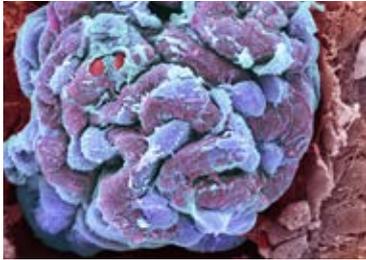


# research



Obesity associated with increased risk of GFR decline and mortality (this page)



Surgical treatment of Achilles tendon rupture reduces risk of re-rupture p 60



No increased risk of VTE associated with transdermal HRT p 62

COVER FEATURE: Dual antiplatelets therapy after TIA or minor stroke reduces risk of recurrent stroke (p 74)

## ORIGINAL RESEARCH Meta-analysis of individual participant data in a global consortium

### Adiposity and risk of decline in glomerular filtration rate

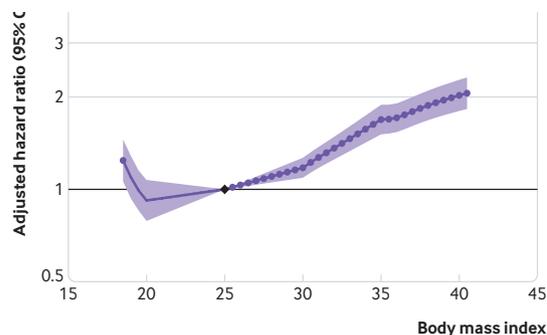
Chang AR, Grams ME, Ballew SH, et al; for the CKD Prognosis Consortium (CKD-PC)

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Find this at: <http://dx.doi.org/10.1136/bmj.k5301>

**Study question** Is adiposity (as measured by body mass index, waist circumference, and waist-to-height ratio) associated with the risk of decline in glomerular filtration rate (GFR)?

**Methods** Using individual participant data collected in 1970-2017 in a global consortium, random effects meta-analyses were conducted in 39 general population cohorts (n=5 459 014), six cohorts with high cardiovascular risk (n=84 417), and 18 cohorts with chronic kidney disease (CKD; n=91 607). Waist circumference data were available in 21 general population cohorts (n=594 496).



Association between body mass index and risk of GFR decline in general population cohorts, as shown by meta-analysed hazard ratios and 95% confidence intervals related to body mass index. Association is modelled by linear splines with knots at body mass indices 20, 25, 30, and 35. Circles indicate points with significant differences in risk from the reference point at body mass index 25

Main outcomes were GFR decline (estimated GFR decline  $\geq 40\%$ , initiation of kidney replacement therapy or estimated GFR  $< 10$  mL/min/1.73 m<sup>2</sup>) and all cause mortality.

**Study answer and limitations** Over a mean follow-up of eight years, 246 607 (5.6%) individuals in the general population cohorts had GFR decline and 782 329 (14.7%) died. Adjusting for age, sex, race, and current smoking, hazard ratios for GFR decline were 1.18 (95% confidence interval 1.09 to 1.27) for body mass index 30, 1.69 (1.51 to 1.89) for body mass index 35, and 2.02 (1.80 to 2.27) for body mass index 40 (versus body mass index 25 as reference). Results were similar in all estimated GFR subgroups. After adjustment for additional comorbidities, the corresponding associations were weaker (1.03 (0.95 to 1.11), 1.28 (1.14 to 1.44), and 1.46 (1.28 to 1.67), respectively). In the high cardiovascular risk and CKD cohorts (mean follow-up six and four years, respectively), risk associations between higher body mass index and GFR decline were weaker than in the general population. In all cohort types, associations between higher waist circumference and higher waist-to-height ratio with GFR decline were similar to that of body mass index, but there was no increased risk of death associated with lower waist circumference or waist-to-height ratio as was seen with body mass index.

**What this study adds** This study indicates that obesity is associated with increased risk of GFR decline and mortality in individuals with and without CKD.

**Competing interests, funding, and data sharing** Part support from the US National Kidney Foundation and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). ARC was supported by the NIDDK. CKD-PC has agreed with collaborating cohorts not to share data outside the consortium. Each participating cohort has its own policy for data sharing.

# Management of Achilles tendon rupture

**ORIGINAL RESEARCH** Systematic review and meta-analysis

## Operative treatment versus non-operative treatment of Achilles tendon ruptures

Ochen Y, Bekes RB, van Heijl M, et al  
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**Study question** What are the re-rupture rates, complication rates, and functional outcomes after operative versus non-operative treatment of Achilles tendon ruptures?

**Methods** The PubMed/Medline,

Embase, CENTRAL, and CINAHL databases were searched for comparative studies, both randomised controlled trials and observational studies, reporting on the comparison of operative versus non-operative treatment of acute Achilles tendon ruptures. Outcomes were pooled using random effects models and presented as risk difference, risk ratio, or mean difference, with 95% confidence interval.

### Study answer and limitations

A significant reduction in re-ruptures was seen after

operative treatment compared with non-operative treatment (risk difference 1.6%; risk ratio 0.43, 95% confidence interval 0.31 to 0.60;  $P<0.001$ ;  $I^2=22\%$ ). Operative treatment resulted in a significant higher complication rate than non-operative treatment (risk difference 3.3%; risk ratio 2.76, 1.84 to 4.13;  $P<0.001$ ;  $I^2=45\%$ ). Comparison of literature remains difficult owing to a wide variety of rehabilitation protocols, weightbearing restrictions, treatment modalities, patient oriented outcome measures,

duration of follow-up, and presentation of data.

**What this study adds** Operative treatment of acute Achilles tendon ruptures reduces the risk of re-rupture compared with non-operative treatment, although the incidence of re-ruptures is low and differences are small (2.3% v 3.9%). Operative treatment results in a higher risk of other complications than non-operative treatment (4.9% v 1.6%), mostly attributable to an increased risk of infection.

**COMMENTARY** Patients need better evidence on functional outcomes, including a return to sport

Acute ruptures of the Achilles tendon are common and can lead to major functional limitations, with noticeable loss of strength and endurance.<sup>1</sup> Many such patients fail to resume sporting activities in the short term, and the injury produces ongoing problems even after 10 years.<sup>2</sup> Much of recent research has tried to determine the optimal methods of either surgical or non-surgical treatment using a randomised controlled trial study design, with the primary outcome in most of such studies being the prevention of re-ruptures. Ochen and colleagues carefully analysed 29 studies in this specialty, including 19 observational and 10 randomised controlled trials.<sup>3</sup>

This rigorous work is to be commended and the results are sound: compared with non-operative management, surgery significantly reduced the risk of re-rupture, but significantly increased the risk of other

## A personalised approach incorporating fully informed shared decision making remains essential

complications.<sup>3</sup> Is this the end for surgical management?

Well, not quite. The risk of re-rupture was low after both surgery (2.3%) and conservative management (3.9%). The rate of postoperative complication after surgery was also low (4.9%), and the differences between surgical and non-operative management were small for both outcomes. The differences may have been statistically significant, but the clinical relevance is questionable.<sup>3</sup>

Several techniques are available for percutaneous or minimally invasive repair of acute tears of the Achilles tendon. Comparative studies<sup>4-6</sup> and a systematic review<sup>7</sup> show that minimally invasive and open surgery of the Achilles tendon produce equivalent results. Minimally invasive and percutaneous surgery carry a greater risk of iatrogenic injury to the sural nerve<sup>1</sup>: however, the functional impairment induced by such a complication is minor and does not compromise

the function of the foot and ankle, and the leg. Novel percutaneous repair techniques have been developed to minimise the risk of sural nerve injury.<sup>8</sup>

### Strength and endurance

As Ochen and colleagues show, the difference in re-rupture rate between operative and non-operative management is small.<sup>2</sup> However, other outcomes are equally important to patients, and other studies have shown that patients treated conservatively take longer to return to sport, are less strong, and have less confidence in their Achilles tendon.<sup>5,6</sup> Future studies should be powered to evaluate recovery of strength and endurance in the gastro-soleus complex and return to high level physical activities, as well as other patient centred functional outcomes. These studies will require greater numbers of participants, followed up for longer than in previous studies.

### Elongated tendon

Many surgeons in the UK manage acute rupture of Achilles tendon conservatively. This has resulted in a growing cohort of people with a healed Achilles tendon that is elongated, altering the relation between the tendon and the gastro-soleus muscle complex.<sup>9</sup> These individuals develop a more acute Achilles tendon resting angle,<sup>9</sup> and they are not able to push off properly when walking, ascending and descending stairs, and running. They have problems similar to patients with a chronic Achilles tendon rupture. Corrective operations have been described,<sup>10</sup> but reconstructive surgery is more technically demanding than primary repair procedures—recovery is long and often less optimal than following primary surgical repair.<sup>10</sup>

The most common functional evaluation score, the Achilles Tendon Total Rupture Score,<sup>11</sup> is generally lower after non-operative management than surgical management.<sup>2,3</sup> Although the difference is not

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Patients should be counselled about complications, and the final decision for operative or non-operative management should be based on patient specific factors and shared decision making. This review emphasises the potential benefits of adding high quality observational studies in meta-analyses to complement randomised controlled trials for the evaluation of objective outcome measures after surgical treatment.

Competing interests, funding, and data sharing None.

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statistically significant,<sup>2,3</sup> it might still have a noticeable effect on patients' confidence and return to activity.

#### **Apparently cheaper**

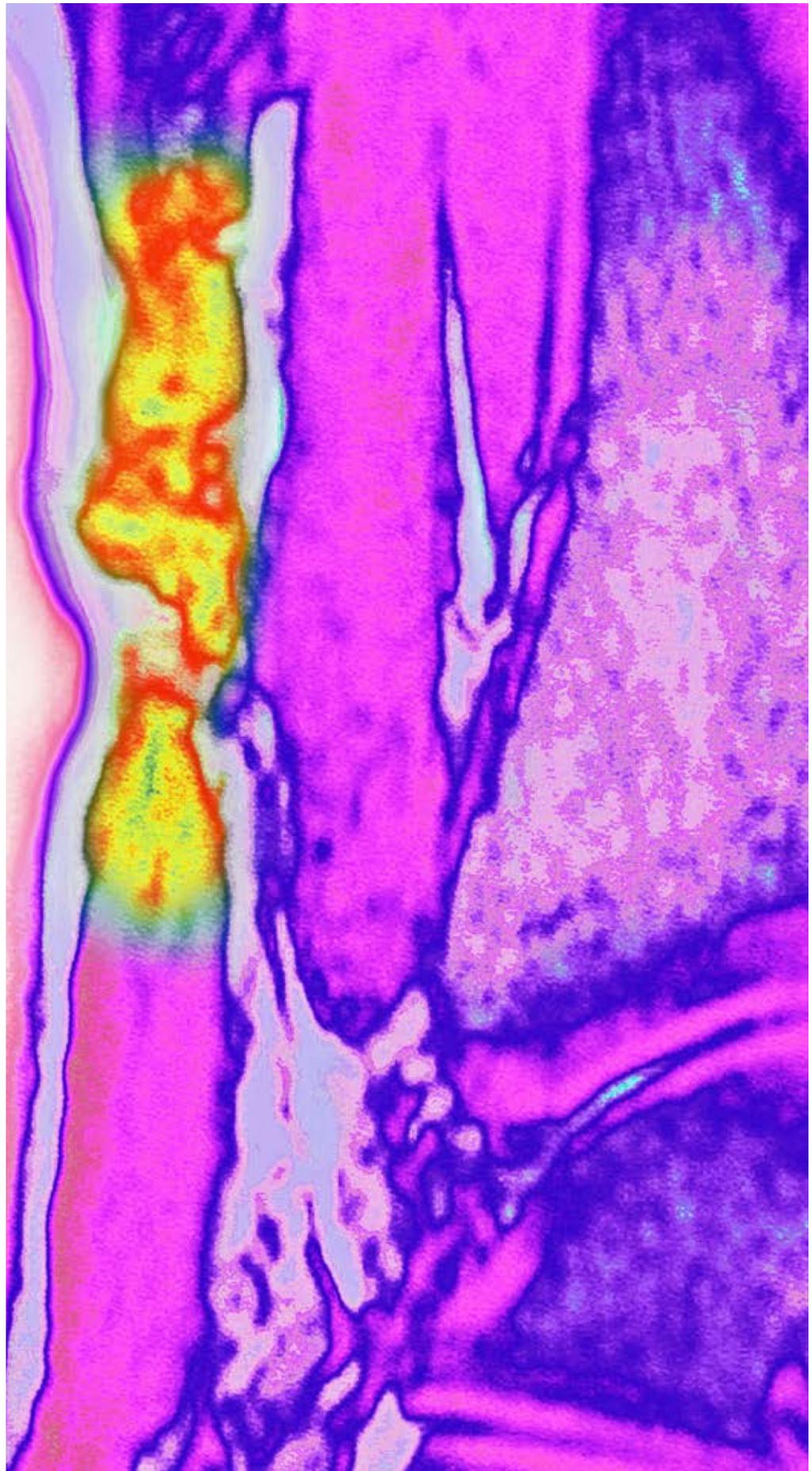
In the absence of better evidence on the long term outcomes that matter most to patients, this debate is likely to continue. Non-operative management of Achilles tendon rupture is apparently cheaper and avoids surgical complications.

However, less invasive surgical repair techniques performed under local anaesthesia in outpatients can be safe and effective.<sup>12</sup> A recent cost effectiveness analysis showed a 57% likelihood for surgical treatment to be cost effective at a willingness to pay per quality adjusted life year threshold of €50 000 (£44 900).<sup>13</sup>

A personalised approach incorporating fully informed shared decision making remains essential for the management of acute ruptures of the largest and strongest tendon of the human body.<sup>14</sup>

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## Use of hormone replacement therapy and risk of venous thromboembolism

Vinogradova Y, Coupland C, Hippisley-Cox J

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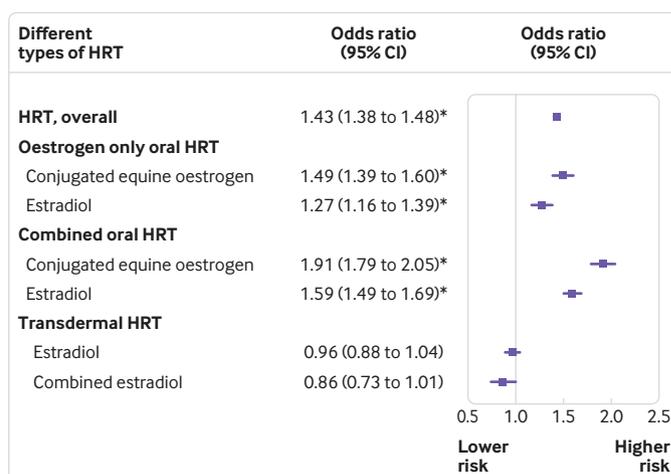
**Study question** What are the risks of venous thromboembolism for women using different types of hormone replacement therapy?

**Methods** This study used data from the two largest UK primary care databases, QResearch and Clinical Practice Research Datalink (CPRD), and linked hospital admissions, mortality, and social deprivation data. Parallel case-control studies were run on each database and the findings then combined. In total, 80 396 incident cases of venous thromboembolism that were diagnosed in women aged 40-79 between 1998 and 2017 were matched to 391 494 female controls by age, practice, and date of diagnosis (index date). Information on all prescriptions for hormone replacement therapy in the year before the index date was used in the analysis, including hormone type, dose, and route of administration. Current use was defined as exposure within 90 days before the index date. All findings were adjusted for demographics, smoking status, alcohol consumption, relevant comorbidities and recent medical events, and other prescribed drugs.

**Study answer and limitations** Overall, 5795 (7.2%) women who had venous thromboembolism and 21 670 (5.5%) controls had been exposed to hormone replacement therapy within 90 days before the index date. Of these two groups, 4915 (85%) and 16 938 (78%) women used oral therapy, respectively, which was associated with a significantly increased risk of venous thromboembolism compared with no exposure (adjusted odds ratio 1.58, 95% confidence interval 1.52 to 1.64), for both oestrogen only preparations (1.40, 1.32 to 1.48) and preparations containing oestrogen combined with a progestogen (1.73, 1.65 to 1.81). Transdermal preparations were not associated with risk of venous thromboembolism (0.93, 0.87 to 1.01). The main limitations of this large observational study were uncertainty about adherence to drugs and limited information about precise indications for prescribing.

**What this study adds** This study adds clarity about the relative risks of venous thromboembolism in women using oral hormone replacement therapy and shows lower risks for estradiol preparations than for conjugated equine oestrogen preparations. The study confirms previous findings of no increased risk associated with transdermal treatment and highlights the relatively low prescribing of this type of treatment.

**Funding, competing interests, and data sharing** Full details of funding, data sharing, and competing interests are available on [bmj.com](http://bmj.com).



**Adjusted odds ratios of venous thromboembolism for different types of hormone replacement therapy.** Odds ratios are adjusted for current use of conjugated equine oestrogen cream, estradiol pessaries, oral progestogen, progestogen cream, or vaginal preparations, past use of HRTs, smoking, alcohol consumption, Townsend deprivation fifth (QResearch only), body mass index, comorbidities, recent medical events, current and past use of antidepressants, antipsychotics, aspirin, oral contraceptives, tamoxifen, and years of data. Cases are matched to controls by age, general practice, and index date. \*P<0.01



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