# Interspinous process device versus standard conventional surgical decompression for lumbar spinal stenosis: randomized controlled trial

Wouter A Moojen,[1 2] Mark P Arts,[2] Wilco C H Jacobs,[1] Erik W van Zwet,[3] M Elske van den Akker-van Marle,[4] Bart W Koes,[5] Carmen L A M Vleggeert-Lankamp,[1] Wilco C Peul,[1 2] for the Leiden-The Hague Spine Intervention Prognostic Study Group (SIPS)

EDITORIAL by Fairbank

[1]Department of Neurosurgery, Leiden University Medical Center, Leiden, Netherlands
[2]Department of Neurosurgery, Medical Center Haaglanden, The Hague, Netherlands
[3]Department of Medical Statistics and Bioinformatics, Leiden University Medical Center
[4]Department of Medical Decision Making, Leiden University Medical Center
[5]Department of General Practice, Erasmus Medical Center, Rotterdam, Netherlands
Correspondence to: W A Moojen
w.a.moojen@lumc.nl

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## STUDY QUESTION

s interspinous process device implantation more effective in the short term (eight weeks) than conventional surgical decompression for patients with intermittent neurogenic claudication due to lumbar spinal stenosis?

## SUMMARY ANSWER

The use of interspinous implants did not result in a better outcome than conventional decompression, but the reoperation rate was significantly higher.

## WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Bony decompression and treatment with interspinous process devices are superior to conservative and non-surgical treatment for intermittent neurogenic claudication due to lumbar spinal stenosis. Interspinous implants surgery is not superior to bony decompression, and the reoperation rate is significantly higher.

### Design

We used a randomized design with variable block sizes, with allocations stratified according to center. Allocations were stored in prepared opaque, coded, and sealed envelopes, and patients and research nurses were blind throughout the follow-up.

### Participants and setting

Five neurosurgical centers recruited 203 participants for this study; 159 participants with intermittent neurogenic claudication due to lumbar spinal stenosis at one or two levels with an indication for surgery were blindly randomized into two groups to receive an interspinous process device or conventional bony decompression.

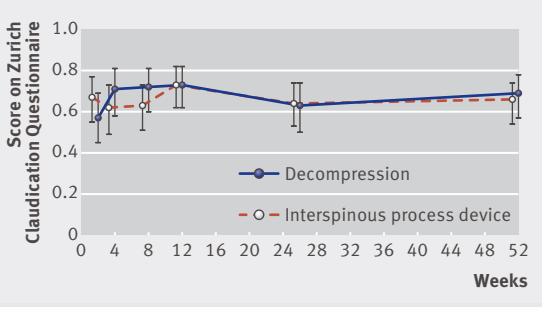
### Primary outcome(s)

The primary outcome at eight weeks was the score on the Zurich Claudication Questionnaire.

### Main results and the role of chance

At eight weeks, the success rate according to the Zurich Claudication Questionnaire for the interspinous process device group (63%, 95% confidence interval 51% to 73%) was not superior to that for standard bony decompression (72%, 60% to 81%). No differences in disability (Zurich Claudication Questionnaire; P=0.44) or any other outcomes were observed between groups during the first year after surgery.

**Zurich Claudication Questionnaire score in two groups during follow-up**




### Harms

The repeat surgery rate in the interspinous implant group was 29% in the early post-surgical period and was higher than the 6% seen for the conventionally treated group (P<0.001). Furthermore, of the patients who initially received an interspinous process device and who were reoperated on, only 48% scored successful recovery on the Zurich Claudication Questionnaire.

### Bias, confounding, and other reasons for caution

We noted no significant differences in baseline characteristics between patients in the two treatment arms. We found no clinically significant heterogeneity in the outcomes between the five centers. The results for the primary outcome were not sensitive to loss to follow-up.

### Generalisability to other populations

Selection bias could have been introduced by the opinion of the including neurosurgeon that patients with severe spinal stenosis on magnetic resonance imaging should not be offered an interspinous process device and were thus not included in this trial.

### Study funding/potential competing interests

Paradigm Spine funded this trial.

### Trial registration number

Dutch Trial Register: NTR1307.

# Exploration and confirmation of factors associated with uncomplicated pregnancy in nulliparous women: prospective cohort study

Lucy C Chappell,[1] Paul T Seed,[1] Jenny Myers,[2] Rennae S Taylor,[3] Louise C Kenny,[4] Gustaaf A Dekker,[5] James J Walker,[6] Lesley M E McCowan,[3] Robyn A North,[1] Lucilla Poston[1]

EDITORIAL by Knight

[1]Division of Women's Health, Women's Health Academic Centre, King's College London and King's Health Partners, UK
[2]Maternal and Fetal Health Research Centre, Manchester Academic Health Science Centre, University of Manchester and Central Manchester Foundation Trust, UK
[3]Department of Obstetrics and Gynaecology, Faculty of Medical and Health Sciences, University of Auckland, New Zealand
[4]The Irish Centre for Fetal and Neonatal Translational Research (INFANT), Department of Obstetrics and Gynaecology, University College Cork, Republic of Ireland
[5]Department of Obstetrics and Gynaecology, Lyell McEwin Hospital, University of Adelaide, Australia
[6]Reproduction and Perinatal Health Research Group, University of Leeds, St James University Hospital, Leeds, UK
Correspondence to: L C Chappell
lucy.chappell@kcl.ac.uk

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## STUDY QUESTION

Which variables at 15 and 20 weeks' gestation, particularly those amenable to modification before pregnancy, are associated with a subsequent uncomplicated pregnancy?

## SUMMARY ANSWER

Normalising body mass index, increasing fruit intake before pregnancy, reducing blood pressure, stopping misuse of drugs, and being in paid employment are all associated with subsequent uncomplicated pregnancy outcomes.

## WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Previous literature has focused on the association between risk factors and subsequent adverse pregnancy outcomes, not on healthy pregnancy. Identification of factors amenable to modification could inform development of interventions to increase normal pregnancy outcomes.

### Participants and setting

5628 nulliparous women with singleton pregnancies recruited to the Screening for Pregnancy Endpoints (SCOPE) study in Auckland, New Zealand; Adelaide, Australia (exploration (n=2129) and local replication (n=1063) datasets); London, Manchester, and Leeds, United Kingdom; and Cork, Republic of Ireland (external confirmation dataset (n=2432)).

### Design, size, and duration

Prospective observational multicentre cohort study, between November 2004 and August 2008. Of the 5628 women, 3452 (61.3%) had an uncomplicated pregnancy.

**Unadjusted risk ratios for variables associated with subsequent uncomplicated pregnancy remaining significant in log probability regression model for external confirmation dataset (n=2432)**

| Variables | Risk ratio (95% CI) |
|---|---|
| **Decreased risk of uncomplicated pregnancy/detrimental** | |
| Body mass index at 15 weeks' gestation: | |
| ≥30 (*v*<25) | 0.74 (0.65 to 0.84) |
| 25-29.9 (*v*<25) | 0.87 (0.80 to 0.94) |
| Mean blood pressure (per 5 mm Hg increase) at 15 weeks' gestation: | |
| Diastolic | 0.92 (0.91 to 0.94) |
| Systolic | 0.95 (0.94 to 0.96) |
| Misuse of drugs in first trimester* | 0.90 (0.84 to 0.97) |
| **Increased risk of uncomplicated pregnancy/beneficial** | |
| Prepregnancy fruit intake at least 3 times/day | 1.09 (1.01 to 1.18) |
| Hours worked in paid employment (per 8 hours increase) at 15 weeks' gestation | 1.02 (1.01 to 1.04) |

*Use of marijuana, cocaine/crack, amphetamines, 3,4 methylenedioxymethamphetamine, opiates, hallucinogens, and binge alcohol ≥6 units/session.

### Main results and the role of chance

Unadjusted risk ratios for potentially improvable variables associated with subsequent uncomplicated pregnancy remained significant in log probability regression models in the external confirmation dataset. Detrimental factors not amenable to alteration were a history of hypertension while using oral contraception, socioeconomic index, family history of any hypertensive complications in pregnancy, vaginal bleeding during pregnancy, and increasing uterine artery resistance index. Smoking was noted to be a detrimental factor in the initial two datasets but did not remain in the final model.

### Bias, confounding, and other reasons for caution

We attempted to reduce confounding by inclusion of terms for all major explanatory variables. Exploration of variables in the development dataset was followed by replication and confirmation in two other datasets, one local and one external, increasing the robustness of the associations. The variables in the final model are consistent with biological plausibility, but the predictive nature of these variables requires validation in different cohorts.

### Generalisability to other populations

The study invited nulliparous women with no major medical conditions to participate, to assist in identification of risk factors without the additional complexities of pre-existing medical conditions. This enables the findings to be generalised to other similar populations of healthy pregnant women, but not automatically to other groups (nulliparous women with medical disorders or multiparous women).

### Study funding/potential competing interests

This study was funded by New Enterprise Research Fund, Foundation for Research Science and Technology; Health Research Council (04/198); Evelyn Bond Fund, Auckland District Health Board Charitable Trust; Premier's Science and Research Fund, South Australian Government; Guy's and St Thomas' Charity, Tommy's Charity; UK National Health Services (NEAT grant FSD025), University of Manchester Proof of Concept Funding, National Institute for Health Research; Health Research Board, Ireland (CSA/2007/2). JM is supported by an Action Medical research endowment fund and Manchester Biomedical Research Centre. RAN, LMEMcC, JM, GAD, LP, RST, and LCK declare their institutions received money to fund the SCOPE study including some salary component (except for GAD).

Reproductive medicine updates from *BMJ* http://www.bmj.com/specialties/reproductive-medicine

# Risk of first venous thromboembolism in pregnant women in hospital: population based cohort study from England

Alyshah Abdul Sultan,[1] Joe West,[1] Laila J Tata,[1] Kate M Fleming,[1] Catherine Nelson-Piercy,[2] Matthew J Grainge[1]

[1]Division of Epidemiology and Public Health, University of Nottingham, Clinical Sciences Building Phase 2, City Hospital, Nottingham NG5 1PB, UK
[2]Women's Health Academic Centre, Guy's and St Thomas' Foundation Trust, St Thomas' Hospital, London SE1 7EH, UK
Correspondence to: A Abdul Sultan
**alyshah.sultan@hotmail.com**
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## STUDY QUESTION

Does admission into hospital increase the risk of venous thromboembolism during pregnancy and, if so, for how long does this increased risk remain after discharge?

## SUMMARY ANSWER

The overall rate of antepartum venous thromboembolism is substantially increased during admissions to hospital not related to delivery (18-fold increase compared with the risk outside hospital), and this increase is sustained during the 28 days after discharge (sixfold increase in risk).

## WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Admission to hospital is known to increase the risk of venous thromboembolism by around 100-fold outside pregnancy; it is unknown if a similar magnitude exists for pregnant women. We report a high rate during inpatient admissions among pregnant women, which persists throughout the 28 days after discharge, with a particularly high rate among those admitted for three or more days.

### Participants and setting

We used information from women with one or more pregnancies resulting in live or still birth from primary and secondary care centres in England.

### Design, size, and duration

This cohort study used linked primary (Clinical Practice Research Datalink) and secondary (Hospital Episode Statistics) care data, comprising 206 785 women who underwent 245 661 pregnancies resulting in live or still birth. Our main exposure was defined as admission to hospital during pregnancy other than for delivery (for which venous thromboembolism was not the reason for admission). Our comparative analyses accounted for maternal characteristics and comorbidities related to pregnancy.

**Overall rate of antepartum venous thromboembolism (VTE) by admission to hospital and after hospital stay**

| Variable | No of VTE | Rate* (95% CI) | Adjusted IRR (95% CI)† |
|---|---|---|---|
| Time outside hospital | 150 | 97 (83 to 114) | 1.00 |
| Hospital admission | 6 | 1752 (787 to 3900) | 17.5 (7.69 to 40.0) |
| After discharge | 20 | 676 (436 to 1048) | 6.27 (3.74 to 10.5) |
| **Variation by duration of hospital stay (combining admission/after discharge)** | | | |
| Time outside hospital | 150 | 97 (83 to 114) | 1.00 |
| <3 days | 13 | 558 (331 to 943) | 4.05 (2.23 to 7.38) |
| ≥3 days | 13 | 1511 (858 to 2661) | 12.2 (6.65 to 22.7) |

IRR=incidence rate ratio.
*Rate calculated per 100 000 person years.
†Adjusted for maternal age, calendar year, BMI, gestational infection, cardiac disease, varicose veins, gestational diabetes, and hyperemesis.

### Main results and the role of chance

Overall, antepartum admission to hospital was associated with a high risk of venous thromboembolism (absolute rate 1752/100 000 person years), corresponding to a 18-fold increase (incidence rate ratio 17.5, 95% confidence interval 7.69 to 40.0) compared with time outside hospital. The rate of venous thromboembolism was also high during the 28 days after discharge (6.27, 3.74 to 10.5; absolute rate 676). The rate during admission and after discharge combined was highest in the third trimester (5.57, 3.32 to 9.34; absolute rate 961) and those aged ≥35 (21.7, 9.62 to 49.7). While these rates were highest for those with three or more days in hospital (13.2, 7.3 to 23.9; absolute rate 1639), there was also a fourfold (4.05, 2.23 to 7.38; absolute rate 558) increase in risk for those admitted to hospital for less than three days.

### Bias, confounding, and other reasons for caution

Despite the use of large linked datasets containing information on around 245 000 pregnancies, the number of hospital related events of venous thromboembolism was small. Therefore we are cautious about recommending thromboprophylaxis for all pregnant women admitted to hospital on the basis of these results. Our results also relied on accurate assessment as to whether venous thromboembolism was the cause or consequence of the admission; agreement between authors who independently evaluated clinical records, however, was high.

### Generalisability to other populations

Our study used an open cohort approach, with prospectively collected data and information from linked primary and secondary care data sources from all over England. This covers 3% of the total UK population with similar age and sex distribution. It makes our findings generalisable not only nationally but also to other developed nations with similar healthcare systems.

### Study funding/potential competing interests

AAS is funded by a scholarship awarded by the Aga Khan Foundation. JW is funded by a University of Nottingham senior clinical research fellowship, which also contributes to AAS's funding. CN-P was co-developer of the currently available guidelines on venous thromboembolism prophylaxis in pregnancy issued by the Royal College of Obstetricians and Gynaecologists (green top guideline 37a). CN-P has also received honorariums and payments from Leo Pharma and Sanofi Aventis.

# Non-publication of large randomized clinical trials: cross sectional analysis

Christopher W Jones,[1] Lara Handler,[2] Karen E Crowell,[2] Lukas G Keil,[3] Mark A Weaver,[4] Timothy F Platts-Mills[3]

[1]Department of Emergency Medicine, Cooper Medical School of Rowan University, One Cooper Plaza, Camden, NJ 08103, USA
[2]Health Sciences Library, University of North Carolina Chapel Hill, USA
[3]Department of Emergency Medicine, University of North Carolina Chapel Hill, USA
[4]Department of Biostatistics, University of North Carolina Chapel Hill, USA
Correspondence to: C W Jones
**cjones.unc@gmail.com**

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## STUDY QUESTION

How often do large randomized clinical trials that have been registered with ClinicalTrials.gov remain unpublished after trial completion, and how often are the results from unpublished studies available on ClinicalTrials.gov?

## SUMMARY ANSWER

Among the 585 randomized trials with at least 500 participants registered and completed prior to 2009, a published manuscript containing trial results could not be identified for 171 (29%) trials. Of these unpublished studies, 133 (78%) also had no results available in the ClinicalTrials.gov results database.

## WHAT IS KNOWN AND WHAT THIS PAPER ADDS

It is known that non-publication of trial results is common among small studies across a wide range of clinical topics. This paper shows that non-publication is also an important problem among large clinical trials.

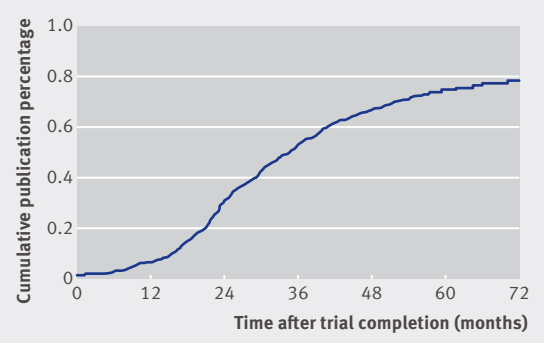
### Participants and setting

We included trials that were prospectively registered with ClinicalTrials.gov, had a planned or actual enrollment of at least 500 participants, and were completed prior to January 2009.

### Design

PubMed, Google Scholar, and Embase were searched to identify published manuscripts corresponding to the included clinical trials. If no such manuscript was found after three independent literature searches by different investigators we classified trials as unpublished. When no published manuscript was identified, we reviewed the ClinicalTrials.gov results database to determine whether trial results were available on the ClinicalTrials.gov website.

**Kaplan-Meier estimate of cumulative publication percentage by time elapsed from trial completion to publication**




### Primary outcome

Our primary outcome was the percentage of registered trials for which no corresponding publication could be identified.

### Main results and the role of chance

Of the 585 registered trials included in this study, 171 (29%) were unpublished. An estimated 299 763 study participants were enrolled in these 171 unpublished trials. 133 of the 171 unpublished trials (78%) had no results available in ClinicalTrials.gov.

### Bias, confounding, and other reasons for caution

We performed multiple independent literature searches and attempted to contact study authors in an effort to ensure that no relevant publications were missed. Despite these measures, it is possible that we failed to identify published manuscripts corresponding to some of the registered studies. It is also possible that results from some of the included studies may be published in the future. These limitations might have resulted in an overestimation of the true percentage of unpublished trials.

### Generalisability to other populations

The trials included in this cross sectional analysis were large studies covering a wide range of clinical specialties. These results may not apply to smaller studies or those that have been conducted recently.

### Study funding/potential competing interests

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