**Original Research** Systematic review and network meta-analysis

**Choice of implant combinations in total hip replacement**


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**Study question** What is the most effective implant combination for implant survival after primary total hip replacement?

**Methods** This was a systematic review and network meta-analysis of published randomised controlled trials comparing the effectiveness of different hip implant combinations. Implant combinations were defined by bearing surface materials (metal-on-polyethylene, ceramic-on-polyethylene, ceramic-on-ceramic, or metal-on-metal), head size (large ≥36 mm or small <36 mm), and surgical fixation technique (cemented, uncemented, hybrid, or reverse hybrid). The reference implant was the metal-on-polyethylene, small head, cemented combination. The primary outcome was revision surgery after primary total hip replacement.

**Study answer and limitations** Newer implant combinations were not found to be superior to the reference implant combination for revision surgery or clinical outcomes. Resurfacing hip replacements and metal-on-metal, small head, cemented implants increased the risk of revision surgery compared with the reference implant combination. For example, the hazard ratio for revision surgery with metal-on-metal implants compared with the reference implant was 4.4 (95% credible interval 1.6 to 16.6). The hazard ratio for requiring resurfacing for metal-on-metal implants compared with the reference implant was 12.1 (2.1 to 120.3). Seventy seven randomised controlled trials were included in the review, with follow-up from 3 months to 13 years (median 2 years); 15 studies (3177 hips) provided data for the network meta-analysis. The results were limited by the low number of studies with long term follow-up, and poor reporting across studies.

**What this study adds** The findings are in line with observational evidence from joint registries, suggesting that resurfacings and metal-on-metal implant combinations increase the risk of revision surgery after primary total hip replacement compared with the reference metal-on-polyethylene, small head, cemented implant combination; but no evidence that other implant combinations are superior to the reference implant combination was found.

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Low vitamin D levels as a risk factor for cancer

**ORIGINAL RESEARCH** Mendelian randomisation study

**Circulating vitamin D concentration and risk of seven cancers**

Dimitrakopoulou VI, Tsilidis KK, Haycock PC, et al, on behalf of GECCO, PRACTICAL, and GAME-ON Network (CORECT, DRIVE, ELLIPSE, FOCA-CAC, TRICL-ILCCO)

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**Study question** Are circulating concentrations of vitamin D causally associated with risk of colorectal, breast, prostate, ovarian, lung, and pancreatic cancer, and neuroblastoma?

**Methods** To overcome limitations of conventional observational research and randomised trials and determine whether vitamin D status is linked to disease or just a correlate marker of overall health, the authors used Mendelian randomisation and estimated associations between four single nucleotide polymorphisms associated with vitamin D and risk of seven cancers. A total of 70 563 cancer cases and 84 418 controls were used from large genetic epidemiology networks, including 22 898 cases of prostate cancer, 15 748 cases of breast cancer, 12 537 cases of lung cancer, 11 488 cases of colorectal cancer, 4369 cases of ovarian cancer, 1896 cases of pancreatic cancer, and 1627 cases of neuroblastoma.

**Study answer and limitations** There was little evidence that the multi-polymorphism score indicating 25-hydroxyvitamin D (25(OH)D) concentrations was associated with the risk of any of the seven cancers. Specifically, the odds ratios per 25 nmol/L increase in genetically determined concentrations were 0.92 (95% confidence interval 0.76 to 1.10) for colorectal cancer, 1.05 (0.89 to 1.24) for breast cancer, 0.89 (0.77 to 1.02) for prostate cancer, and 1.03 (0.87 to 1.23) for lung cancer. The study was powered to detect effect sizes of moderate magnitude for most cancer outcomes, but the existence of causal clinically relevant effects of low magnitude cannot be excluded.

**What this study adds** These results provide little evidence of a linear causal association between circulating vitamin D concentration and risk of colorectal, breast, prostate, ovarian, lung, and pancreatic cancer, and neuroblastoma.

**Funding, competing interests, data sharing** National Cancer Institute/National Institutes of Health; World Cancer Research Fund International Regular Grant Programme; Cancer Research UK. No competing interest to declare and no data to share.

**COMMENTARY** New evidence challenges the benefits of vitamin D supplementation for cancer prevention

Arguably, to date the most clinically effective way to reduce the burden of cancer has been through primary prevention. One promising such strategy has been to target vitamin D insufficiency as epidemiological and animal studies have found that low levels of vitamin D are associated with an increased risk of cancer.

Furthermore, vitamin D insufficiency affects 40% of the general population, is easily diagnosed by a simple blood test, and can be treated safely and inexpensively. This may partially explain the 60-fold increase in the use of vitamin D supplements in the US general population between 2000 and 2014, where 18% currently take ≥1000 IU of vitamin D daily.

**Limiting bias**

Yet the most prudent way to test the efficacy of vitamin D would be through large scale randomised controlled trials because observational studies may be biased by residual confounding (vitamin D levels are confounded by known drivers of cancer risk, such as smoking, obesity, and the healthy user effect). Yet such trials are cumbersome and rely on the public purse, as vitamin D is not patentable. In this issue Dimitrakopoulou and colleagues present new evidence that is clinically relevant in the absence of high quality trial data.

The authors used Mendelian randomisation, a study design that greatly limits potential bias from confounding since the genetic determinants of vitamin D level are randomised at conception and are not associated with known vitamin D confounders. These genetic variants provide the opportunity to vary vitamin D levels in the population free from confounding, much like randomisation does in clinical trials. Furthermore, as they are allocated at conception and remain stable over the lifetime, these variants provide an estimate of the causal effect of decades of lowered vitamin D level. The most troubling assumption of such studies is that the genetic determinants act on cancer only through vitamin D levels. Bias from this assumption is not likely here, however, since all genetic variants are in or near genes that have known biological functions with a direct impact on vitamin D level.

In their Mendelian randomisation analysis, Dimitrakopoulou and colleagues used four common genetic alleles that were strongly associated with lowered levels of 25-hydroxyvitamin D, the commonly measured biomarker of vitamin D status in blood, in a cohort of almost 34 000 individuals. They examined if these alleles were associated with a reduced risk of seven different types of cancer (colorectal, breast, prostate, ovarian, lung, pancreatic, and neuroblastoma) in separate large epidemiological cohorts, together comprising 70 563 cancer cases and 84 418 controls. Their study had sufficient statistical power to detect moderate effects on cancers (with minimum odds ratios between 1.15 and 1.5) for a genetically determined 25 nmol/L decrease in 25-hydroxyvitamin D concentration. In general, their results failed to provide evidence of a causal association between reduced vitamin D level and risk of cancer, for all seven types of cancer studied, as well as for some cancer subtypes. These results persisted despite sensitivity analyses probing the assumptions of Mendelian randomisation.

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Discordant results

Although convincing, the study by Dimitrakopoulou and colleagues is limited by its insufficient power to detect smaller effects of vitamin D in cancer. This might explain the discordance between their results and those of a recent Mendelian randomisation study examining the association of genetically lowered vitamin D level with ovarian cancer on 10065 cases and 21 654 controls, which showed an odds ratio of ovarian cancer of 1.27 (95% confidence interval 1.06 to 1.51) per genetically determined 20 nmol/L decrease in 25-hydroxyvitamin D concentration. Both Mendelian randomisation studies tested the linear effect of vitamin D level in the general population (what would be expected if small doses of vitamin D supplementation were used broadly in the population), but they do not give insight into non-linear effects—that is, whether correction of more profound vitamin D deficiency can prevent cancer. This is relevant because the effects of vitamin D on bone are predominant at extremely low 25-hydroxyvitamin D levels. Despite these limitations, the study by Dimitrakopoulou and colleagues provides direct insight into what has recently become common clinical practice: the use of vitamin D supplementation in people with generally normal vitamin D levels.

Effect size

Can we now cross common cancers off the list of vitamin D’s beneficial effects? Current evidence suggests that we cannot do so for ovarian cancer. Also, we cannot exclude small effects and effects unique to frank vitamin D deficiency. Nevertheless, it seems unlikely that vitamin D exerts large effects on the cancers tested. This evidence suggests that trials testing these hypotheses would need enormous samples.

It thus seems plausible that some of the previously attributed effect sizes may be influenced by confounding. Since large scale, long duration randomised controlled trials for vitamin D supplementation are not currently feasible, the results from Dimitrakopoulou and colleagues provide useful data for the millions of people who have recently started taking vitamin D supplements. Mendelian randomisation studies in even larger cancer cohorts will provide more definitive answers—and more rapidly than clinical trials.

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ORIGINAL RESEARCH Umbrella review of the literature

Obesity and gynaecological and obstetric conditions
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Study question What is the strength and validity of the evidence of an association between adiposity and the risk of developing any obstetric or gynaecological condition, and are interventions aimed at reducing adiposity associated with risk?

Methods Umbrella review of meta-analyses of observational and interventional studies assessing the association between adiposity and development of any obstetric or gynaecological condition. The evidence from systematic reviews of observational studies was graded as strong, highly suggestive, suggestive, or weak after application of a comprehensive set of statistical criteria. Intervventional studies were assessed separately.

Study answer and limitations Of the 144 meta-analyses of observational cohort studies, there was strong evidence for an association with eight obstetric or gynaecological outcomes in 11 (8%) meta-analyses: higher risk of endometrial cancer, ovarian cancer, antenatal depression, total and emergency caesarean section separately, pre-eclampsia, fetal macrosomia, and low Apгар score (at one minute). The summary effect estimates ranged from 1.21 (95% confidence interval 1.13 to 1.29) for an association between a 0.1 unit increase in waist to hip ratio, and the risk of endometrial cancer up to 4.14 (3.61 to 4.75) for the risk of pre-eclampsia for BMI >35 compared with ≤25. Only three out of these outcomes were also assessed in meta-analyses of trials evaluating weight loss interventions. These showed a significantly reduced risk of total caesarean section and pre-eclampsia but not of fetal macrosomia. This review relied on previously published meta-analyses, and the assessment of the quality of primary studies was beyond the scope of the review.

What this study adds This umbrella review is a comprehensive critical appraisal of the literature exploring the strength and validity of the published associations between obesity, interventions to reduce it, and the risk of obstetric and gynaecological morbidity. Among 258 observational or interventional meta-analyses assessing the association between obesity and the incidence of 84 different obstetric or gynaecological outcomes, there was strong evidence to support the association of only eight outcomes. Although other associations could be genuine as well, there is still uncertainty about them.

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