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DOI:
10.1136/bmjopen-2023-073431

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (Harvard):
Patel, A, Caruana, EJ, Hodson, J, Morrison, R, Khor, B, Gysling, S, Trevis, J, Mangel, T, Benson, R, Zakeri, R, Manders, J, Vaja, R, Rogers, L, Baker, P, Pournaras, DJ, Thickett, D, Hewison, M, Naidu, B & Lim, E 2024, 'Role of vitamin D supplementation in modifying outcomes after surgery: a systematic review of randomised controlled trials', *BMJ open*, vol. 14, no. 1, e073431. https://doi.org/10.1136/bmjopen-2023-073431

BMJ Open

Role of vitamin D supplementation in modifying outcomes after surgery: a systematic review of randomised controlled trials

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To cite: Patel A, Caruana EJ, Hodson J, *et al*. Role of vitamin D supplementation in modifying outcomes after surgery: a systematic review of randomised controlled trials. *BMJ Open* 2024;**14**:e073431. doi:10.1136/bmjopen-2023-073431

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2023-073431).

Received 08 March 2023
Accepted 22 December 2023

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ABSTRACT

Background There is increasing evidence to suggest vitamin D plays a role in immune and vascular function; hence, it may be of biological and clinical relevance for patients undergoing major surgery. With a greater number of randomised studies being conducted evaluating the impact of vitamin D supplementation on surgical patients, it is an opportune time to conduct further analysis of the impact of vitamin D on surgical outcomes.

Methods MEDLINE, EMBASE and the Cochrane Trials Register were interrogated up to December 2023 to identify randomised controlled trials of vitamin D supplementation in surgery. The risk of bias in the included studies was assessed using the Cochrane Risk of Bias tool. A narrative synthesis was conducted for all studies. The primary outcome assessed was overall postoperative survival.

Results We screened 4883 unique studies, assessed 236 full-text articles and included 14 articles in the qualitative synthesis, comprising 1982 patients. The included studies were highly heterogeneous with respect to patient conditions, ranging from open heart surgery to cancer operations to orthopaedic conditions, and also with respect to the timing and equivalent daily dose of vitamin D supplementation (range: 0.5–7500 mcg; 20–300 000 IU). No studies reported significant differences in overall survival or postoperative mortality with vitamin D supplementation. There was also no clear evidence of benefit with respect to overall or intensive care unit length of stay.

Discussion Numerous studies have reported the benefits of vitamin D supplementation in different surgical settings without any consistency. However, this systematic review found no clear evidence of benefit, which warrants the supposition that a single biological effect of vitamin D supplementation does not exist. The observed improvement in outcomes in low vitamin D groups has not been convincingly proven beyond chance findings.

Trial registration number CRD42021232067.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This was the first systematic review to comprehensively assess the impact of vitamin D supplementation on a pan-surgical population exclusively.
⇒ Despite a robust and thorough search strategy, some relevant research may have been missed.
⇒ Meta-analysis was not possible, given the limitations of pooling data amidst gross heterogeneity.

INTRODUCTION

Public Health England and Food Standards Agency data suggest that vitamin D deficiency (serum 25-hydroxyvitamin D (25(OH)-D) <30 nmol/L) is present in 23% of people aged 19–64 years and in 21% of people aged 65 years and over. From January to March, this increases to 40% of people aged 19–64 years and 30% of people aged 65 years and over.[1 2] While vitamin D deficiency is clearly linked to impaired calcium homeostasis and bone metabolism, there has been growing interest in the possible impact of vitamin D on extraskeletal function.[3] This includes effects on immune[4] and vascular function[5] that have potential implications for surgery and surgical outcomes.

Over 310 million major surgeries are performed globally per year, with varying rates of postoperative morbidity and mortality.[6 7] There is a lack of consensus on the association between circulating vitamin D levels and postoperative outcomes in patients undergoing surgery. However, it has been suggested that hypovitaminosis D is associated with adverse outcomes in patients undergoing surgery.[8] In selected surgical cohorts (cardiac, thoracic and gastrointestinal), there is a trend towards prolonged intensive care unit (ICU) stays and mechanical ventilation in vitamin D-deficient patients.[9–11] The same group[9] determined that there is an

independent association between low levels of the active form of vitamin D, 1,25-dihydroxyvitamin D and the risk of postoperative infections in these patient groups.

There are also data supporting a link between vitamin D deficiency and cardiovascular disease[10]; however, despite experimental and observational studies demonstrating this association, randomised trials have not so far shown a beneficial effect of vitamin D supplementation on subclinical or clinical cardiovascular outcomes. Similarly, for all-cause mortality, meta-analytical evidence of level one randomised data has shown no association with vitamin D supplementation when compared with control in both surgical and non-surgical patients.[12] This may be a result of the heterogeneity of the study populations included within the analysis, the baseline vitamin D status and the dose, mode of administration and duration of vitamin D supplementation. This heterogeneity is further compounded in surgical cohorts by the added physiological insult of surgery, which may differ according to the access routes of surgery,[13 14] which in itself is an evolving field.

With a greater number of randomised controlled trials (RCTs) being conducted evaluating the impact of vitamin D supplementation in surgical patients, it is an opportune time to perform a systematic review of the literature in this area. As such, the primary aim of this study was to assess the association between vitamin D supplementation and overall postoperative survival by combining data from RCTs of patients undergoing any form of surgery. The secondary aim was to assess other clinical outcomes, including postoperative complications and the length of hospital stay.

METHODS

Protocol and guidance

The protocol for this review was prospectively registered with PROSPERO (CRD42021232067). The results of the review are reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidance.[15]

Inclusion criteria

All clinical trials using an RCT design were considered eligible for inclusion. Studies were included if they enrolled adults (using accepted age cut points as defined in individual studies according to country of trial origin, usually above 18 years of age) who had undergone surgery for any health condition, irrespective of approach (full exposure or minimally invasive) and compared vitamin D supplements alone at any dose with either a placebo or no treatment. Studies with mixed adult and paediatric populations were included if the adult population contributed at least 50% of the study cohort and if the outcomes of interest could be segregated by patient cohort (ie, paediatric or adult).

Exclusion criteria

We excluded studies if they met any of the following criteria: did not explore the outcomes of interest, as defined below; incomplete reporting of outcomes as defined by the Cochrane Risk of Bias tool[16]; inability to differentiate between surgical and non-surgical cohorts in large mixed population studies such as anaesthetic and critical care studies or if vitamin D was used in combination with some other form of medication that can affect vitamin D levels, such as steroids, lipid-lowering agents, weight loss drugs or non-pharmacological intervention.

Outcomes

The primary outcome was overall postoperative survival. Secondary outcomes included:

1. Short-term postoperative survival (30-day, 60-day, 90-day, 12-month or in-hospital mortality).
2. Length of an ICU stay.
3. Length of hospital stay.
4. Any postoperative in-hospital organ injury.
5. All types of postoperative infections (including surgical site infections (both deep and superficial if recorded), organ-specific infections and sepsis).
6. Health-related quality of life outcome measures (eg, SF-36 (short form survey instrument - 36 items) or EQ-5D (EuroQol Research Foundation) scores)
7. Patient-reported outcome measures (eg, Crohn's disease activity index (CDAI)).

Postoperative or postintervention circulating vitamin D levels were not regarded as an outcome of interest, given the gross variability that exists as a result of different dosing strategies.

Search strategy and selection criteria

One of the authors (JM) conducted searches of the following databases on 11 December 2023: Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, MEDLINE (Ovid, from 1 January 1946 onwards), Embase (Ovid, from 1 January 1974 onwards), Web of Science (Science and Social Science Citation Index) and LILACS (online supplemental figure 1). The Cochrane sensitivity-maximising RCT filter[16] was applied to MEDLINE (Ovid), and adaptations of this were applied to the other databases, with the exception of CENTRAL. We also conducted a search of ClinicalTrials.gov (www.ClinicalTrials.gov) and the WHO International Clinical Trials Registry Platform Search Portal (apps.who.int/trialsearch/) for ongoing or unpublished trials. We imposed no restriction on the language of publication or publication status. We additionally reviewed the reference lists of all included studies and any relevant systematic reviews identified to identify any additional studies that had not been identified by the initial search. We also examined any relevant retraction statements and errata for the included studies.

Study selection

After the removal of duplicates, independent researchers (RM, SG, BK, JT, TM, RB, RZ, RV and LR) screened all titles and abstracts. Full texts were obtained for studies deemed eligible, and further screening was performed

when studies were deemed eligible. Disagreements were resolved by steering group consensus.

Data collection

Three independent researchers (SG, BK and JT) used a pre-piloted standardised online data extraction tool using Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia; available at www.covidence.org). The data collected included study and patient characteristics, indicators of study quality and the aforementioned primary and secondary outcomes. When RCTs had more than two arms, data were pooled from the separate treatment arms, where possible, or were treated as separate patient cohorts otherwise. Disagreements were resolved by steering group consensus.

Assessment of the risk of bias and quality of evidence

Researchers independently assessed the quality of all included trials by using the Cochrane Collaboration risk of bias tool.[16] They also examined the quality of the evidence for outcomes using the Jadad method.[17]

Data synthesis

The data were synthesised and tabulated in online supplemental tables 1–5. Owing to the interstudy heterogeneity in the reporting of data as well as differing assumptions of distribution for similar outcome measures, we were unable to pool the data for any of the outcomes of interest and perform quantitative meta-analyses.

Role of the funding source

There was no funding source for this study.

Patient and public involvement

None.

RESULTS

Literature review

We screened 4883 unique studies published between 1980 and 2023 and assessed 236 full-text articles after removing non-human, non-surgical studies (figure 1). Conference abstracts without complete reporting, review articles,

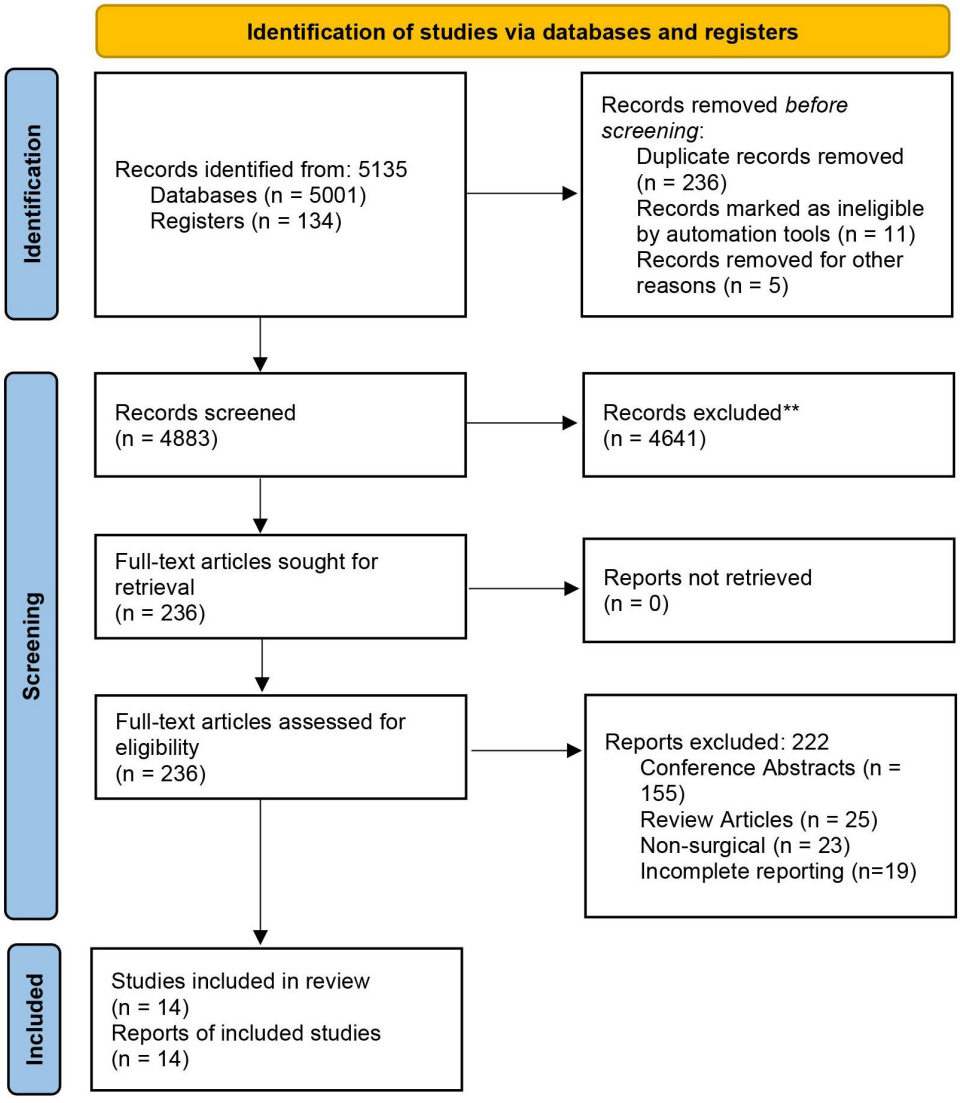

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analysis flow diagram.

outcomes of non-interest and incompletely reported papers were then excluded. This left 14 articles assessing 1982 patients for inclusion in the narrative systematic review, the details of which are reported in online supplemental tables 1–3 and summarised subsequently.

Characteristics of the included studies

All included studies had been published in the last 10 years (online supplemental table 1). Six studies[18–23] were from Europe and two from the USA.[24 25] Only 4 of the 14 studies[20 23 25 26] were multicentre, and the majority had no published protocol. All studies randomised patients into two arms (vitamin D supplementation vs control), although Hao *et al*[27] additionally divided patients into two cohorts by the relative decline of parathyroid hormone prior to randomisation; these were treated as two separate cohorts for analysis. The included studies focused on a wide range of patient conditions, including open heart surgery, cancer operations and both elective and emergency orthopaedic conditions requiring surgery (online supplemental table 2). Consequently, there was considerable heterogeneity in patient characteristics between studies, with the average age ranging from 31 to 67 years and the proportion of male patients from 14% to 90% across the study cohorts.

Three studies only included patients with vitamin D insufficiency, with the remainder including patients regardless of their preoperative vitamin D level. The timing of the intervention was highly variable, with patients commencing treatment between 1 day and 5 weeks preoperatively in nine studies and postoperatively in the remaining five studies (online supplemental table 3). In the vitamin D supplementation arms, the duration of treatment was also very heterogeneous, with three studies[19 23 28] administering a single dose, six using a short course (ie, <1 month) and a longer course used in the remaining five studies. Consequently, the dose of vitamin D also varied considerably, ranging from 1250 to 7500 mcg in the single-dose studies and effective daily doses ranging from 0.5 to 3750 mcg in those that administered a course of treatment. The majority of studies administered some form of placebo in the control arm, with three studies instead stating that they gave no treatment to control patients.

Bias assessment (online supplemental table 4) found the majority of studies to be low risk with respect to random sequencing, incomplete outcomes and selective reporting. Some studies had a high risk of bias with respect to blinding, generally those that did not administer a placebo to the control arm. Across all studies, the mean Jadad score was 4 (range: 1–5).

Primary outcome

Overall survival

Details of the outcomes reported by the included studies are summarised in online supplemental table 6. The primary outcome of this review, namely overall survival, was assessed by only a single study.[29] This study recruited patients undergoing surgery for digestive tract cancer, who were randomised at their first postoperative follow-up appointment (at a median of 24 days) to commence treatment with either vitamin D supplementation (n=251) or a placebo (n=166), which continued until the end of the trial. Over a median of 3.5 years of follow-up, no significant difference in overall survival was observed, with an HR for the vitamin D versus control arms of 0.95 (95% CI 0.57 to 1.57, p=0.83) and survival rates at 5 years of 82% and 81%, respectively. Additionally, the study assessed relapse-free survival as well as cancer-specific and non-cancer deaths separately and reported no significant differences between the vitamin D versus control arms for any of these secondary outcomes.

Secondary outcomes

Postoperative mortality

Short-term mortality rates were reported by four studies[23 28–30] (n=631 patients); however, there was inconsistency with how the outcome was defined. Naguib *et al*[30] reported in-hospital mortality, and Parekh *et al*[23] used 90-day survival. Hajimohammadebrahim-Ketabforoush *et al*[28] reported the mortality rate at 6 months, at which point there had been no deaths in either arm; hence, the postoperative mortality rates were also 0%. Urashima *et al*[29] did not explicitly state the postoperative mortality rate, instead reporting a Nelson-Aalen cumulative hazard curve of survival over the 6 years postrandomisation. Across the four studies, there were a total of only 12 postoperative deaths, with no study reporting a significant difference between arms. Data were not pooled owing to the different follow-up periods capturing early phase hazards across the four studies.

Length of hospital stay

Comparisons of length of hospital stay were reported for eight studies.[19 21 23 24 26–28 30] Of these, Hao *et al*[27] reported outcomes for two subgroups, defined by the relative decline of parathyroid hormone (≤70% and >70%), which were treated separately for analysis, giving a total of nine cohorts (n=1051 patients). Two studies reported significantly shorter lengths of hospital stay in the vitamin D arm, namely Hajimohammadebrahim-Ketabforoush *et al*[28] (median: 5 vs 8 days, p=0.008) and Naguib *et al*.[30] (mean: 8.0 vs 9.5 days, p=0.033). No significant differences were observed in the other studies, with the majority reporting near-identical averages in the two groups. The pooling of studies for this outcome was not performed for two reasons. Primarily, the fact that some studies summarised length of hospital stay as a median and IQR,[23 26 28] and others reported SD that was almost as large as the mean (eg, Barker *et al*.[24] control group: mean=8.0 days, SD=7.4) implied that the length of hospital stay likely followed a skewed distribution. As such, since meta-analysis of means assumes normality of the underlying distribution, pooling the data would have given unreliable results, likely overestimating the degree of variability. In addition, the considerable heterogeneity between studies, with averages in

the control group arm ranging from 2 to 13 days, would have added to the unreliability of such a pooled estimate.

Length of ICU stay

Four of the studies[23 24 28 30] included in the analysis of the length of hospital stay additionally reported the length of ICU stay (n=364 patients). Of these, significantly shorter stays in the vitamin D arm were again reported by Hajimohammadebrahim-Ketabforoush *et al*[28] (median: 1 vs 2 days, p=0.010) and Naguib *et al*[16] (mean: 54.5 vs 76.3 hours, p=0.044). No significant differences were detected in the other two studies, although both of these found a tendency for longer lengths of ICU stay in the vitamin D arm. For similar reasons as the length of hospital stay, the data across these four studies were not pooled for meta-analysis.

Quality of life

Only two studies reported quality of life outcomes and quantified this using different approaches; hence, no formal meta-analysis of this outcome was performed. Aberg *et al*[18] assessed patients using the SF-36 questionnaire 12 months after parathyroidectomy. They reported no significant differences between the vitamin D supplementation (n=66) and control (n=69) arms for any of the SF-36 domains, with median scores of 49 versus 51 (p=0.317) for the physical component and 53 versus 52 (p=0.868) for the mental component. De Bruyn *et al*[20] included patients undergoing ileocolonic resection from Crohn's disease, with the outcomes being the improvement in a range of quality of life scores between the preoperative and 6-month assessments. They reported no significant differences between the vitamin D supplementation (n=72) and control (n=71) arms for any of the scores analysed; for example, the mean change in the EQ-5D was 15.5 (SE=2.3) and 13.1 (SE=2.4), yielding p=0.48.

Other outcomes

The other outcomes assessed by the studies were all related to postoperative complications. These were highly heterogeneous and so could not be pooled; hence, no formal meta-analysis was performed. Only one study reported a significant difference in outcomes between the vitamin D supplementation and control arms, with Naguib *et al*[30] finding significantly lower rates of hospital-acquired infection in patients undergoing heart valve replacement surgery who received vitamin D supplementation (35.5% vs 56.1%, p=0.017). However, no significant differences were observed for the other complications that they considered, including myocardial infarction (p=0.831) and severe bleeding (p=0.653). Other studies assessed serious adverse events,[24] acute kidney injury,[31] acute respiratory distress syndrome[23] and patient-important complications,[25] all of which reported rates to be similar in the vitamin D and control groups, with no significant differences detected.

DISCUSSION

Several retrospective and observational studies have reported low perioperative vitamin D levels to be associated with a range of adverse outcomes in the postoperative patient.[8] In light of these findings, it is tempting to extrapolate that vitamin D supplementation could potentially improve postoperative outcomes. However, studies correlating vitamin D levels with outcomes are often subject to considerable confounding and selection bias, given that several risk factors for hypovitaminosis D are also associated with patient outcomes (eg, obesity and frailty). As such, observational associations between vitamin D levels and postoperative outcomes do not necessarily imply that vitamin D supplementation will result in improved outcomes. Consequently, there has recently been interest in the potential benefits of vitamin D supplementation in for critically ill patients. A recent meta-analysis by Shen *et al*[32] assessed the impact of vitamin D supplementation in critically ill patients and found no evidence of a significant survival benefit, but did find a significant reduction in the length of hospital stay. Additionally, a large-scale clinical trial in clinically ill, vitamin D-deficient patients found no significant benefit of vitamin D supplementation for any clinical outcomes assessed.[33]

In light of these findings, we felt that a similar investigation into the effect of vitamin D supplementation on the population of patients undergoing surgery was warranted. This was particularly pertinent due to the lack of consensus across the increasing number of studies in this area. The resulting systematic review highlights the need for robust experimental design, standardisation in the timing and dosing of supplementation intervention groups and explicit outcome reporting. In addition, a lack of studies with longer-term follow-up was identified, which is exemplified by the fact that only a single study reporting long-term overall survival was identified. Short-term postoperative survival was more commonly reported, with data being available from four studies.[23 28–30] However, the postoperative mortality rate in these studies was generally low, with a total of only 12 deaths in 631 patients. As such, all four studies were considerably underpowered to be able to detect a clinically meaningful difference in this outcome, leading to an inflated false-negative rate. Consequently, there were insufficient data to draw any reliable conclusions on the association between vitamin D supplementation and postoperative mortality. A meta-analysis of this outcome was not performed on account of the variability in the time at which postoperative mortality was assessed. Surgical mortality has traditionally been assessed at arbitrary intervals out to 1 year without an agreed optimum time point, as evidenced by the fact that all four studies reporting this outcome measured it at different time points. It has been suggested that surgery has the greatest impact on the risk of death when assessed closest to the time of the operation.[34] Parametric hazard function modelling by Sergeant *et al*[34] has shed more light on understanding time-varying

trends of mortality after coronary artery bypass graft (CABG) surgery and found that the instantaneous hazard of death remains elevated well past 90 days and stabilises around 180 days (6 months) postoperatively. It was deduced that a combination of early in-hospital mortality and 180-day mortality are the optimum time points at which to capture the early phase of the hazard of death post-CABG. This may well be relevant to major surgery on the whole, but without robust data capture, this is a large assumption, and further work would be required to identify the optimum timing of postoperative assessment of mortality rates for future studies.

Length of hospital stay was a commonly reported outcome, being included in eight studies. However, considerable heterogeneity was observed, with the wide range of different surgeries being assessed likely being a major contributor to this. Two studies reported a significant reduction in the vitamin D supplementation arm relative to controls. However, this was in contrast to the remaining studies, which generally reported similar averages in the two arms, generally with a negligible trend towards longer lengths of hospital stay in the vitamin D supplementation arm. Five studies[19 21 24 27 30] assumed a normal distribution when summarising the length of hospital stay and ICU stay[24 30] data, reporting these as means with SDs. However, in many cases, these statistics indicated that the underlying data likely followed a skewed distribution. For example, some SD values were of a similar magnitude to the mean, implying that some patients would be expected to have a negative length of hospital stay if the underlying distribution were actually normal. This is also supported by the fact that the other studies reported medians and IQRs, which are commonly used in the absence of a normal distribution. As such, pooling these studies would likely have given unreliable results, particularly since most standard meta-analysis models make the assumption of underlying normality.

The two studies reporting a significant difference in the length of hospital stay additionally found significant differences in the length of ICU stay. However, these were again inconsistent with the remaining studies, both of which showed a non-significant tendency for a longer length of stay in the vitamin D supplementation arm. As such, while a reliable formal meta-analysis was not possible for the reasons described previously, the considerable heterogeneity and inconsistency of the direction of any effect do not imply a consistent benefit of vitamin D supplementation for this outcome.

Of the other outcomes considered, quality of life was only reported in two studies, which found no significant difference between arms across a range of different measures. Naguib *et al* reported a significantly lower rate of hospital-acquired infection in the vitamin D supplementation arm, compared with controls, which also coincided with significantly shorter lengths of hospital and ICU stays in this arm. However, no other study reported data for this outcome, with no significant differences being detected for other complication-related outcomes that were reported. As such, the potential effect of vitamin D on infection-related outcomes is an area that may warrant further research.

It has been suggested that vitamin D status at the time of surgery is the most relevant predictor of long-term outcomes, compared with vitamin D status in the days to weeks after surgery and that minimal benefits can be gained by supplementation at the time of surgery.[8] This may go some way to explain the lack of significance in the majority of the studies included in this systematic review since most studies commenced vitamin D supplementation either shortly before or after the index surgery. As such, it is possible that this would have given insufficient time for the supplemental vitamin D to be absorbed and to have positive effects before the physiological insult of surgery. Consequently, in future studies, the commencement of vitamin D supplementation earlier in the preoperative period may result in greater benefit. However, this will only be applicable to elective non-urgent surgeries, which take a sufficiently long period from diagnosis to surgery.

Vitamin D supplementation has shown benefits in low vitamin D groups in terms of reduced postoperative infection and hospital and ICU stays in cardiac surgery[30]and reduced postoperative atrial fibrillation rates following CABG[19] and improved survival following digestive tract cancer resection.[29] Meta-analytical data hypothesised that vitamin D supplementation would be of benefit to vitamin D-deficient patients with lung cancer with respect to survival.[29] The benefit of vitamin D in deficient patients may vary across different cancer types. It is worth noting that the perceived benefit of vitamin D supplementation in low-baseline subgroups must be interpreted with caution, particularly when the primary outcome measures in the overall cohort are null, along with the potential for type I error owing to multiple comparison testing. Future trial designs where vitamin D status is manipulated in the perioperative period must measure baseline levels preoperatively and seek to either titrate vitamin D therapy according to a specific circulating concentration or aim for fixed dosing only if there is adequately powered subgroup stratification according to the baseline level. Moreover, normalising individual vitamin D concentrations and determining a vitamin D response index to quantify perceived responses to treatment based on genomic susceptibility are also likely to be of importance.[35]

Vitamin D supplementation has not been shown to result in a lower incidence of cancer or cardiovascular events when compared with control.[36] The dose of vitamin D used in the included trials varied between studies, such that it was difficult to compare equivalent daily doses owing to different treatment regimens and dosing intervals. A similar review has found this to be a reason behind the difficulty in determining an effective daily dose of vitamin D supplementation.[12] The authors asserted that long-term vitamin D status is expected to be a much more accurate, reliable and important clinical

parameter compared with a daily dose of vitamin D supplementation. Allied to this, the whole premise of vitamin D dosing is meaningless unless it can be shown to have a proven effect on serum vitamin D levels at long-term follow-up. In order to elevate serum 25(OH)-D, patients would need daily supplementation for at least 3 months prior to an operation. The earliest preoperative dosing time was 5 weeks,[22] with other studies dosing in the postoperative period,[18 20 25 27 29] which is unlikely to have an impact on serum 25(OH)-D levels. Single high-dose bolus supplementation, as performed in some of the included trials,[19 23 28] may well raise serum 25(OH)-D levels rapidly but will also trigger catabolic feedback enzymes that negate the likely beneficial effects of vitamin D.[4 5] So, while bolus dosing is tempting in surgical settings due to short inpatient stays, it is less likely to be effective. A meaningful trial in this area should account for all these factors.

Numerous studies have reported several benefits of vitamin D supplementation in different surgical settings without any consistency, which warrants the supposition that a biological effect may not exist. The observed improvement in outcomes in the low vitamin D groups may be attributable to chance. Focusing on a specific question with a specific outcome that has biological rationale should be the aim of future randomised trials in this area, taking into account all design factors highlighted above.

Limitations

The primary limitation was the heterogeneity of the included studies, which assessed a variety of doses, durations, preparations (vitamin D2 vs vitamin D3 preparations) and timings of vitamin D supplementation in a range of surgical interventions and within an assortment of patient populations. As such, if the effectiveness of vitamin D supplementation varied across these factors, then it is possible that a clinically relevant benefit within a specific scenario may have been missed. Subgroup analyses to identify such an effect were not possible due to the small number of studies.

The studies also reported a range of different outcomes, making it difficult to find similar studies to pool using meta-analysis. For the outcomes of lengths of hospital and ICU stay, it was neither possible nor appropriate to pool the data owing to the inherent weakness in trying to conform the reported data to distribution assumptions. Some studies reported a median and IQR, but others did not; estimating means and SD from this data would have incurred suboptimal accuracy, particularly where the studies reported statistics without decimal places. If the distribution were instead skewed, then this would lead to the SDs being inflated, resulting in an overestimate of the variability in the data and an inflated false-negative rate in the meta-analysis models. For postoperative mortality, the small number of studies and low event rate will have resulted in low statistical power, meaning that only large differences would have been detectable. The overall quality of reporting outcomes needs to be improved with adherence to robust clinical guidance.[37 38] Meaningful analysis is likely to require population-level data with robust primary source data for meta-analysis.

Conclusion

Overall, this systematic review did not identify clear evidence of the benefit of vitamin D supplementation on overall survival, postoperative mortality or the length of the ICU or hospital stay. Further investigation is warranted in order to determine if there is a long-term effect on survival in postoperative patients and whether there is a specific impact on particular patient subgroups based on their baseline vitamin D status and the type of surgery they are undergoing.

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Contributors All authors contributed to this piece of work. AP, EJC and EL designed the study, gathered the data and wrote the manuscript. AJP, JH and EL carried out the data analysis. RM, BK, SG, JT, TM, RB, RZ, JM, RV and LR conducted the initial data analysis, interrogation of methodology and refined the search strategy. PB, DJP, DT MH, BN and EL provided analytical support and supervised the writing of the manuscript. AJP is the guarantor.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. All data relevant to the study are included in the article or uploaded as supplementary information.

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