D supplementation program guidelines, each student was expected to monthly intake one pearl of 50,000 IU vitamin D for nine months during autumn, winter, and spring. In addition, to reduce the risk of vitamin D toxicity, the supplementation did not perform in summer.

Study perspective

Because the MOHME is responsible for paying for the medical approach such as the national vitamin D supplementation program based on their well-documented evidence, we performed our cost-effectiveness analysis based on the MOHME perspective.

Comparators and time horizon

In this cost-effectiveness analytical study, we considered a medical alternative of the vitamin D supplementation strategy versus no intervention to determine the cost-effectiveness of a nationwide vitamin D supplementation among Iranian adolescents to prevent cardiovascular diseases in the older ages. Our study considered a one-year horizon to capture the national vitamin D supplementation program's cost and quality of life.

Choice of health outcomes and effectiveness measurement

In this study, the values of QALYs for healthy individuals and CVD patients were considered as the variables for assessing the vitamin D supplementation program's effectiveness on CVD prevention. To calculate the QALYs values in patients with CVDs and healthy ones, we calculated the average of the utility value estimates in cardiovascular disease as reported in previous studies.[4,24]

The serum concentrations of vitamin D less than 30 ng/mL and more than 30 ng/mL were considered vitamin D deficiency and vitamin D sufficiency, respectively.[25]

The required data were retrieved from a recent CASPIAN-V cohort study as our reference study,[26] which was conducted among 2596 Iranian adolescents and aimed to assess serum vitamin D's relationship with the prevalence of MetS.[15] These data were consistent with the designed model of vitamin D supplementation to evaluate the cost-effectiveness.

The obtained data from the Caspian Study Data Center showed that of 1846 students with vitamin D deficiency, 79 students (4.28%) had MetS, while only 19 people (2.53%) out of 750 vitamin D sufficient students developed MetS (Table 1). As shown in Table 1, it seems that vitamin D–deficient adolescents are 50 percent less likely to develop MetS than those with normal vitamin D serum levels.

Based on the previous studies, 76% of Iranian adolescents were vitamin D–deficient before the vitamin D supplementation program.[30] A monthly intake of 50,000 IU vitamin D for nine months can reduce the prevalence of vitamin D deficiency among adolescents up to 17.2%[34] (Table 2).

Table 1
The association between the serum levels of vitamin D and lipid markers in subjects with or without MetS obtained from CASPIAN-V cohort database.[a]

Vitamin D categories	Total	Without MetS	With MetS
Vitamin D deficiency <30 ng/mL	1846	1767	79
Vitamin D sufficiency >30 ng/mL	750	731	19

MetS, metabolic Syndrome.
[a] Data were shown as number.

Table 2
Main input parameters of CEA model.

Statistic variable	Base case	SD/(CI)	Distribution	Source
Costs (S)				
Total costs of vitamin D therapy	0.604	±0.12	Gamma	[a]
The 2018-adjusted[c] costs of CVD management for each patients[b]	455	±45	Gamma	36
Direct medical costs of the vitamin D supplementation national program for each student	0.354	±0.095	Gamma	[a]
Indirect medical costs of the vitamin D supplementation national program for each student	0.25	±0.025	Gamma	[a]
Utilities				
Non-CVD individual	0.76	–	Beta	20,45
Individual with CVD	0.64	±0.19	Beta	4,24
Probability				
The possibility of vitamin D deficiency before starting vitamin D supplementation	76%	–	–	31
The possibility of vitamin D sufficiency before starting vitamin D supplementation	24%	–	–	31
The possibility of vitamin D deficiency after starting vitamin D supplementation	17.2%			35
The possibility of vitamin D sufficiency after starting vitamin D supplementation	87.2%			35
The prevalence of MetS incidence in people with vitamin D deficiency	4.3%			15
The prevalence of MetS incidence in people with adequate vitamin D level	2.4%			15

MetS, metabolic Syndrome; **CVD,** cardiovascular diseases**.**
[a] The Nutrition Improvement Office of the Ministry of Health.
[b] The expenditure data in 2018 were calculated at a dollar exchange rate declared by Iran's Central Bank.
[c] According to Iran's Central Bank reports, the inflation rate in 2018 was 9.6.

Statistical analysis and choice of model

In the current study, a decision tree model was considered to evaluate vitamin D supplementation's cost-effectiveness (Fig. 1). Over the other kinds of analytical models, the decision tree model is more understandable and easier to follow model with a logical approach, which provides different branches for different serum levels of vitamin D and presents each subject's information.[28] We constructed the decision tree model in Microsoft Excel and programmed it through TreeAge Pro Inc. DATA software 4.0 (Version 2011).

The ICER was used to report the final results of cost-effectiveness analysis, which can be measured as the differences between the total costs of vitamin D supplementation and no intervention divided by the difference between the related values of QALYs for them, as the following equation:[21]

$$\text{The incremental costeffectiveness ratio (ICER) is calculated as follow} = \frac{\text{Costs of intervention} - \text{costs of no intervention}}{\text{QALYs of intervention} - \text{QALYs of no intervention}}$$

The ICER shows the costs of supplementation per each QALY gained compared to the no intervention. The ICER value was finally compared with the threshold of cost-effectiveness, which is the maximum level of the willingness-to-pay (WTP) per QALY gained. According to the recent study conducted in Iran,[29] we considered the range of 1032–2666 as the threshold of ICER.

Assumption

By considering the high prevalence of vitamin D deficiency in Iranian students,[30] MOHME conducted a national program of vitamin D supplementation (50,000 IU/monthly for nine months) among Iranian adolescents. Based on the recent studies, monthly supplementation with one pearl of vitamin D (50,000 IU) can increase vitamin D levels in serum effectively[31,32] and can be effective in cardiovascular disease prevention.[8,9] By considering the evidence suggesting the risk of some chronic illnesses developments such as CVD in adulthood is associated with the vitamin D–deficient status in adolescents,[33] the present analytical study was conducted in a time frame in the age group of Iranian adolescents and young people who have been covered by the vitamin D supplementary national program. It was assumed that the vitamin D supplementation program among adolescents is a cost-effective strategy to reduce the CVD risk in adulthood.

Sensitivity analysis

In this study, according to the changes in the price of the pearls of vitamin D, the cost of CVD treatment, and the estimated values of QALYs in the previous articles, we performed a probabilistic sensitivity analysis (PSA) through the Monte-Carlo simulation to assess the effects of these parameters' variations on the cost-effectiveness of the supplementation.

Estimated costs

The total project associated costs included both direct and indirect medical costs. The direct costs included the acquisition of vitamin D pearls, while the indirect medical costs included vitamin D supplementation administration, such as training the executors and controlling and supervising the program process. To account for this, we collected the required data from the Nutrition Improvement Office of Iran's Ministry of Health and modified them to 2018. We ultimately converted the total project costs to US dollars (USD). Based on the Central Bank of the Islamic Republic of Iran reports, the inflation rates were equal to 9.6 in 2018.[27]

Based on the findings of a study in 2015, the total medical costs associated with CVD were about 13,074,700 Iranian Rials for each patient.[35] Based on Iran's inflation rate in 2018, CVD costs would be about 19,111,120 Iranian Rials or 455 USD.

According to the MOHME reports in 2018, the direct medical costs to purchase nine vitamin D pearls (50,000 IU) ranged from 9908 to 19,816 Iranian Rials (equivalent to 0.236–0.472 USD). The indirect medical cost to perform or supervise the program per one year was about 11,049 Iranian Rials (0.25 USD). Thus, we estimated that the total costs of the national vitamin D supplementation program for each student about 20,957 to 30,865 Iranian Rials (0.499–0.72 USD) (Table 2).

Results

Cost-effectiveness analysis

To determine the nationwide vitamin D supplementation program's cost-effectiveness, we compared the two strategies of vitamin D supplementation in a group with no supplementation in the other group through a decision tree model (Fig. 1). Based on the related data in Table 2, vitamin D supplementation could decrease the vitamin D deficiency from 76% to 17.2%. Moreover, the incidence of MetS reduced from 4.3% to 2.4% after a one-year

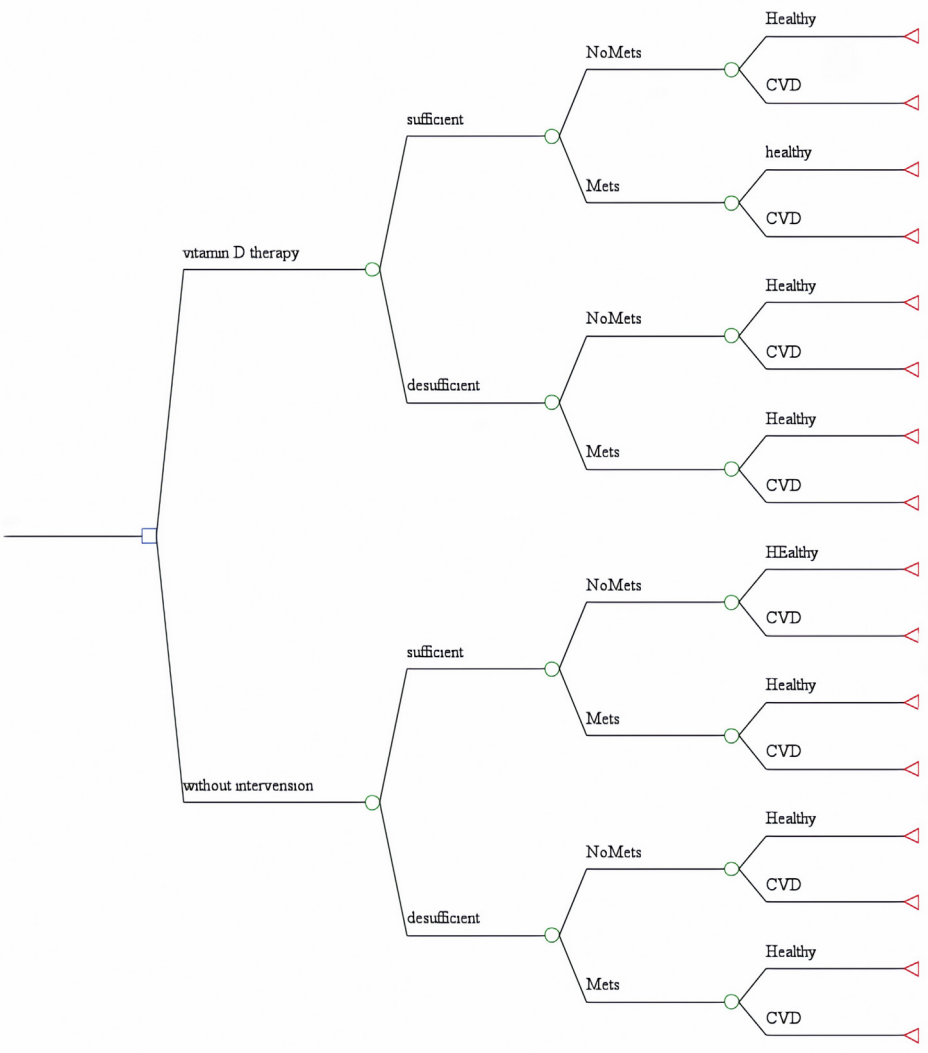

Fig. 1. The decision tree model diagram (vitamin D intervention vs no intervention).

supplementation with vitamin D. As shown in Table 3, vitamin D supplementation has the estimated ICER of about 1090 USD per extra QALYs based on the reduction in CVD prevention. The cost per QALYs of 1090 shows that the strategy of vitamin D supplementation has fewer medical costs and more preventive effects. It seems that vitamin D supplementation in adolescents is a cost-effective and dominant strategy through the cost-saving and QALYs increment.

Sensitivity analysis

As shown in Table 2, performing the sensitivity analysis for model variables by the Monte-Carlo method showed that vitamin D therapy was the predominant strategy with an 89% probability (Figs. 2 and 3).

Discussion

Our analytical study found that a monthly intake of 50,000 IU vitamin D supplementation for nine months in adolescents would be a substantial cost-effective strategy for MOHME to prevent CVD. Our findings are consistent with a previous cost-effectiveness study of vitamin D supplementation among migrants in Australia.[23]

Based on our findings, a reduction from 4.3% to 2.4% in the prevalence of MetS was shown by correcting the serum levels of vitamin D. It seems that vitamin D–deficient adolescents are 50 percent less likely to develop MetS than those with normal vitamin D serum levels. Because of the direct relationship between MetS and CVD development,[16] it could be concluded that improving serum levels of vitamin D may also reduce the risk of cardiovascular

Table 3
Results of the base case cost-effectiveness analysis.

Strategy	Cost ($)	Incr Cost ($)[a]	Eff[b]	Incr Eff[c]	ICER($)
No intervention	43.51256	0.24613	0.74852	0.00023	1090.06519
Vitamin D supplementation	43.26643	0	0.74875	0	

[a] Incremental costs.
[b] Effectiveness.
[c] Incremental effectiveness.

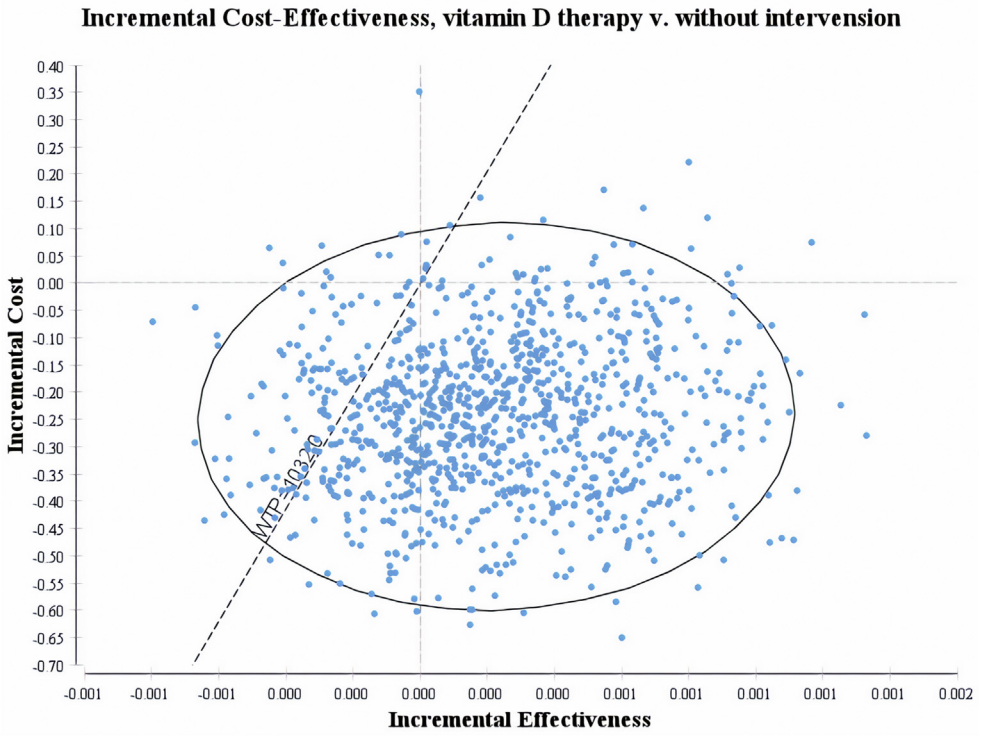

Fig. 2. The incremental cost-effectiveness scatter plot (all samples are in the acceptable range).

disease. Apart from the effective role of vitamin D supplementation, the national program of monthly intake of 50,000 IU vitamin D for nine months costs about 0.49 USD for each student. The total estimated medical costs associated with CVD were about 455 USD (2018-modified) for each patient, according to the strong evidence.[35] The estimated ICER was calculated about 1090 USD per extra QALYs and revealed that this interventional strategy has fewer medical costs and more CVD preventive effects than no intervention. It seems that vitamin D supplementation among adolescents is a cost-saving and dominant strategy to reduce the prevalence of MetS compared to no intervention. Therefore, our cost-effectiveness analysis confirms that vitamin D supplementation in Iranian adolescents who are significantly vitamin D–deficient is likely conservative, and it may reduce the prevalence

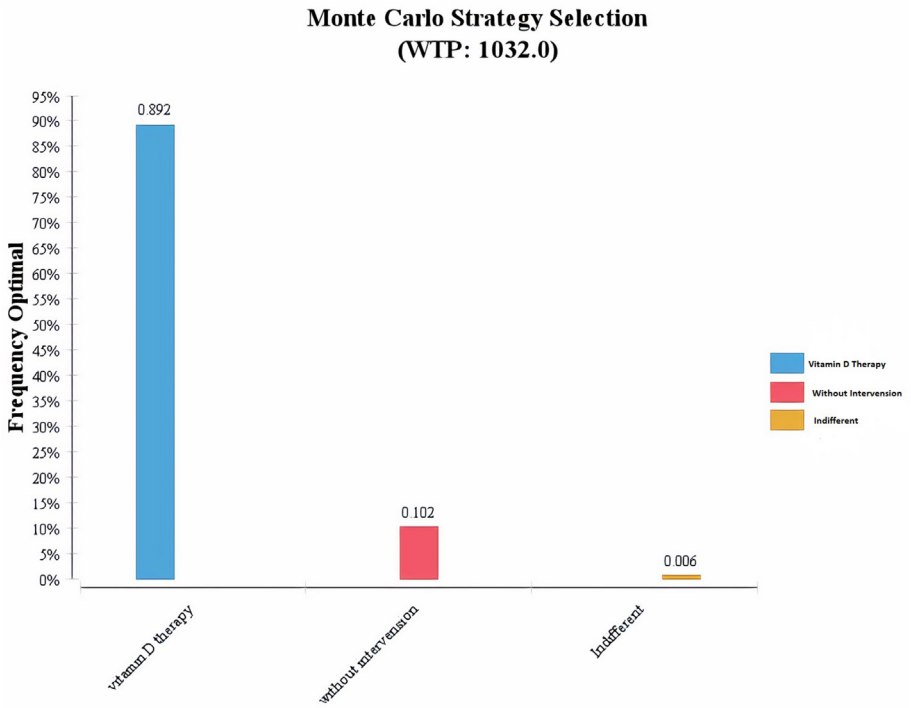

Fig. 3. The Monte Carlo strategy selection.

of MetS to prevent CVD events in adulthood. The sensitivity analysis did not indicate any effect of medical price changes on the cost-effectiveness of this program.

Based on the findings of a systematic review and meta-analysis conducted among healthy Iranian children in 2018, the prevalence of vitamin D deficiency in Iranian boys and girls was estimated at 35% and 61%, respectively. In addition, this study revealed that 31% of Iranian children and adolescents were vitamin D insufficient.[36] Insufficient and deficient vitamin D levels were associated with a higher prevalence of MetS from 2.4% to 4.3% than the normal population. This result seems consistent with the recent studies. In 2017, a cross-sectional study evaluated the association between vitamin D deficiency and MetS in 1205 Qataris reported serum levels of vitamin D in patients with Mets were 8% lower than the healthy ones ($P < 0.05$).[37] Recently, another cross-sectional study among 216 Iranian adolescent girls reported that 96% 0f the participants were vitamin D–deficient, and approximately 11% had diagnosed-MetS.[38] Thus, it could be concluded that correcting the serum levels of vitamin D in adolescents might be considered a beneficial approach to reduce CVD prevalence in older ages.

The recent studies could also explain the relation between vitamin D deficiency with CVD prevalence. A prospective case–control study among 100 subjects with chronic stable angina and 100 healthy individuals as the matched control group indicated that the vitamin D deficiency was significantly higher in the case group (75% subjects were vitamin D–deficient [<20 ng/mL]) than the control group (10% had vitamin D deficiency).[39] Vitamin D supplementation would be highly beneficial to prevent CVD. However, several review studies have shown controversial effects of vitamin D supplementation on cardiovascular disease. The effect of vitamin D supplementation on cardiovascular risk factors was assessed in a systematic review and meta-analysis conducted on 81 related articles. The results showed that vitamin D supplementation could significantly reduce systolic and diastolic blood pressure, total cholesterol, triglycerides and substantially increase the HDL-C levels. The results remained significant in sensitivity analysis, and it seems that vitamin D supplementation can be an effective approach to improving the risk of cardiovascular disease.[40] However, a meta-analysis with different results has also been published. In 2018, a meta-analysis examined the effect of vitamin D supplementation on cardiovascular disease risk among 83,291 individuals obtained from 21 clinical trials. The results showed that vitamin D supplementation was not associated with reducing cardiovascular outcomes than the placebo.

The relative risk of myocardial infarction, stroke, and vascular death has not changed with vitamin D supplementation.[41] Besides the small number of the included trials, CVD events were not the primary outcomes of the included trials. In 2015, a systematic review and meta-analysis was conducted to investigate the effect of vitamin D supplementation on blood pressure control on data from 46 trials (4541 patients). No effect was reported even though the subgroup meta-analysis.[42] The small number of eligible trials included in this systematic review were mainly performed in one center with a low to a modest size, and no one had the high quality. Another meta-analysis of the 51 clinical trials with a low degree of heterogeneities showed that vitamin D supplementation had no significant effects on the relative risk of myocardial infarction and stroke. There were also no significant changes in serum lipids, serum glucose, blood pressure, and the risk of death from cardiovascular disease.[43] The results seem biased since the included trials were not designed to evaluate cardiovascular outcomes, 18% of the included studies were unblinded. Based on our literature review, only one meta-analysis and systematic review was performed to examine the effect of vitamin D supplementation on cardiovascular disease among children. Among 1088 children aged 4–19 years, vitamin D supplementation was associated with a significant increase in serum vitamin D levels and increased only in low-density lipoprotein cholesterol (LDL-C) levels. However, a meta-regression analysis showed a significant reduction in the homeostatic model assessment for insulin resistance (HOMA-IR) levels among obese/overweight children and adolescents.[44]

Despite the cost-effectiveness of the vitamin D supplementation program in CVD prevention, performing these kinds of national supplementation programs imposes a heavy burden on health care systems, thus evaluating their cost-effectiveness is reasonable, especially for developing countries. A recent study conducted in Iran suggested that CVD management's total costs are not suitable enough; however, the health care and insurance systems provide supports.[35] In Iran, about 462 USD were estimated per patient to manage the CVD in 2015 (about 455 USD in 2018), while the total cost of supplementation with vitamin D is about 4.85 USD for each high school adolescent in 2018. Thus, it seems that prophylactic correlation of serum concentrations of vitamin D among Iranian adolescents at an increased risk of vitamin D deficiency could be a cost-effective approach to reducing CVD prevalence in adulthood. Regarding the generalizability of our findings, it is necessary to pay attention to these two points. First, the results of this study can be generalized to countries that have similar health structures to Iran and performing the national health interventions can be done at low costs. Second, performing a national vitamin D supplementation program could be a cost-effective strategy in CVD prevention in countries with high vitamin D deficiency levels. In people with high levels of sunlight exposure or diets rich in vitamin D, the prevalence of vitamin D deficiency is likely to be low; thus performing the national supplementary program would not be cost-effective.

Until now, just one study was designed to assess the cost-effectiveness of vitamin D supplementation to prevent CVD risk factors[23] and reported that vitamin D supplementation in high-risk populations was considered worthy. The data about serum levels of vitamin D were obtained from another study conducted among women with a low sample size to assess their effectiveness. In addition, they considered the blood pressure as the variable to show the effects of the supplementation. However, the previous one did not reveal any significant relationship between vitamin D levels and blood pressure.[42] To the best of our knowledge, the current is the first analytical research developed to evaluate the cost-effectiveness of a national vitamin D supplementation among adolescents in preventing CVD. The same population data was used to show more accurate effectiveness results. Thus, our constructed model was much more accurate than the mentioned study. Besides our strengths, the limitation should be stated. As our limitation of the current study, we examined only the studying adolescents, and the data on dropouts were not available. However, dropouts had a very small population. In addition, we evaluated the cost-effectiveness of vitamin D supplementation in CVD prevention among the whole population, which includes people with deficient, inadequate, and normal levels of vitamin D. The subgroup analysis was not perfumed because of the lack of related data.

Conclusion

The current cost-effectiveness study suggested that correcting the serum levels of vitamin D through a national vitamin D supplementation program offers substantial cost-saving to MOHME over a one-year time horizon to reduce the prevalence of MetS and help to CVD prevention. With this in mind, the healthcare system costs would also be decreased based on the findings. Apart from the possible CVD protective effects of vitamin D supplementation, a considerable quality-adjusted life-year increment is expected.

Further clinical and observational studies are required to confirm our findings.

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Competing interests

All authors declare that they have no competing interests.

Authors' contributions

NZ, RH, MRH, and SMH contributed to conceptual design of the study. NZ, ZA, and MZ contributed to the data collection. NZ and MRH contributed to the data analyses and interpretation. NZ drafted the manuscript. AD reviewed the core manuscript. RH and MRH supervised performing the study and provided intellectual comments. All authors reviewed and approved the final version of manuscript.

Consent for publication

Not applicable.

Availability of data and materials

The data used during the current study are available from the corresponding author on reasonable request. However, all used data were from published literature.

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