# research


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**ORIGINAL RESEARCH** Prospective study in UK Biobank

## Association of habitual glucosamine use with risk of cardiovascular disease

Ma H, Li X, Sun D, et al

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**Study question** Is habitual glucosamine use associated with risk of cardiovascular disease (CVD) events?

**Methods** In this prospective cohort study, 466 039 participants from the UK Biobank who did not have CVD at baseline completed a questionnaire on supplement use, which included glucosamine. These participants were enrolled from 2006 to 2010 and followed up to 2016. The main outcome measures were incident CVD events, including CVD death, coronary heart disease, and stroke.

**Study answer and limitations** During a median follow-up of seven years, there were 10 204 incident CVD events, 3060 CVD deaths, 5745 coronary heart disease events, and 3263 stroke events. After adjustment for age, sex, body mass index, race, lifestyle factors, dietary intakes, drug use, and other supplement use, glucosamine use was associated with a significantly lower risk of total CVD events (hazard ratio 0.85, 95% confidence interval 0.80 to 0.90), CVD death (0.78, 0.70 to 0.87), coronary heart disease (0.82, 0.76 to 0.88), and stroke (0.91, 0.83 to 1.00). A limitation of this study was its observational nature, and so it was difficult to separate the effects of a healthy lifestyle from the habitual use of supplements.

**What this study adds** Habitual use of glucosamine supplement to relieve osteoarthritis pain might also be related to lower risks of CVD events.

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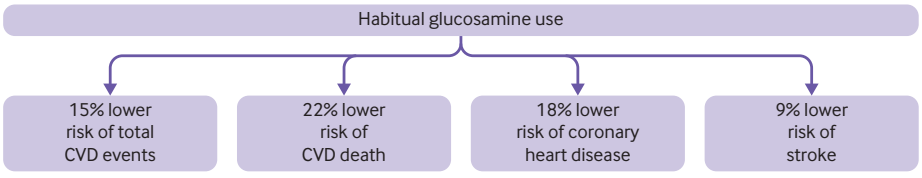


Association of habitual glucosamine use with risk of cardiovascular disease (CVD)

# Tramadol for postoperative pain

**ORIGINAL RESEARCH** Cohort study

## Chronic use of tramadol after acute pain episode

Thiels CA, Habermann EB, Hooten WM, Jeffery MM

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**Study question** What is the risk of prolonged opioid use in patients receiving tramadol compared with other short acting opioids?

**Methods** This was an observational study of opioid-naive patients undergoing elective surgery, using the US commercial and Medicare Advantage insurance administrative claims data (OptumLabs Data Warehouse) from 1 January 2009 to 30 June 2018. The primary outcome was the risk of persistent opioid use after discharge for patients treated with tramadol alone versus other short acting opioids, using three commonly used definitions of prolonged opioid use from the literature: additional opioid use, persistent opioid use, and the CONSORT definition.

**Adjusted risk ratios* (95% CIs) and P values† for persistent opioid use (three definitions) in patients who received tramadol only, tramadol and another short acting opioid, or any long acting opioids (reference group: short acting opioids excluding tramadol)**

| Opioid type | Additional opioid use after surgery‡ | Persistent opioid use after surgery§ | CONSORT definition of opioid dependence¶ |
|---|---|---|---|
| Other short acting | Reference | Reference | Reference |
| Tramadol only | 1.06 (1.00 to 1.13); P=0.049 | 1.47 (1.25 to 1.69); P<0.001 | 1.41 (1.08 to 1.75); P=0.013 |
| Tramadol plus short acting | 1.05 (0.96 to 1.14); P=0.261 | 1.04 (0.86 to 1.21); P=0.685 | 1.40 (1.05 to 1.74); P=0.022 |
| Any long acting | 0.95 (0.87 to 1.03); P=0.218 | 1.18 (1.02 to 1.35); P=0.029 | 1.69 (1.36 to 2.02); P<0.001 |

*Risk ratios calculated as ratio of predictive margins after logistic regression including covariates of year, surgery, female sex, beneficiary type, race/ethnicity, census division, age category, categorical measurement of morphine milligram equivalents at discharge, and flags for each of Elixhauser comorbidities.
†P values from hypothesis test that risk ratio does not equal 1.
‡At least one opioid fill 90-180 days after surgery.
§Any span of opioid use starting in 180 days after surgery and lasting ≥90 days.
¶Opioid use episode starting in 180 days after surgery that spans ≥90 days and includes either ≥10 opioid fills or ≥120 days' supply of opioids.

**COMMENTARY** Prescribe with care and review treatment regularly

For newspapers, broadcasters, and even researchers, the US opioid crisis is a story that keeps on giving. This modern day scourge, killing 130 Americans a day,[1] is a health catastrophe, but just as its antecedents and evolution are infinitely complicated, broad brush comments and solutions are unhelpful in turning the tide of opioid related deaths in North America and in mitigating against disaster in other countries where opioids are liberally prescribed.[2]

In the linked paper, Thiels and colleagues should be applauded for their focused and cautiously interpreted study of the relation between opioids prescribed after surgery and long term use.[3]

They followed the opioid use trajectory of 357 844 people treated with opioids following operations. Although tramadol was infrequently prescribed, patients receiving it were more likely to fill a further opioid prescription using one of three definitions of prolonged use.

### Altered perception

By showing that prescription of tramadol was associated with an increased risk of later opioid use compared with other opioids, the authors dispel the perception of tramadol as "opioid-lite." They call for appropriate scheduling of the drug and advocate caution in prescribing it.

In the UK, tramadol was licensed in 1994 for the treatment of moderate to severe pain and was marketed in hospitals for treating acute pain. With little further promotion, sales of tramadol rose steadily. Tramadol's low intrinsic affinity for the μ-opioid receptor suggested that side effects, particularly respiratory depression and the propensity for addiction and misuse, would be minimal.

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**Showing that prescription of tramadol was associated with an increased risk of later opioid use dispels the perception of tramadol as "opioid-lite"**

The principal metabolite of tramadol (O-desmethyltramadol), however, has much greater receptor potency, and rapid metabolisers of the drug may be at greater risk. Tramadol also inhibits monoaminergic reuptake, increasing synaptic noradrenaline (norepinephrine) and serotonin. This action accounts for additional analgesic effects but also extra adverse effects and withdrawal symptoms.[4]

This dual action made tramadol a popular choice for treating persistent pain, as the multiplicity of neurochemical pain signalling systems suggest that so-called "rational polypharmacy" is a logical approach.[5] Emerging concerns about use of conventional "strong" opioids nudged prescribers to suggest apparently less potent alternatives, and the withdrawal of co-proxamol, along with concerns about COX-2 inhibitors and more recently conventional non-steroidal anti-inflammatory drugs, gave tramadol a clear run without competition. From the early days of tramadol prescribing, tramadol related deaths rose steadily, and in consequence the drug was reclassified as a schedule 3 controlled drug in the UK in 2014.[6 7]

So how should we position tramadol in the repertoire of pain management? For long term pain, little evidence exists for the effectiveness of any opioid, including tramadol, beyond the duration of a clinical trial.[8] Opioids probably help fewer than one in 10 patients treated with these drugs for chronic pain. But the small proportion who do get meaningful pain relief also experience improvements in quality of life.[9] Because of this, opioids and other marginally effective medicines remain in the game.

**Study answer and limitations** Receipt of tramadol alone was associated with a 6% increase in the risk of additional opioid use relative to people receiving other short acting opioids (risk ratio 95% confidence interval 1.00 to 1.13; risk difference 0.5 percentage points), 47% increase in the adjusted risk of persistent opioid use (1.25 to 1.69; 0.5 percentage points), and 41% increase in the adjusted risk of a CONSORT chronic opioid use episode (1.08 to 1.75; risk difference 0.2 percentage points). The findings of this study are limited to commercially insured and Medicare Advantage patients in the US, and other aspects of the safety profile of tramadol were not studied.

**What this study adds** People receiving tramadol alone after surgery had similar to somewhat higher risks of prolonged opioid use compared with those receiving other short acting opioids. Providers should use caution when prescribing tramadol in the setting of acute pain.

Funding, competing interests, and data sharing This study had no external funding. OptumLabs data are available for research through a virtual data warehouse, but the authors are not able to distribute the data.

Medicines are not the mainstay of long term pain management, but if tried they should be prescribed with caution and stopped within two weeks if the patient reports no benefit. Patients treated for longer need regular review to assess continued efficacy.[10]

### Acute pain

By contrast, opioids have an important and established role in the management of severe acute pain. Challenges arise when patients leave the closely supervised hospital environment. A recent report by the US Centers for Disease Control and Prevention highlighted that if the supply of opioid prescribed at discharge is too small, patients may return for more, increasing the risk of long term use. Oversupply of medicines at discharge also increases risk, however.[11]

People differ in their analgesic needs, so how do we get this right? Abandoning opioids for acute pain is not an option, so we should prescribe with care and monitor and manage acute pain medicines rationally. As for tramadol and Thiels and colleagues' findings, we need to know more about how and why prescribers make their analgesic choices and understand the symptoms that bring patients to request further analgesia. Better communication with patients at the time of discharge and between hospitals and primary care teams avoids unintended continuation of treatment and should mitigate some of the potential hazards of prescribing for acute pain.

Thiels and colleagues' principal conclusion, a call to avoid underestimating tramadol in relation to other opioid products, should be heeded. Prescribing of any opioid should be in accordance with the evidence and with the effects and side effects reported by individual patients, as well as with the patient's and prescriber's full knowledge of the likelihood and risks of long term use.

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# Breast cancer risk in transgender people receiving hormone treatment

de Blok CJM, Wiepjes CM, Nota NM, et al

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**Study question** What is the incidence of breast cancer in transgender people in the Netherlands?

**Methods** This study included 2260 trans women (male sex assigned at birth, female gender identity) and 1229 trans men (female sex assigned at birth, male gender identity) receiving gender affirming hormone treatment. The cohort was linked to the Nationwide Network and Registry of Histopathology and Cytopathology in the Netherlands. To calculate the follow-up time, data on mortality were retrieved from Statistics Netherlands. Standardised incidence ratios were calculated using incidence ratios of the general Dutch male and female population.

**Study answer and limitations** An increased risk of breast cancer was observed in trans women compared with cisgender men (standardised incidence ratio 46.7, 95% confidence interval 27.2 to 75.4) and a lower risk in trans men compared with cisgender women (0.2, 0.1 to 0.5). Owing to the study design, limitations of this study include missing or incomplete data about type of hormone use, family history, genetic mutations, benign breast lesions, breast density, tobacco and alcohol use, and body mass index.

**What this study adds** The risk of breast cancer in trans women increased during a relatively short duration of hormone treatment. As the absolute risk of breast cancer in transgender people remains low, these results suggest that breast cancer screening guidelines for cisgender people are sufficient for transgender people using hormone treatment.

Funding, competing interests, and data sharing
This study received no funding. The authors declare no support from any organisation, and no financial or other relationships or activities with any organisations that might have an interest in or could appear to have influenced this work. Statistics Netherlands prohibit data sharing at an individual level.

**Standardised incidence ratios of 18 cases of breast cancer (15 invasive and three non-invasive) in 17 trans women and four cases of invasive breast cancer in four trans men**

| Variables | Observed cases | Expected cases | Standardised incidence ratio (95% CI) | Expected cases | Standardised incidence ratio (95% CI) |
|---|---|---|---|---|---|
| | | Reference: incidence ratio in cisgender men | | Reference: incidence ratio in cisgender women | |
| **Trans women (n=2260)** | | | | | |
| Invasive | 15 | 0.32 | 46.7 (27.2 to 75.4) | 59.95 | 0.3 (0.2 to 0.4) |
| Age (years): | | | | | |
| ‹30 | 0 | 0.00 | - | 0.14 | - |
| 30-50 | 9 | 0.01 | 659.4 (321.6 to 1210.0) | 9.16 | 1.0 (0.5 to 1.8) |
| ›50 | 6 | 0.31 | 19.5 (7.9 to 40.6) | 50.65 | 0.1 (0.1 to 0.3) |
| Non-invasive | 3 | 0.03 | 96.1 (24.5 to 261.6) | 12.10 | 0.3 (0.1 to 0.7) |
| Age (years): | | | | | |
| ‹30 | 0 | 0.00 | - | 0.01 | - |
| 30-50 | 1 | 0.00 | 5288.0 (264.6 to 26 080.0) | 1.25 | 0.8 (0.0 to 4.0) |
| ›50 | 2 | 0.03 | 64.5 (10.8 to 213.0) | 10.83 | 0.2 (0.0 to 0.6) |
| **Trans men (n=1229)** | | | | | |
| Invasive | 4 | 0.07 | 58.9 (18.7 to 142.2) | 18.54 | 0.2 (0.1 to 0.5) |
| Age (years): | | | | | |
| ‹30 | 0 | 0.00 | - | 0.14 | - |
| 30-50 | 2 | 0.01 | 282.3 (47.3 to 932.5) | 4.78 | 0.4 (0.1 to 1.4) |
| ›50 | 2 | 0.06 | 32.9 (5.5 to 108.8) | 13.62 | 0.2 (0.0 to 0.5) |
| Non-invasive | 0 | 0.01 | - | 3.55 | - |

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