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Health and economic impact of the use of vitamin D/calcium for fracture prevention: literature review

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Summary

Objetives: Health policies regarding fracture prevention programs must consider the health and economic impact of strategies such as the intake of vitamin D/calcium-fortified foods or vitamin D/calcium supplements. We review the available evidence on these strategies in terms of health and cost-effectiveness benefits.

Material and methods: We searched PubMed/MedLine's data bases to identify published studies from the last 10 years (up to December, 2020) assessing the impact of vitamin D/calcium-fortified foods or vitamin D/calcium supplements intake for fracture prevention connected to health and cost-effectiveness benefits.

Results: 11 articles were included in total. On one side, the identified studies suggest substantial benefit regarding fracture prevention, mortality, and life years and quality-adjusted life years gained. On the other side, economical assessment reveal that the use of vitamin D/calcium-fortified foods or vitamin D/calcium supplements are cost-beneficial, at least for the population over aged 70 or with high fracture risk. In addition, these strategies seem to save direct costs, especially for elderly women with high fracture risk.

Conclusions: The use of vitamin D/calcium-fortified foods or vitamin D/calcium supplements reduces the amount of fragility-induced fractures, and so, it is a potentially favourable strategy, economically speaking.

Key words: vitamin D, costs and cost analysis, public health, dietary supplement, fortified foods.

Introduction

Osteoporotic fractures, especially those of the hip, are one of the main causes of disability in the elderly population, triggering a considerable decrease of life quality and lifespan. Besides, more than 30% of people die during the first year after suffering one of these fractures[1]. In 2010, the European Union recorded nearly 3.5 million fragility-induced fractures that led to 43,000 deaths. From an economical point of view, these fractures meant an expenditure of 37 billion euros, a sum that is expected to rise by 52% in 2025[2].

Vitamin D and calcium are essential compounds for bone metabolism and prevention of osteoporotic fractures. Two recent meta-analyses have reported that low levels of 25(OH)D are related to the increase of fragility-induced fractures due to bone mass loss and bone structure deterioration[3,4].

In Europe, the prevalence of vitamin D deficiency (defined as 25(OH)D <20ng/ml) is estimated to be 40%[5]. One of the natural sources of vitamin D is the exposure to the sun. However, due to factors such as latitude, physical inactivity or the use of sun creams, the synthesis of vitamin D obtained in this way tends to be insufficient. In fact, and contrary to what one might surmise, this deficiency is lower in the north of Europe than in the south (<20% vs. 30-60%, respectively)[6] despite receiving less sunlight. One of the reasons for this difference is the increased consumption of vitamin D-fortified foods or vitamin D/calcium supplements in Nordic countries[6].

With the aim of reversing this situation, it is paramount to ensure an adequate intake of vitamin D and calcium. The Spanish Society for Bone and Mineral Metabolism Research (SEIOMM), the Spanish Society of Rheumatology (SER) and the Spanish Society of Endocrinology and Nutrition (SEEN) consider key to ensure levels of 25(OH)D to be at least 30ng/ml[7-9]. To maintain an adequate level of 25(OH)D, an intake of 400-1,000 IU/day and 500-1,200 mg/day of calcium are required, preferably from foods. These amounts may vary according to age, patient type and guidelines consulted[7-9]. In the case of patients with osteoporosis and vitamin D deficit, SER recommends a daily intake of 800-2,000 IU of vitamin D supplements, depending on their baselines[9]. Unfortunately, calcium ingestion, and especially that of vitamin D, is not enough, as 38% and 93% of people do not consume them, respectively[10].

The aim of the vitamin D/calcium supplements is to decrease the fragility-induced fracture risk. Nevertheless, there is a debate about the benefits of supplementation on the general population. While some studies suggest that an ideal vitamin D/calcium intake reduces the fracture risk[11,12], other studies indicate that the decrease of this risk

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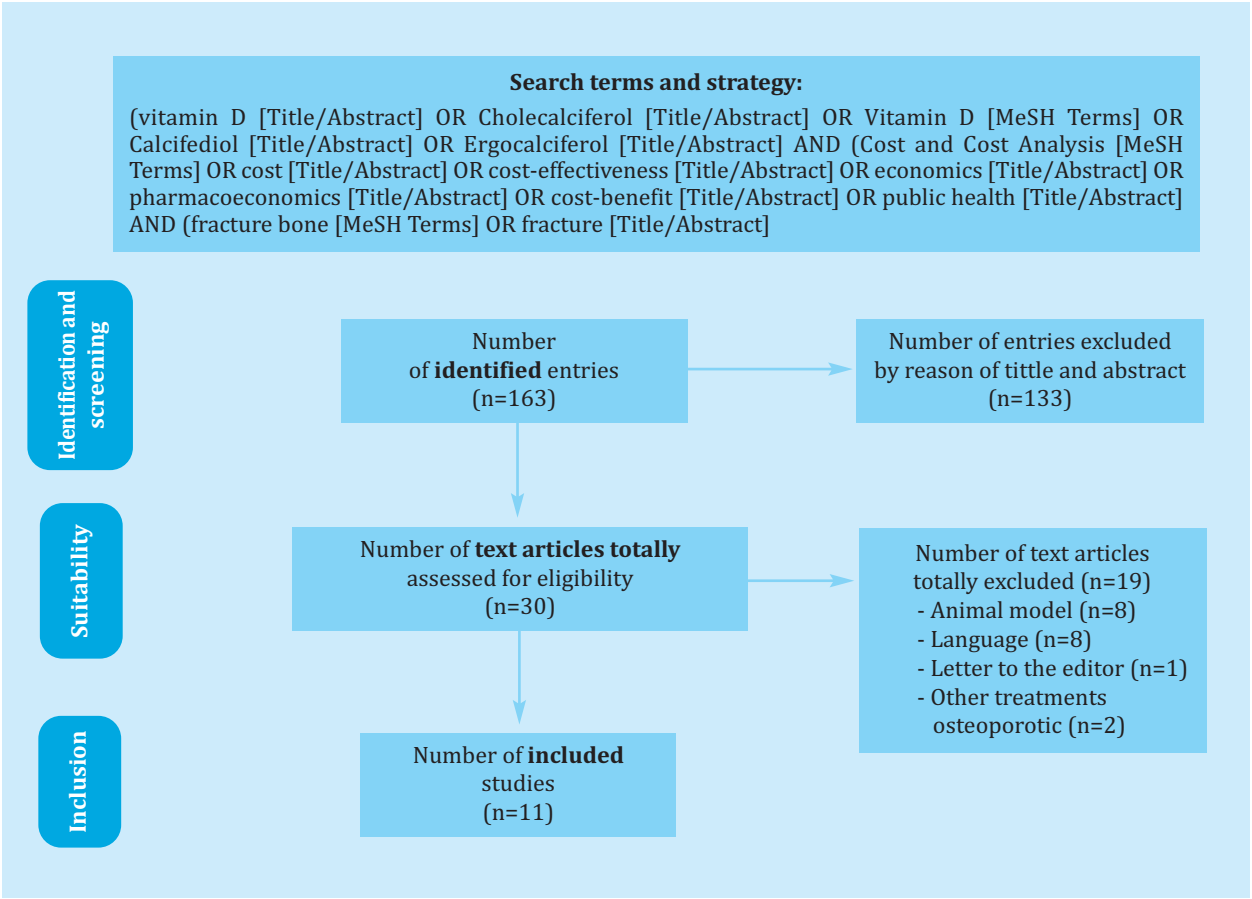
Figure 1. Search strategy and PRISMA diagram



is not of statistical significance[13,14]. Despite this, it is important to state that a considerable proportion of people with optimal vitamin D values are included in most of the studies aimed to analyse the effects of supplementation. That is it cannot be assumed that supplements lack of effect on people with hypovitaminosis. In fact, the lower the concentration of 25(OH)D, the higher the response[15]. Likewise, combined analyses imply that the decrease of fractures thanks to vitamin D supplements would only be possible in people with vitamin D deficit[13].

Vitamin D supplements are not expensive, however, given the high number of people who need them, the monitoring of these people's 25(OH)D serum levels could pose a considerable cost. In order to assist those responsible for the shaping of health policies on preventive nutrition programs, it is important to gauge the health and economic impact that consuming vitamin D-fortified foods or vitamin D/calcium supplement has.

This review aims to identify and outline the available evidence on vitamin D/Ca supplements in order to prevent fragility-induced fractures in terms of health and cost-effectiveness benefits.

Materials and methods

We carried out a review of the PubMed international database in order to identify those studies regarding the economical or health impact of vitamin D/calcium- fortified foods or vitamin D/calcium supplements intake. In order to do that, we have used a combination of MeSH terms and less specific terms related to vitamin D, costs and fragility-induced fractures.

We selected all the articles published in English or Spanish over the past 10 years (up to December, 2020). We excluded those articles assessing vitamin D/calcium supplements in combination with other drugs, as well as those about the effects of vitamin D/calcium supplements, clinical trials, letters to the editor and speeches at conferences.

Results

Characteristics of the studies

163 studies were found in total, 11 of which were finally included (Figure 1)[16-26].Their characteristics are shown in table 1.

The studies assess the use of vitamin D supplements [n=1], vitamin D/calcium supplements [n=5] and vitamin D/calcium-fortified foods [n=5] for fracture prevention from two angles:

1) Health benefits [n=10] (deaths prevented, fractures prevented, life years gained, quality adjusted life years gained -QALYs- and net cost).
2) Economical assessment [n=11] (€//QALY gained, €/life years gained -LYG- and cost-effectiveness incremental ratio -ICER-).

The studies were carried out in France (n=3), The Netherlands (n=3), Germany (n=1), United Kingdom (n=1), Norway (n=1), USA (n=1) and USA/Europe (n=1). We did not find any studies conducted in Spain.

All studies followed a very heterogeneous methodology: economic model, population characteristics, supplementation type, doses, strategy effectiveness and cost-effectiveness threshold (Table 1).

Table 1. Characteristics of the selected articles

Author, year	Country	Method	Age	Sex	Pathology	Study	Intervention	Dosis	HFRr
Childs, 2016[16]	USA	Hindcasting and economic	All	W/M	PF	E	VitD + Ca supplements	VitD: 1.600 IU/day Ca: 1.200 mg/day	5%*
Hiligsmann, 2015[17]	The Nether-lands	Markov microsimulation	≥60	W/M	O	PH/E	VitD + Ca supplements	VitD: 800 IU/day Ca: 1.000 mg/day	18%
Poole, 2014[23]	UK	Economic	≥65	W/M	G	PH/E	VitD supplements	VitD: 800 IU/day	30%
Weaver, 2019[25]	EU USA	Analysis cost benefit	≥50	W/M	O	PH/E	VitD + Ca supplements	VitD: 600 IU/day Ca: 1.000 mg/day	14%
Zarca, 2014[26]	France	Markov microsimulation	≥65	M	G	PH/E	VitD + Ca supplements	VitD: 100.000 IU/ 15-90 days	10%
Hagen, 2016[19]	Norway	Markov state-transitoin	65	M	G	PH/E	VitD + Ca supplements	VitD: 200 IU/day Ca: 1.000 mg/day	16%
Ethgen, 2015[17]	The Nether-lands	Population-based (Markov microsimulation)	≥50	W/M	G/O/RF	PH/E	VitD + Ca fortification	VitD: 800 IU/day Ca: 1.000 mg/day	18%
Ethgen, 2016[18]	The Nether-lands	Markov microsimulation	≥65	M	G/O/RF	E	VitD + Ca fortification	VitD: 400 IU/day Ca: 800 mg/day	18
Sandmann, 2015[24]	Germany	Spreadsheet	≥65	M	G	PH/E	VitD + Ca fortification	VitD: 800 IU/day Ca: 200 mg/day	19%
Hiligsmann, 2017/2018[21,22]	France	Markov microsimulation	≥60	W/M	G	PH/E	VitD + Ca fortification	VitD: 800 IU/day Ca: 1.000 mg/day	16%

HFRr: hip fracture risk reduction; W: woman; M: man; PF: previous fracture; O: osteoporosis; G: general population; RF: high risk of fracture; PH: public health; E: economical assessment; VitD: vitamin D; Ca: calcium; IU: international units *: unwelded fracture.

Health benefits

Different authors have estimated the number of fractures prevented annually attributed to vitamin D/calcium food fortification or vitamin D/calcium supplements: 323,566 (USA), 544,687 (EU), 64,932 (France), 45,800 (United Kingdom), 36,705 (Germany), 30,376 (The Netherlands), 16,130 (Norway) (Table 2). Considering the mortality linked to hip fracture (adjusted by age and sex) Poole et al. esteemed that vitamin D supplements should prevent 1,700 deaths per year in Great Britain[23]. Simultaneously, Ethgen et al. and Hiligsmann et al. suggest, based on the excess of mortality, that 6,605 years (The Netherlands) and 29,169 years (France) could have been gained1[7,21].

One of the most used indicators for public health is the QALYs, which take into account the quantity and quality of life gained. A QALY is a year lived in perfect health. Three of the studies predict a gain of 0.008 to 0.022 QALYs per patient thanks to vitamin D/calcium-fortified foods or vitamin D/calcium supplements[19,20,26]. This fluctuation seems to depend on factors such as age and sex. Ethgen et al. stated that the older the subject, the superior the QALYs gained, regardless of the group of women observed (osteoporosis-free, low bone density or high risk of fracture)[17]. Similar results were reported by Hiligsmann et al., who also noticed that the QALYs gained due to the intervention were higher in women than in men (23,067 vs. 9,502, respectively)[20].

Hagen et al. considered three scenarios for cardiovascular risk due to vitamin D/calcium supplements:

1) Risk-free
2) Medium risk
3) High risk.

The results showed that, while there was a gain of 0.022 QALYs per patient in the first scenario, in the second and third scenarios there would be a net health loss (-0.052 y -0.078, respectively)[19].

Economic impact

From an economic perspective, this supplementation/fortification addressed to the general population seems to be cost-effective from the 70[17,21]-80[18] year age range. In the case of people with osteoporosis, this intervention could be cost-effective from 60[20]-70[18] years of age, and in people with a high risk of fracture, from 50-60 years[17]. Regarding sex, the assessed strategies were even more cost-effective in women, except for the case of those men with high risk of fracture (Table 3).

Zarca et al. analyzed the ICER of four different strategies:

1) Do not treat (comparative value)
2) General treatment with no monitored effectiveness
3) Treating and monitoring
4) Screening and treating the population with vitamin D defiency.

As a result, "treating and monitoring" and "screening and treating" turned out to be cost-effective strategies (5,219 and 9,104 €/QALYs, respectively) and of dominance over "treating but not monitoring". In addition, the acceptability curves showed the screening to be the highest chances to be cost-effective (around 6,000 €/QALYs)[26]. Acceptability curves present the probability that a stra-

Table 2. Main public health results

Autor	Country	Intervention-population	Prevented fractures/year	Prevented fractures/year/100,000	Prevented deaths/year	LYG	Increased gain in QALYs
Childs[16]	USA	S-PF	NE	NE	NE	NE	NE
Hiligsmann[20]	The Netherlands	S-O	NE	NE	NE	NE	0.008-0.021
Poole[23]	UK	S-G	45,800 (hip)	71.2*	1,700	NE	NE
Weaver[25]	EU USA	S-O	544,687 (EU) (hip) 323,566 (USA) (hip)	122.1* (EU) 98.6* (USA)	NE	NE	NE
Zarca[26]	France	S-G	NE	NE	NE	NE	0.015-0.020
Hagen[19]	Norway	S-G	16,130* (all)	306.8*	NE	NE	No CVE: 0.022 Medium CVEr: -0.077 High CVEr: -0.078
Ethgen[17]	The Netherlands	F–G/O/RF	30,376 (hip and vertebral)	178.9*	NE	6,605	NE
Ethgen[18]	The Netherlands	F–G/O/RF	NE	NE	NE	NE	2 servings daily: 0.006-0.026
Sandmann[24]	Germany	F-G	36,705 (all)	45.2*	NE	NE	NE
Hlligsmann[21,22]	France	F-G	64,932 (all)	97.2*	NE	29,169	NE

LYG: life years gained; QALYs: quality-adjusted life years; S: supplementation; F: fortification; PF: previous fracture; O: osteoporosis; G: general population; RF: high risk of fracture; NE: not evaluated or specified; CVE: cardiovascular event; CVEr: cardiovascular event risk*: calculated from the study's original data and population's data at the time of the study.

tegy is optimal for a given cost-effectiveness threshold. To this effect, the percentages of simulations in which the assessed alternative has an incremental cost-effectiveness lower than the threshold for different values of it are calculated.

The net cost of the use of supplements or foods fortified with vitamin D/calcium in order to prevent fragility-induced fractures has been analysed in 7 of the 11 articles included in this review, and we can say there is a great diversity of results among them[16,19-21,23-25]. Hiligsmann et al. appraised the net cost of the intake of fortified foods by the general population over 65 years of age in France to be 1,556 million euros. By contrast, Poole et al. witnessed a net cost of -22 million pounds, due mainly to the savings on over 80-year-olds. In patients with osteoporosis or high risk of fracture, three studies predict savings on the population over 50-65 years of age[16,24,25], while Hiligsmann et al.'s model opts for those over 80[20]. Conversely, Hagen et al. estimated a 322 €/patient net cost, but as high as 1,033 €/patients when there is high risk of cardiovascular events led by calcium supplements[19].

Lastly, Hiligsmann et al. evaluated the economic impact of vitamin D and calcium fortification in France during the next 40 years and they witnessed a progressive benefit intensification, in particular, in 2060, when the cost per QALY gained will fall from 58,244 € in 2015 to 42,616 €[22].

Discussion

This literature review has identified 11 studies assessing the health benefits and the economic impact of vitamin D/calcium-fortified foods or vitamin D/calcium supplements.

The available evidence suggests that the intake of adequate amounts of vitamin D or calcium via fortified foods or vitamin D/calcium supplements may have substantial benefits for the public health (fractures and deaths prevention, LYG and QALYs). From an economical perspective, all models indicate these interventions to be cost-effective, at least regarding the elderly population or those with a higher risk of fracture, even leading to an economical saving.

One aspect to be considered is the economical evaluation is the role of complementary strategies, such as the screening and monitoring of levels of 25(OH)D. This way, only patients with a deficiency in vitamin D could be treated or the treatment effectiveness could be monitored in order to adapt the dosage. Zarca et al.[26] address this perspective when stating that the hypovitaminosis screening, followed by treatment, would be the most cost-effective strategy.

At the moment, there is some controversy about the effect of calcium supplements on cardiovascular risk[27]. Interestingly, Hagen et al. assessed three risk scenarios, concluding that the benefits (on the health and economical) will only appear if vitamin D and calcium supplementation do not lead to a cardiovascular risk rise[19]. Anyhow, it is important to note that the supplementation/fortification negative effects for cardiovascular risk have not yet been proven, and if it exists, it could be related to higher than recommended vitamin D or calcium levels[28,29]. On another note, the vitamin D's potential extraosseous benefits (ex. Pre-eclampsia, diabetes, cancer etc.) at the moment for debate, could lead to improving the registered data or even make up for possible side effects.

Table 3. Main economical results

Autor	Country	Intervention-population	Cost-effectiveness threshold	ICER	Net cost
Childs[16]	USA	S-PF	NA	NE	**-65 866 $/hospital/year** **-27,9 $/patient/years***
Hiligsmann[20]	The Nether-lands	S-O	45,000 €/QALY	60 years: **40,578** (W)/**23,477** (M) €/QALY 65 years: **16,266** (W)/**19,695**(M) €/QALY 70 years: **7,912** (W)/**10,250** (M) €/QALY 80 years: **-12,815** (W)/**-6,723** (M) €/QALY	60 years: 316 (W) /274 (M) €/patient 65 years: 211 (W)/230 (M) €/patient 70 years: 127 (W)/138 (M) €/patient 80 years: **-270** (W)/**-99** (M) €/patient
Poole[23]	UK	S-G	NA	NE	65-69 years: 10,115 £ million/year 70-74 years: 56,1 £ million/year 75-79 years: 12,6 £ million/year 80-84 years: **-39,0 £ million/year** ≥85 year: **-153,6 £ million/year** ≥65 year:: **-22,4 £ million/year**
Weaver[25]	EU USA	S-O	NA	NE	50-59 years: **-1.011 € million/year** (EU); **-700 $ million/year** (USA) 60-69 years: **-1.323 € millon/year** (EU); **-729 $ million/year** (USA) 70-79 years: **-1.911 € million/year** (EU); **-904 $ million/year** (USA) ≥80 years: **-1.462 € million/year** (EU); **-978 $ million/year** (USA) Total: **-5.710 € million/year** (EU); **-3.312 $ million/year** (USA)
Zarca[26]	France	S-PF	WHO threshold	"Treating and monitoring": **5,219 €**/QALY "Screening and treating": **9,104 €**/QALY	NE
Hagen[19]	Norway	S-O	60,000 €/QALY	No CVE: **14,453 €**/QALY Medium CVEr: Controlled High CVEr: Controlled	65 years: a) 322 €/patient (no CVE) b) 322 €/patient (CVEm) c) 1,033 €/patient (CVEa)
Ethgen[17]	The Nether-lands	F-G/O/RF	120,000 €/LYG	2 servings daily (G/O/RF), women : 50 years: 296,532/300,277/168,701 €/LYG 60 years: 184,479/174,359/**96,744 €**/LYG 70 years: **91,430**/**74,707**/**35,687 €**/LYG 80 years: **30,759**/**19,910**/**3,369 €**/LYG 2 servings daily (G/O/RF), men: 50 years: 255,753/203,563/**118,823 €**/LYG 60 years: 151,392/121,582/**70,057 €**/LYG 70 years: **85,627**/**61,349**/**31,423 €**/LYG 80 years: **37,048**/**24,231**/**8,916 €**/LYG	NE
Ethgen[18]	The Nether-lands	F-G/O/RF	45,000 €/QALY	2 servings daily (G/O/RF): 65 years: 123,122/56,498/48,018 €/QALY 70 years: 62,975/**32,467**/**32,685 €**/QALY 80 years: **15,576**/**6,868**/**3,390 €**/QALY	NE
Sandmann[24]	Germany	F-O	NA	NE	≥65 years: **-314.8 € million/year**
Hiligsmann[21]	France	F-G	30,000 €/QALY	2 servings daily: 60-69 years: 155,006 (W)/218,176 (M) €/QALY 70-79 years: **24,997** (W)/92,676 (M) €/QALY ≥80 years: **1,907** (W)/**27,683** (M) €/QALY ≥60 years: 38,256 (W)/106,113 (M) €/QALY	≥60 years: 1.556 € million
Hiligsmann[22]	France	F-G	30,000 €/QALY	2 servings daily, ≥60 years (2015/2040/2060): 58,244/45,732/42,616 €/QALY	NE

In bold: cost-effectiveness or net saving; ICER: cost-effectiveness incremental ratio; S: supplementation; F: fortification; PF: previous fracture; O: osteoporosis; G: general population; RF: high risk of fracture; NE: not evaluated or specified; NA: not applicable; W: woman; M: man; QALYs: quality-adjusted life years; LYG: life years gained; CVE: cardiovascular event; CVEr: cardiovascular event risk; WHO: World Health Organization.

In long-term health policies, forward-looking projections could be very interesting, even more so considering that population's aging leads to an increase in the incidence of osteoporosis, and this to fragility-induced fractures[2]. In this light, Hiligsmann et al. noticed a clear tendency towards the increase of health benefits (with the avoidance of up to 78% of the fractures) and the rising of cost- effectiveness[22].

Our literature review, however, has a series of potential limitations. On the one hand, it is limited to a single database (PubMed/Medline) and we were not able to assess the quality of the evidence. Besides this, and due to the different methodology of the practices, we were not able to directly compare them.

At the same time, many of the identified studies present their own limitations:

1)The studies assume the effectiveness of vitamin D and calcium supplements shown in the literature this effectiveness is thus extrapolated to the fortification of foods, sometimes following different doses.

2) Hardly any possible side effects have been taken into consideration (only one study does so), nor different potential benefits of the supplementation/fortification.

3) Most of the studies showed 100% adherence.

4) Those articles assessing fortified foods calculate the costs for the Health System and do not take into consideration people's established practices. In other words, the percentage of people who are already consuming the recommended fortified portions and that of those who are not. Regarding the latter, only the difference between the cost of fortified and non-fortified products should be calculated.

In conclusion, the available evidence suggests that the intake of vitamin D/calcium-fortified foods or vitamin D/calcium supplements reduce the fracture risk (with resulting health benefits) and it is a cost-effective strategy which can even allow cutting costs regarding certain sub-populations. Nevertheless, more studies should be needed, especially observational studies concerning the Spanish context, in order to assess these strategies' real impact over the Spanish public health.

Conflict of interests: The authors declare no conflict of interest.

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