Review

Vitamin D supplementation in patients with cystic fibrosis: A systematic review and meta-analysis

Márk Félix Juhász[a], Orsolya Varannai[a,b,c], Dávid Németh[a], Zsolt Szakács[a,d], Szabolcs Kiss[a,c], Vera Dóra Izsák[a,b,c], Ágnes Rita Martonosi[a,b,c], Péter Hegyi[a,d], Andrea Párniczky[a,b,*]

[a] Institute for Translational Medicine, Medical School, University of Pécs, Pécs, Hungary
[b] Heim Pál National Pediatric Institute, Budapest, Hungary
[c] Doctoral School of Clinical Medicine, University of Szeged, Szeged, Hungary
[d] János Szentágothai Research Center, University of Pécs, Pécs, Hungary

ABSTRACT

Despite routine supplementation, vitamin D insufficiency is often seen in cystic fibrosis (CF) patients on account of pancreatic insufficiency. Vitamin D is a crucial component of bone health and affects nearly all cells of the immune system. However, clinical benefits or harms associated with supplementation are poorly documented. In this systematic review, we included randomized controlled trials (RCTs) that compared vitamin D supplementation with placebo (i.e. 'non-increased dose') in CF patients. Analysing the 8 included RCTs, the intervention group had significantly higher serum 25-hydroxyvitamin D (se25OHD) levels, but there were no significant differences found in the quantitative synthesis of clinical outcomes, including bone disease-, respiratory status- and immunological status-related outcomes. Based on our current results, while a higher vitamin D dose elevates se25OHD, it does not seem to influence clinical outcomes. Future RCTs should include outcomes of past studies and apply longer follow-up periods to document long-term patient-important outcomes.

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1. Introduction

Cystic fibrosis (CF) (OMIM: #219700), is a hereditary disease caused by mutations in both alleles of the cystic fibrosis transmembrane conductance regulator (CFTR) gene located on the long arms of chromosome 7. It is one of the most common autosomal recessive disorders, affecting approximately 1 out of every 3,000 live-born worldwide [1]. Mutations – more than 2,000 documented to date, divided into six classes – generally result in the absence or the reduced/annulled function of the CFTR-protein, a transmembrane Cl⁻-channel present in the apical surface of epithelial cells throughout the body. The defect of this channel causes the damage of multiple organs, mainly: the airways, pancreas, gastrointestinal (GI) tract, liver and reproductive system [2].

In the pancreatic and biliary ducts, the defective CFTR-channels will result in thickened secretion production, chronic obstruction of these ducts, leading to chronic pancreatitis and exocrine insufficiency. Loss of exocrine function will lead to fat malabsorption and the deficiency of fat-soluble vitamins, including vitamin D [2–4]. Nutritional status and the level a micro- and macronutrients have a strong association with lung function and greatly determine the morbidity and mortality of CF patients [5].

Vitamin D is crucial for bone health: mainly stimulating the calcium (Ca) absorption from the gut, its deficiency can lead to secondary hyperparathyroidism and bone loss [6]. Vitamin D also affects nearly all cells of both the innate (monocytes, macrophages, dendritic cells, etc.) and the adaptive (B- and T-cells) immune system, with sufficient vitamin D levels decreasing the risk of respiratory infections, thus possibly delaying CF progression and mortality [5,7]. As of 2019, the Cystic Fibrosis Foundation recommends different, consensus-based doses of cholecalciferol (D3) rather than ergocalciferol (D2) in different age groups of CF patients to be el-

evated when necessary, with the goal of reaching a serum 25-hydroxyvitamin D (se25OHD) concentration of at least 30 ng/ml (75 nmol/l) [8]. However, clinical benefits and harms of vitamin D supplementation in this population are poorly documented. The last systematic review of controlled trials was conducted in 2014 [9] with only three of the included randomized controlled trials (RCTs) supplying useful information and with inconclusive results on account of the heterogeneity and small sample size of the RCTs.

As more RCTs have been published since, our aim was to re-evaluate the clinical benefits and possible adverse events accompanying a higher vitamin D dose in CF patients by conducting a systematic review and meta-analysis of RCTs in the topic.

2. Methods

2.1. Protocol and registration, reporting

This meta-analysis was registered with PROSPERO under registration number CRD42020155847. There have been no deviations from the registered protocol. We adhered to the recommendations of the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)'-group in reporting our findings and writing the review [10].

2.2. Eligibility criteria

Only randomized controlled trials were considered eligible for inclusion in this systematic review. We determined eligibility based on the PICO of trials in the following manner:

P - Population: We included studies that examined CF patients, either paediatric or adult or both. There were no other restrictions based on the examined participants of these trials – exacerbation and stable disease were both allowed, also comorbidities and sub-populations of CF patients with the intent of conducting post-hoc analyses if feasible and necessary. Trials where only an examined subpopulation of participants have CF were also allowed; however, at the end, no such trials were eligible for inclusion.

I – Intervention: We included studies that, as an intervention, supplemented vitamin D to the participants in any dose, any form (vitamin D3 or D2) and for any duration. Compounds consisting of multiple active substances including vitamin D were also allowed. Studies utilizing sunshine as a means of vitamin D supplementation were not eligible for inclusion.

C – Comparator: Placebo or if the intervention in given study consisted of a compound with multiple active substances including vitamin D, any otherwise identical therapy lacking vitamin D.

Continued or basal vitamin D supplementation was allowed if it did not categorically differ between the intervention and comparator groups.

O – Outcome: There were no restrictions applied based on examined outcomes in the individual studies. Our primary interests were as entailed by our PICO: Bone mineral density and other quantifiable bone disease-related outcomes; mortality; height and weight Z-score; se25OHD, Ca, and parathyroid hormone (PTH) concentrations; respiratory status (forced expiratory volume in the first second (FEV1), forced vital capacity (FVC), forced expiratory flow at 25% of FVC (FEF25%), other assessed respiratory parameters); measures of immunological status (immunological markers, exacerbation due to infection, antibiotic use); quality of life; adverse events. Apart from these, all other examined outcomes were considered valuable and if a study failed to report on any of the listed outcomes it was still not to be excluded from our systematic review.

Studies were not restricted in eligibility based on length of follow-up.

2.3. Systematic search and selection

We conducted the systematic search – using the same search key as detailed in supplementary material Suppl1. - in 4 databases: Embase, MEDLINE (via PubMed), Cochrane Central Register of Controlled Trials (CENTRAL) and Web of Science. The date of last systematic search was 9th October 2019. There were no restrictions imposed on the search. Citations were exported as a shared pool to a citation manager software, EndNote X9 (Clarivate Analytics). Two independent reviewers (MFJ and OV) conducted the selection by title, abstract and full-text based on the previously disclosed pre-determined set of rules. After selecting by title and abstract – in an inclusive manner -, the rate of agreement was determined and documented by calculating the Cohen's kappa coefficient (κ) and the two citation pools were merged before screening by full text. Any disagreements were settled by an independent third party (ZS). Exclusions made in the full text phase of selection were documented, studies of the same population were linked together. In case of population overlaps for an outcome, the article with the higher number of participants was preferred.

Citations of the studies inspected for eligibility in the full-text phase were reviewed in order to identify any additional eligible trials.

2.4. Data extraction

Information on data extraction is available in the supplementary material.

2.5. Risk of bias assessment

The Revised Risk of Bias Assessment Tool (RoB 2) [11] was used to assess the risk of bias in the individual studies (all RCTs). MFJ and OV independently conducted the assessment, final results are based on consensus. Assessments were made on a study level but the nature of the examined outcomes were consistent – mostly results of laboratory examinations at predetermined points in time. Results of the risk of bias assessment are available in the supplementary material.

2.6. Statistical analysis

All statistical analyses in this study were carried out using Stata 15 SE (StataCorp). Pooled weighted mean difference (WMD) or standardized mean difference (SMD) were calculated with 95% confidence intervals (CI) for continuous outcomes. A random effects model was applied for all analyses, with the DerSimonien-Laird estimation. Statistical heterogeneity was analysed using the I^2 statistic and the chi-square to gain probability-values; I^2 represents the magnitude of the heterogeneity (moderate: 30–60%, substantial: 50–90%, considerable: 75–100%) [12].

2.7. Determination of quality of evidence

Recommendations of the 'Grading of Recommendations Assessment, Development and Evaluation' (GRADE) working group [13] were followed upon assessing the quality of the evidence (MFJ and VI, independently). The GRADEPro Guideline Development Tool [14] was used for preparing the Summary of Findings table and accessory tables.

3. Results

3.1. Systematic search and selection

The systematic search yielded 2,738 hits, 1,011 after duplicate removal. These 1,011 records were screened. 931 studies were ex-
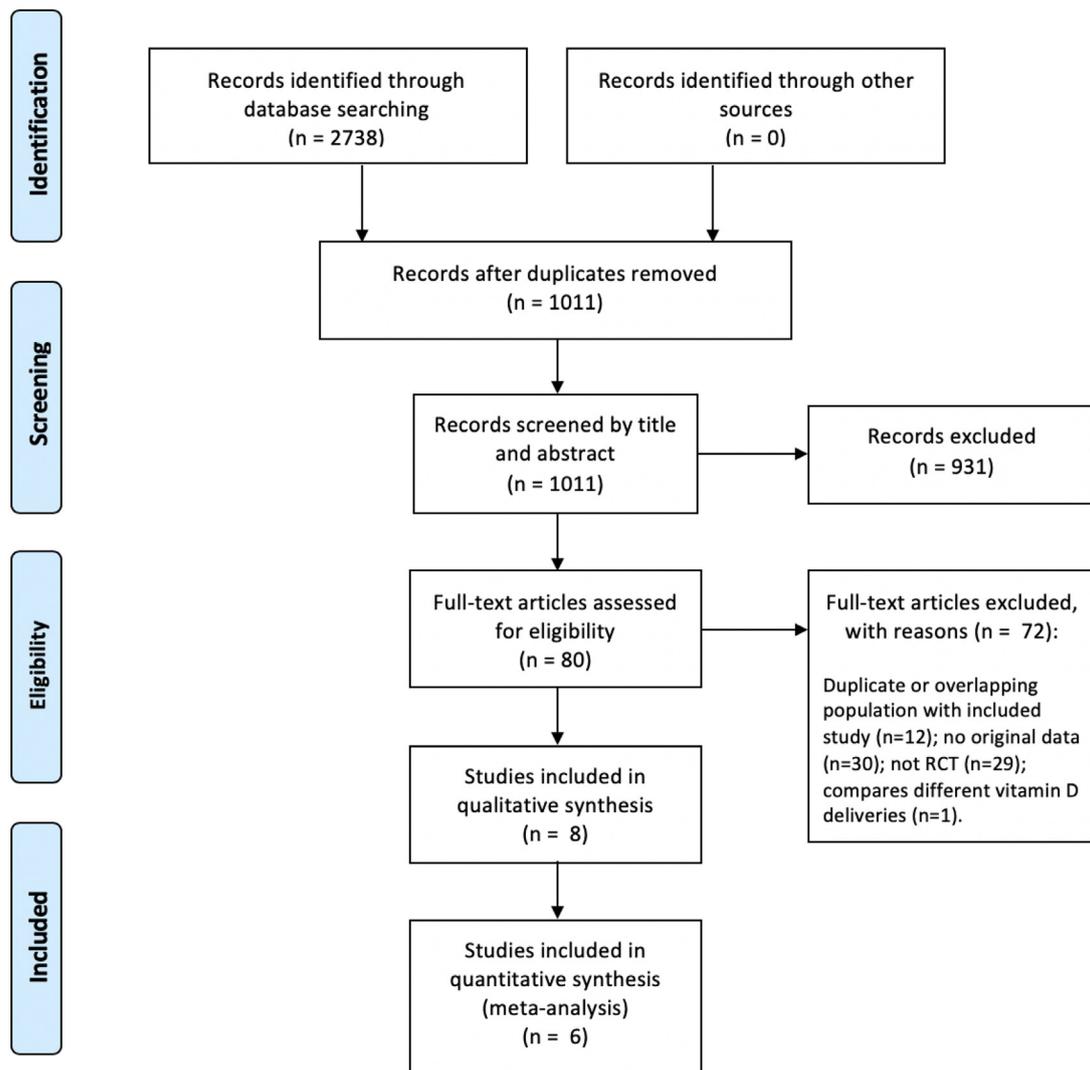
Fig. 1. PRISMA flow diagram indicating the number of studies identified, screened and excluded as well as the number of eligible studies [10].

cluded based on title and abstract (Cohen's kappa: 0.86), leaving 80 studies to be assessed based on reviewing the full text. Out of the 80 articles, 72 were excluded, mostly because the full-text revealed that they did not contain original data or that they were alternative reports / conference abstracts of identical / overlapping study populations. At the end, 8 articles remained of which 2 were conference abstracts not providing useful data for the quantitative syntheses but that could be included in the systematic review (Fig. 1).

3.2. Study characteristics

The main characteristics of included studies are gathered in Table 1.

3.3.1. Primary outcomes
3.3.1.1. Bone mineral density and other quantifiable bone disease-related outcomes. Only 2 of the included studies (Haworth 2004, Hillman 2008) reported on bone health-related outcome measures.

Fig. 2 presents the quantitative synthesis of intervention effects on serum bone alkaline phosphatase (BALP), serum osteocalcin and lumbar spine Z-score – these were the only three parameters that were consistently measured in both studies – with no significant difference between groups neither in the individual studies, nor overall. It is to be noted that Hillman 2008 examined children while Haworth 2004 examined adults. Hillman 2008 also assessed BMC, BMD and Z-score in: whole body, lumbar spine, 1/3 radius and hip - with no significant differences between groups. Haworth 2004 also assessed total hip and distal forearm Z-scores with no significant differences between groups.

3.3.1.2. Mortality. The 2 studies examining adult CF patients admitted with pulmonary exacerbation (Grossman 2012, Tangpricha 2019) provided data on mortality. During the 12-month follow-up 6 out of 30 patients died (1 intervention, 5 placebo; p=0.03) in Grossman 2012 and 3 out of 91 patients died (3 intervention, 0 placebo) in Tangpricha 2019. The other 6 studies examining clini-

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Table 1

Characteristics of included studies. RCT= randomized controlled trial, se25OHD= serum 25-hydroxyvitamin D, IU= international units, SD= standard deviation, med= median, IQR= interquartile range, FEV1= forced expiratory volume in the first second, FVC= forced vital capacity, FEF25%= forced expiratory flow at 25% of FVC, Ca= serum calcium, PTH= serum parathyroid hormone, NA= not available. *= only patients with se25OHD <30 ng/ml were accepted.3.3. Synthesis of results.

| Author year [ref]	Country	Centres, blinding, design	full-text	Nº of patients	Study length	Population at baseline			Interventions, dose of vitamin D (IU)		List of examined outcomes
						Age (years)	se25OHD (ng/ml)	other descriptors	Intervention	Comparator	
Tangpricha 2019 [15]	USA	multicentre quadruple-blind RCT	yes	91	12 months	mean±SD 28.8±7.9	27.0±10.9	pulmonary exacerbation; 93,4% pancreatic insufficient, 33% CFRD	1 × 250,000 IU within 1st 72 h, 50.000/ 2 weeks D3 starting month 3	placebo, 800-2,000 IU/day	se25OHD FEV1, Ca, creatinine, albumin, LL-37, return to baseline FEV1
Pincikova 2017 [16,17]	Sweden	single-centre unblinded RCT	yes	16	5 months	med (IQR): 19 (12;32)	22.87±9.64*	62.5% ≥18 years old, 87.5% pancreatic insufficient, 18.8% mild CF phenotype (at least one class IV or V mutation), 31.3% receiving azithromycin treatment, FEV1% of predicted (mean±SD): 72.7±30.9	35,000 or 50,000 IU / week (<or>16 years) D2 or D3	"continued vitamin D" (dose not stated)	humoral and cellular immunity, se25OHD, FVC, FEF25%,
Kanhere 2017 [18]	USA	single-centre double-blind RCT	yes	23	12 weeks	mean±SD 32±11 (D3), 34±10 (placebo)	25±5 (intervention) - 22±6 (placebo) *	100% pancreatic insufficient, 20% CFRD	50,000 IU /week D3, basal (mean±SD): 1,100±849 IU /day	placebo, basal (mean±SD): 1,770±1643 IU /day	se25OHD, gut and airway microbiota
Grossman 2012 [19,20]	USA	single-centre double-blind RCT	yes	30	12 months	med (range): D3: 24.9 (16.01), placebo: 28.2 (30.89)	30.6±3.2 (intervention) - 28.7±3.5 (placebo)	pulmonary exacerbation; 93,3% pancreatic insufficient, 50% CFRD, 53.3% DF508 homozygous, 23.3% DF508 hetero, 23.3% unkown mutation	1 × 250,000 IU D3 within 48 h, basal (mean (range)): 400 (2,600) IU/day	placebo, basal (mean (range)): 400 (2,800) IU/day	se25OHD, PTH, Ca, humoral immunity, return to baseline FEV1
Hillman 2008 [21]	USA	single-centre double-blind crossover RCT	yes	12	9 months /arm	mean±SD 9.1±2.3	35.4±13.2	all patients taking pancreatic enzymes, Ca intake (mean±SD): 861±390 mg / day, lumbar spine Z-score (mean±SD): -0.97±0.87	I1: 1,600 IU / day D3; I2: 1g/day Ca; I3: 1,600 IU D3 + 1 g Ca / day; C: placebo. Basal vitamin D: 400 IU / day		se25OHD, PTH, bone metabolism markers, albumin, Ca
Haworth 2004 [22]	UK	single-centre double-blind RCT	yes	30	12 months	mean±SD 29.4±7.8 (D3), 25.9±8.0 (placebo)	24.4±10.2 (intervention) - 21.6±10.8 (placebo)	lumbar spine Z score ≤-1, 100% pancreatic insufficient, 8 patients in each group received oral corticosteroids	2 × 800 IU D3 + 1g Ca / day; basal: 900 IU/day	placebo, basal: 900 IU/day	se25OHD, PTH, Ca, bone metabolism markers
Manshadi 2012 [23]	Canada	single-centre double-blind RCT interim	no	40	3 months	mean±SD 34.4±1.4	NA*	23.3% diabetes, 32.4% homozygous delta F, 64.9% Pseudomonas aeruginosa positive, BMI 22.7±3.4 kg/m2, FEV1 2.3 ± 1.1 l	5,000 IU/day D3, basal: yes, dose not stated	placebo, basal: yes, dose not stated	se25OHD
Brown 2006 [24]	USA	double-blind RCT (Nº of centres unknown)	no	59	24 months	mean±SD 12.1±3.1	NA	NA	10 or 20 IU/kg/day calcitriol, (<or>45kg); basal: usual vitamin D, dose not stated + Ca 500 mg / day	placebo, basal: usual vitamin D, dose not stated + Ca 500 mg /day	bone metabolism markers, pubertal stage
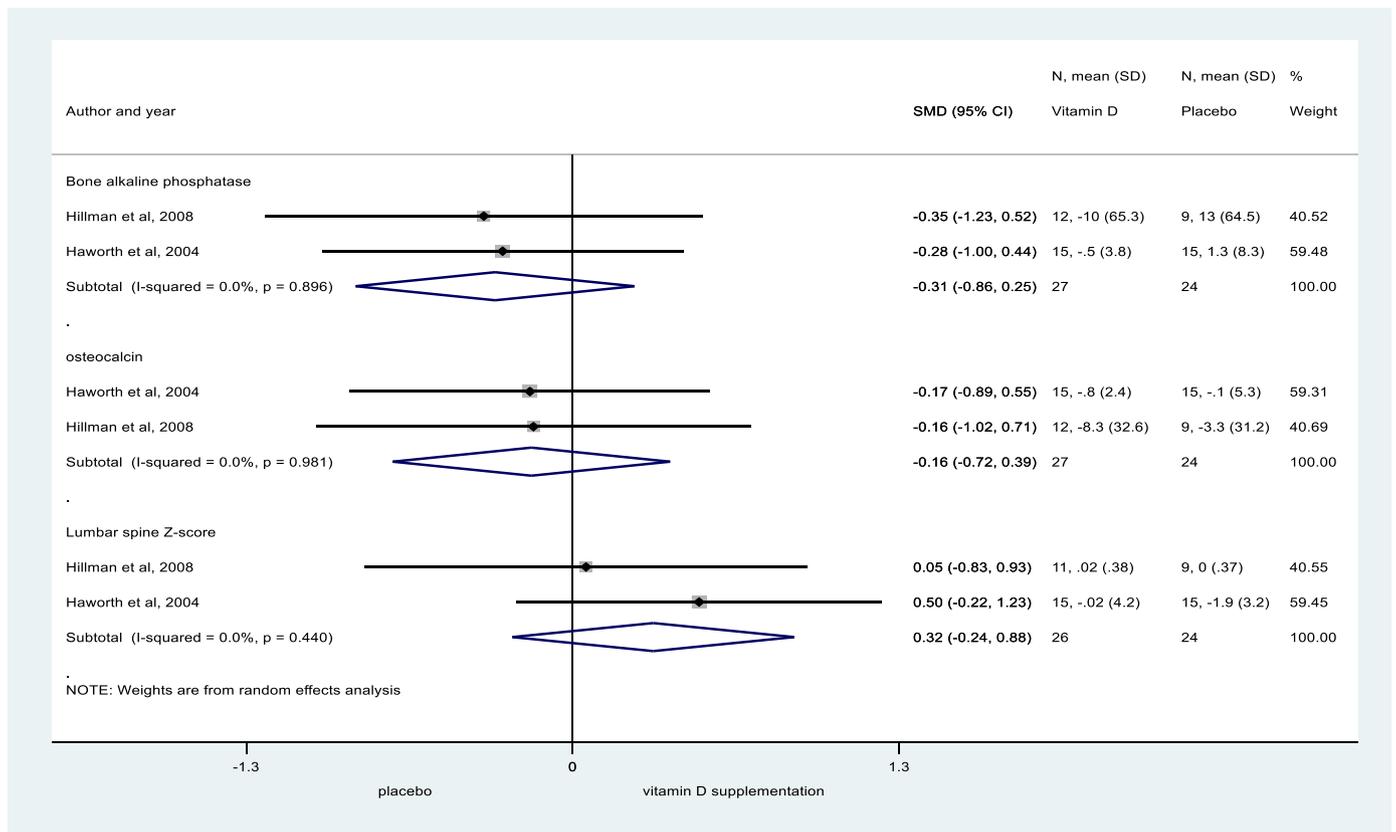
Fig. 2. Forest-plot displaying the meta-analysis of standardized mean differences (SMD) between vitamin D and placebo groups regarding bone-related outcome measures (serum bone alkaline phosphatase (BALP), serum osteocalcin, lumbar spine Z-scores) with no significant differences in either outcome. N=number, SD=standard deviation, SMD= standardized mean difference, CI=confidence interval..

cally stable CF patients did not report on any cases of mortality. In the case of Haworth 2004, Pincikova 2017 and Kanhere 2017 dropouts, missing outcome data and adverse events were thoroughly reported, allowing us to reasonably assume 0 deaths in these studies. In Brown 2006, Hillman 2008 and Manshadi 2012 reporting in these fields were lacking.

3.3.2. Secondary outcomes
3.3.2.1. Serum total 25-hydroxyvitamin D (se25OHD) concentration. Fig. 3 shows the comparison of continuous vitamin D supplementation versus placebo regarding se25OHD concentration, with significantly higher levels with treatment (WMD: +10.48 ng/ml; 95%CI: [+0.72; +20.24]; I^2=89.7%). Haworth 2004 only provided data on change in se25OHD, Grossman 2012 only applied a single dose of vitamin D supplementation thus they were not included in this quantitative synthesis. We decided to include the 12-month outcomes from Tangpricha 2019 despite them starting with a single dose of vitamin D, as they initiated continuous supplementation at the 3-month visit. Manshadi 2012 only provided data for the vitamin D group, Brown 2006 only provided baseline data, thus they could not be included.

3.3.2.2. Respiratory status-related outcome measures. The two studies examining pulmonary exacerbation (Grossman 2012, Tangpricha 2019) reported on return to baseline FEV1% (patients whose FEV1% of predicted returned to within 95% of baseline i.e. the best lung function in the 6 months / 1 year before the study) but in different subgroups of patients, thus results were not pooled. Grossman 2012 analysed patients whose FEV1% of predicted decreased greater than 10% from baseline to admission – 90 vs 50% returned to baseline in the vitamin D vs placebo groups, respec-

tively (p=0.12). Tangpricha 2019 reported 35.3% of vitamin D and 25.3% of placebo patients returning to baseline at month 3, among all patients.

Tangpricha 2019 also reported on mean FEV1% (no significant differences between groups), Pincikova 2017 on FVC (significantly increased in D3 group compared to baseline) and FEF25% (no significant differences).

3.3.2.3. Adverse events. Adverse events reported by the individual studies are gathered in Table 2.

3.3.3. Additional outcomes
All outcomes pre-planned in our protocol and outcomes reported on by multiple studies were assessed. Pooled analysis was possible in the case of serum Ca, PTH, cathelicidin (LL-37) and albumin, without significant differences between groups. These outcomes are available in the supplementary material.

3.4. Quality of evidence

We included seven outcomes in our main Summary of Findings table: long-term survival (not reported), 12-month mortality after exacerbation (not pooled, opposing results, very low certainty), return to baseline lung function after exacerbation (not pooled, favoured vitamin D, very low certainty), adverse event rate (not pooled, no difference, very low certainty), quality of life (not reported), lumbar spine Z-score (no significant difference, very low certainty) and se25OHD (significantly higher in intervention group, moderate certainty). The main Summary of Findings table, and the one of additional outcomes are available in the supplementary material.
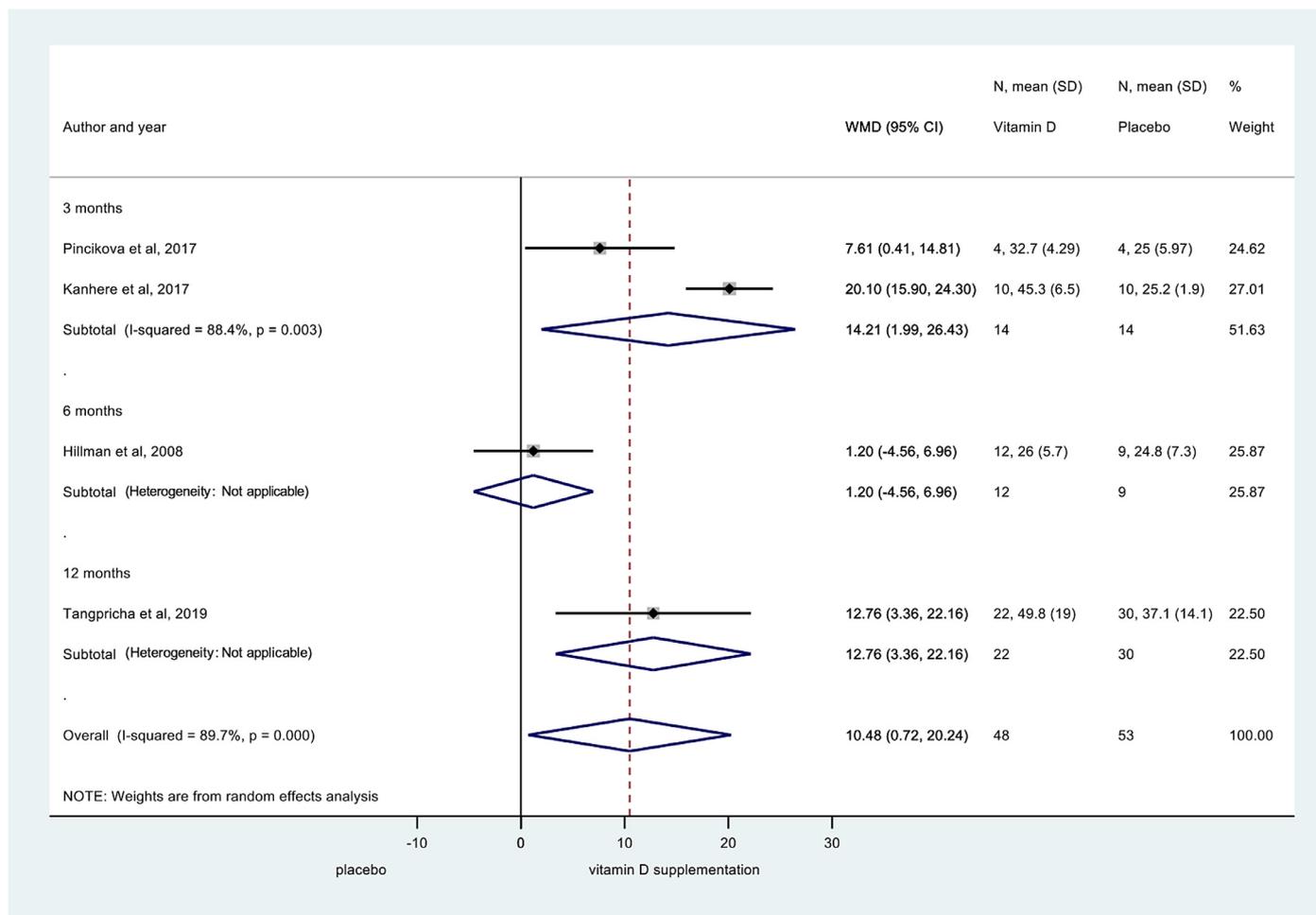
Fig. 3. Forest-plot showing the comparison of vitamin D versus placebo regarding the effect on serum total 25-hydroxyvitamin D concentration (ng/ml) in studies using continuous supplementation. N=number, SD=standard deviation, WMD=weighted mean difference, CI=confidence interval.

Table 2
Adverse events in the included studies.

Study identifier	Adverse events Intervention group	Control group
Tangpricha 2019	n=32; **11 renal** adverse events (1 nephrolithiasis, 2 elevated creatinine, 3 polydipsia, 5 polyuria), **0 gastrointestinal, 4 neurologic** (1 fatigue, 3 increased confusion), **11 pulmonary** (1 cough, 2 chest pain, 2 decreased lung function, 1 dyspnea, 1 hemoptysis, 2 increased sputum, 2 upper respiratory tract infection), 6 other	n=33; **3 renal** adverse events (2 polydipsia, 1 polyuria), **2 gastrointestinal** (1 diarrhea, 1 nausea), **5 neurologic** (3 fatigue, 1 headaches, 1 increased confusion), **14 pulmonary** (4 cough, 2 decreased lung function, 2 dyspnea, 2 hemoptysis, 2 increased sputum, 2 upper respiratory tract infection), 9 other
Kanhere 2017	"There were no clinical signs of hypercalcemia and no reported symptoms of vitamin D toxicity, as assessed by patient questionnaire at the final study visit."	
Grossman 2012	"There were no reported symptoms of vitamin D toxicity as assessed by patient questionnaire at any study visit, no clinical signs of hypercalcemia, no significant changes in mean serum calcium or PTH concentrations."	
Haworth 2004	"The patients did not report any significant adverse events with drug or placebo, and there were no documented episodes of hypercalcaemia."	
Manshadi 2012	"No adverse events were identified during the study period."	
Brown 2006	nephrolithiasis (n=1), asymptomatic hypercalcaemia (n=1)	nephrolithiasis (n=1), persistent hypercalciuria (n=2)
Pincikova 2017	No reports on presence / absence of adverse events.	
Hillman 2008	No reports on presence / absence of adverse events.	

4. Discussion

The meta-analysis of the included RCTs demonstrated significantly higher se25OHD levels in the intervention group and no significant differences between intervention and comparator – neither on a study-level nor in total – regarding: lumbar spine Z-score, serum levels of BALP, osteocalcin, Ca, PTH, LL-37 and albumin. All of the included studies applied a basal vitamin D dose, meaning that only the comparison of this basal to a higher vitamin D dose could serve as a means to evaluate the intervention.

Even though the number of RCTs in the field of interest has doubled since the last systematic review, the lack of significant dif-

Table 3

CF Foundation, European Cystic Fibrosis Society and Thoracic Society of Australia and New Zealand vitamin D guidelines' sections on target se25OHD and dosing. Recommendations on the target se25OHD and dose steps in each age group are based on consensus [8,25,26].

2012 CF Foundation Vitamin D guidelines (reapproved in 2019)						
Age group	Target se25OHD	Initial dose (IU/day)	2nd step	3rd step	4th step	Strength of recommendation
<1 year	≥30 ng/ml	400-500	800-1,000	max 2,000	refer to specialist	Low certainty; consensus recommendation
1-10 years		800-1,000	1,600-3,000	max 4,000		
>10 years		800-2,000	1,600-6,000	max 10,000		
2013 European Cystic Fibrosis Society recommendations (republished in 2019)						
Age group		Target se25OHD		Initial dose (IU/day)		Strength of recommendation
<1 year		≥30 ng/ml		1,000-2,000		Insufficient evidence, consensus recommendation
≥ 1 year				1,000-5,000		
2017 Thoracic Society of Australia and New Zealand recommendations (republished in 2020)						
Age group		Target se25OHD		Initial dose (IU/day)		Strength of recommendation
Infants		≥20 ng/mL end of winter;		Base supplementation on above		Insufficient evidence, consensus recommendation
Young children		≥24-28 ng/mL rest of the year		US and EU recommendations		
Older children						
Adolescents and adults						

ferences between groups should still not be considered as definite ineffectiveness, the quality of evidence being very low. The main reason behind this is the low number of participants in each study and the heterogeneous choice of reported outcomes resulting, in most cases, less than 100 participants per comparison.

However, the tendency of our current results suggests that an increased vitamin D dose (usually an additional 1,600-5,000 IU/day in the included studies) when compared with placebo plus the patients' continued, basal vitamin D dose (usually 400-1,800 IU/day, which is roughly equivalent to the initial regimen recommended by the CF Foundation (Table 3)) while significantly raises se25OHD, does not influence clinical or other laboratory outcome measures.

Based on our results, it seems that a higher dose is unnecessary, as it poses no additional benefits. But it is also of note that, - while only three of the RCTs excluded patients with se25OHD ≥30 ng/mL, - six studies experienced baseline mean se25OHD <30 ng/ml, which is the target minimum se25OHD value recommended by the CF Foundation. This value, in contrast with the >20 ng/ml recommendation for the general population [27,28], was modelled after endocrinology and osteoporosis guidelines given the frequent vitamin D deficiency, lower bone density and bone health markers, and higher rate of fractures among CF patients [29,30]. Accordingly, similar target se25OHD levels are recommended by European (≥30 ng/mL) and Australasian (≥20 ng/mL end of winter, ≥24-28 ng/mL rest of the year) CF Societies [25,26]. It seems that the recommended initial dose is often inadequate for achieving the target se25OHD, thus, even though we observed no clinical benefits, we think it would be sensible to consider a higher initial vitamin D dose for CF patients – more in line with the European recommendations, or the second dose step of the CF Foundation. A higher vitamin D dose, as described by the individual studies, was also not accompanied by a higher rate of adverse events (Table 2).

We would also like to call on future RCTs of vitamin D therapy in CF to include outcomes of preceding studies, enabling the rise of high-quality scientific evidence.

4.1. Strengths and limitations

This is the largest systematic review to date to examine vitamin D supplementation in CF. To our knowledge, this is the first review to include only RCTs, in order to analyse only the highest quality clinical trials. We were able to identify 8 RCTs, of which 6 supplied useful information for meta-analyses – 3 more than in the last systematic review.

Our study has several limitations. First of all, while more RCTs emerged since the last meta-analysis, the choice of outcomes, in most cases, did not overlap. While we understand the importance of presenting novel results, we highly recommend including outcomes of past studies in order to achieve high quality scientific evidence. Partly because of this, and partly because of the low participant number in the studies themselves, high risk of imprecision was noted, all comparisons were well below the optimal information size. Indirectness was also present as all studies applied a basal vitamin D dose. The research question at hand should have been vitamin D versus no vitamin D, which of course, would be unethical in such a high-risk population. We would also like to point out that due to the short follow-up periods, long-term patient-important outcomes, such as mortality and exacerbations, are yet to be documented. While the mean age in most studies was between 20 and 35 years, Hillman 2008 examined a younger (mean age: 9.1 years) population. Also, this was a crossover study, while others applied a parallel design.

4.2. Implications…

… for practice: Additional vitamin D does not seem to influence clinical and laboratory outcomes. However, CF patients receiving vitamin D, especially those receiving their initial dose, should be closely monitored as insufficiency is frequent.

… for research: Outcomes of past studies should be included. RCTs with longer follow-up periods (5 years or more) should also be conducted to observe the long-term effects of supplementation.

Authors' contributions

MFJ wrote the manuscript and took part in the selection and data extraction process. OV, ÁM, VI took part in the selection and extraction process, and contributed to the manuscript. DN conducted the statistical analysis of the data. ZS and SK provided methodological guidance. AP and PH contributed to and supervised the writing of the manuscript and gave medical insight. All authors have (1) contributed to the concept of the study; (2) re-

vised the manuscript; (3) read and approved the final version of the manuscript.

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Declaration of Competing Interest

Authors disclose no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcf.2020.12.008.

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