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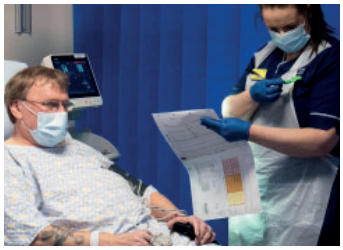

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ORIGINAL RESEARCH: SPECIAL PAPER Reproducibility study

Validity of data extraction in evidence synthesis practice of adverse events

Xu C, Yu T, Furuya-Kanamori L, et al

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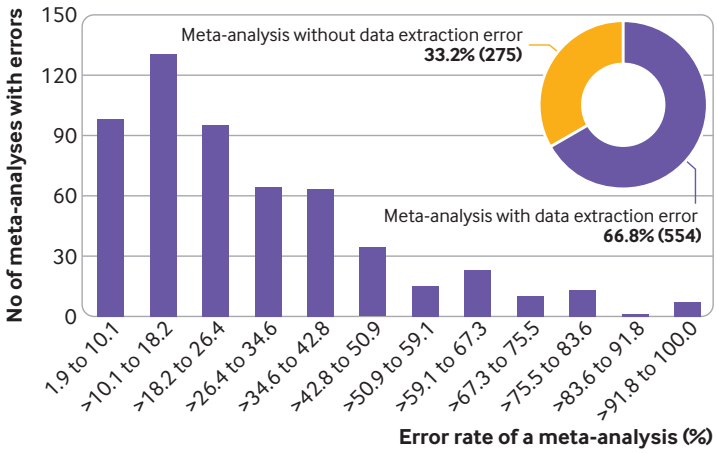
Study question How frequently do data extraction errors occur in systematic reviews of adverse events and to what extent would these errors affect the results?

Methods PubMed was searched for systematic reviews of randomised controlled trials for healthcare interventions, with adverse events as the exclusive outcome, published between 1 January 2015 and 1 January 2020. Metadata from the randomised controlled trials were extracted from the systematic reviews by four authors. The original data sources (eg, full text and ClinicalTrials.gov) were then referred to by the same authors to replicate the data used in these meta-analyses. Data extraction errors were summarised at study level, meta-analysis level, and systematic review level. The potential impact of such errors on the results was further investigated.

Study answer and limitations A total of 201 systematic reviews with 829 pairwise meta-analyses were included. In 554 (66.8%) of the 829 meta-analyses, at least one study had data extraction errors; 171 (85.1%) of 201 systematic reviews had at least one meta-analysis with data extraction errors. Impacts were analysed based on 288 meta-analyses. Data extraction errors led to 10 (3.5%) of the 288 meta-analyses changing direction of the effect and 19 (6.6%) of the 288 meta-analyses changing the significance of the P value. Meta-analyses with two or more different types of errors were more susceptible to these changes. This study only focused on systematic reviews of randomised controlled trials; however, because the sample sizes of the trials tended to be small, the impact might be exacerbated.

What this study adds Systematic reviews of adverse events potentially have serious issues in terms of the reproducibility of the data extraction, and these errors can mislead the conclusions.



Data extraction errors at meta-analysis level. Bar plot is based on studies with data extraction errors (n=554). Error rate within a meta-analysis is calculated by the number of studies with data extraction errors against the total number of studies within a meta-analysis

Funding, competing interests, and data sharing This study was not funded and no competing interests are declared. Data can be obtained from the corresponding author on request.

Vitamin D and risk of type 2 diabetes

ORIGINAL RESEARCH Randomised controlled trial

Effect of active vitamin D treatment on development of type 2 diabetes

Kawahara T, Suzuki G, Mizuno S, et al

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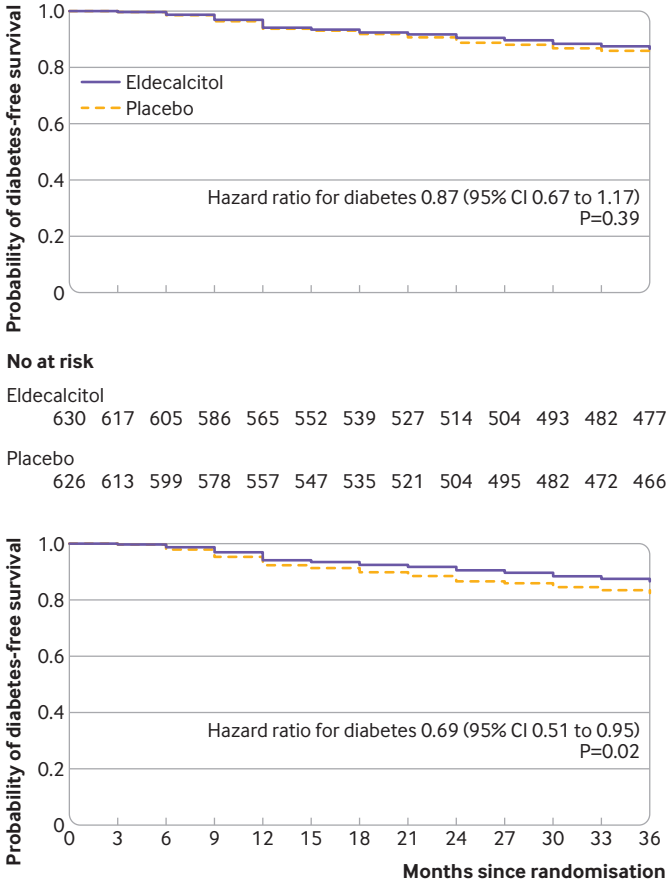
Study question Can eldecalcitol, an active vitamin D analogue, reduce the development of type 2 diabetes among adults with pre-diabetes?

Methods This double blinded, multicentre, placebo controlled trial in Japan randomly assigned individuals aged 30 years and older who had impaired glucose tolerance to receive active vitamin D (eldecalcitol 0.75 µg per day; n=630) or matching placebo (n=626). The study took place between June 2013 and August 2019. The primary endpoint was the incidence of type 2 diabetes. Prespecified secondary endpoints were the regression to normoglycaemia and the incidence of type 2 diabetes after adjustment for confounding factors at baseline. Bone densities and bone and glucose metabolism markers were also assessed.



Kaplan-Meier curves for survival free from type 2 diabetes among adults with impaired glucose tolerance. Before (top) and after (bottom) adjustment for 11 covariables

Funding, competing interests, and data sharing The study was supported by a grant from Kitakyushu Medical Association. No conflicts of interest are reported. Relevant anonymised patient level data are available from the corresponding author on reasonable request.

Study registration UMIN Clinical Trials Registry UMIN000010758.

COMMENTARY Supplements had no clinically meaningful effect in the latest trial

Weight loss and exercise decrease risk of progression to type 2 diabetes mellitus (T2DM) in people with impaired glucose tolerance.[4-7] However, lifestyle interventions are difficult to sustain.[8] The possibility that a vitamin might prevent T2DM development is attractive to both healthcare professionals and patients. Interest in vitamin D is based on epidemiological evidence showing an association between low vitamin D status and increased risk for T2DM.[9]

A link is also biologically plausible: pancreatic β cells have vitamin D receptors, and animal studies show improved production of and sensitivity to insulin associated with vitamin D treatment[10 11]; also, vitamin D has immunomodulatory effects and may modify risk of T2DM by suppressing inflammation, a known risk factor.[12] Until recently, however, scant evidence has been available from interventional studies.

The linked paper by Kawahara and colleagues,[13] which follows a preliminary report from the same group published in 2018,[14] provides interventional evidence that eldecalcitol, an analogue of the biologically active form of vitamin D, does not reduce risk of diabetes in a group of older Japanese participants with impaired glucose tolerance. The secondary outcome, reversion to normoglycaemia, was also not statistically significantly different between treatment groups.

In this double blind, placebo controlled trial, 1256 participants with impaired glucose tolerance took either eldecalcitol 0.75 µg daily or matched placebo.[13] Participants had a mean age of 61.3 years, and 43.6% had baseline serum 25-hydroxyvitamin D concentrations ≤50 nmol/L, defined as risk for deficiency in Japan and the USA and insufficiency in the UK.[15-17]

Participants attended clinic every three months for three years to track incidence of diabetes using fasting plasma glucose concentration and glycated haemoglobin. Serum 25-hydroxyvitamin D, 1,25-hydroxyvitamin D, and bone alkaline phosphatase concentrations, and lumbar spine and femoral neck bone mineral densities, were measured annually. The authors report a significant increase in both lumbar spine and femoral neck bone mineral densities among those taking eldecalcitol.

Further exploration

Post hoc analyses suggested that eldecalcitol decreased progression to T2DM in participants with impaired insulin secretion. However, the clinical relevance of this finding

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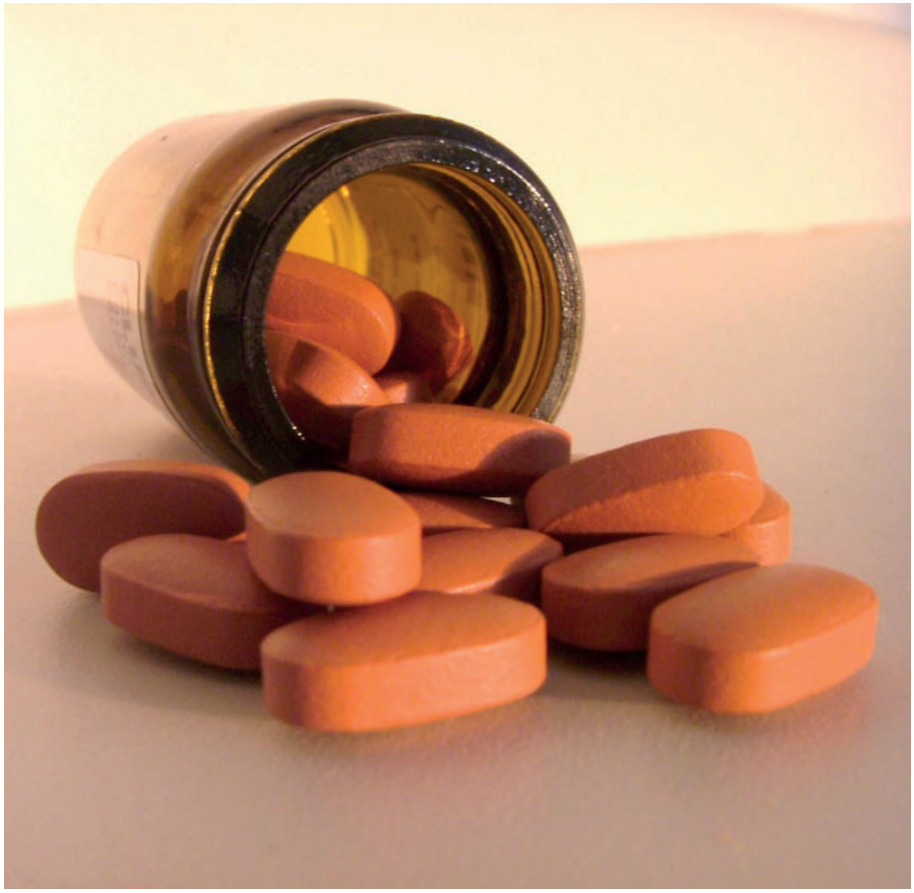
Study answer and limitations During a median follow-up of 2.9 years, 79/630 (12.5%) participants in the eldecalcitol group and 89/626 (14.2%) in the placebo group developed type 2 diabetes (hazard ratio 0.87, 95% confidence interval 0.67 to 1.17). Regression to normoglycaemia was achieved in 145/630 (23.0%) participants in the eldecalcitol group and 126/626 (20.1%) in the placebo group (hazard ratio 1.15, 0.93 to 1.41). Bone mineral densities of the lumbar spine and femoral neck and serum osteocalcin concentrations significantly increased with eldecalcitol compared with placebo (all P<0.001). Eldecalcitol 0.75 µg is the standard dose administered to treat osteoporosis, rickets, and hypocalcaemia in Japan, but whether it was an appropriate dose for prevention of diabetes in the study context is unclear.

What this study adds Although treatment with eldecalcitol did not significantly reduce the incidence of diabetes among people with pre-diabetes, the results suggested the potential for a beneficial effect of eldecalcitol on those with insufficient insulin secretion. Treatment with eldecalcitol was effective in increasing bone mineral densities and serum osteocalcin concentrations.



Findings do not support use of an active vitamin D analogue to reduce the risk of progression to T2DM

remains unclear. Results from post hoc analyses should be considered hypothesis generating only, and further exploration is needed.

Reassuringly, vitamin D specific adverse events such as hypercalcaemia, hypercalciuria, and nephrolithiasis were rare, with no significant differences between groups, although participants with renal insufficiency or any degree of hypercalcaemia were excluded from the trial.

Kawahara and colleagues' findings do not support use of an active vitamin D analogue to reduce the risk of progression to T2DM; their results are consistent with two other recent randomised controlled trials also reporting that vitamin D supplementation did not reduce risk of progression to T2DM in people with impaired glucose tolerance.[18 19]

The new trial was well conducted, with rigorously defined and tested diagnostic criteria, and of sufficient duration, but it may have been underpowered to detect a small effect. A recent meta-analysis of intervention trials found a significant reduction in risk of T2DM of approximately 10% among participants given vitamin D supplements—a difference too small to be detected by the new trial, which was powered to find differences of 36% or more.[20] Although a 10% risk reduction is modest, it may be valuable at the population level and justifies further study.

Vitamin D deficiency and many chronic diseases, including T2DM, share important risk factors, including older age and obesity. Unaccounted for confounding factors may explain the discordance between epidemiological evidence of an association and negative or weak findings in interventional trials; vitamin D deficiency may simply be a marker for disease rather than a cause.

Several questions remain, including whether vitamin D supplementation may be more effective for particular populations, such as people of colour or people with severe vitamin D deficiency (≤25 mmol/L 25-hydroxyvitamin D), and whether longer duration of treatment or younger age at initiation might be more beneficial.

Until further data are available from high quality randomised trials, healthcare professionals should continue to discuss with patients the musculoskeletal health benefits of vitamin D and support them to achieve and maintain lifestyle changes that, although challenging to sustain, are known to decrease development of T2DM.

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Gestational diabetes mellitus and adverse pregnancy outcomes

Ye W, Luo C, Huang J, Li C, Liu Z, Liu F

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Study question What is the association between gestational diabetes mellitus and adverse pregnancy outcomes?

Methods A systematic review and meta-analysis was conducted. Web of Science, PubMed, Medline, and Cochrane were searched from 1 January 1990 to 1 November 2021 for cohort studies and control arms of trials reporting complications of pregnancy in women with gestational diabetes mellitus. Based on the use of insulin in each study, studies were divided into three subgroups: no insulin use (participants never used insulin during the course of the disease), insulin use (different proportions of participants were treated with insulin), and insulin use not reported. Subgroup analyses were performed based on the status of the country (developed or developing), the quality of the study, diagnostic criteria, and screening method. Meta-regression models were applied based on the proportion of participants who had received insulin.

Study answer and limitations 156 studies with 7 506 061 pregnancies were included. In studies with no insulin use, when adjusted for confounders, women with gestational diabetes mellitus had increased odds of caesarean section (odds ratio 1.16, 95% confidence interval 1.03 to 1.32), preterm delivery (1.51, 1.26 to 1.80), low one minute Apgar score (1.43, 1.01 to 2.03), macrosomia (1.70, 1.23 to 2.36), and an infant born large for gestational age (1.57, 1.25 to 1.97). In studies with insulin use, when adjusted for confounders, the odds of an infant born large for gestational age (odds ratio 1.61, 1.09 to 2.37), or with respiratory distress syndrome (1.57, 1.19 to 2.08) or neonatal jaundice (1.28, 1.02 to 1.62), or requiring admission to the neonatal intensive care unit (2.29, 1.59 to 3.31) were higher in women with gestational diabetes mellitus than in those without diabetes. The findings contribute to a more comprehensive understanding of the adverse outcomes of pregnancy related to gestational diabetes mellitus. Adjustment for at least one confounder had limited power to deal with potential confounding effects. Accurately determining the degree of diabetes control in participants with gestational diabetes mellitus was difficult.

What this study adds When adjusted for confounders, gestational diabetes mellitus was significantly associated with pregnancy complications.