Clinical effect modifiers of antibiotic treatment in patients with chronic low back pain and Modic changes - secondary analyses of a randomised, placebo-controlled trial (the AIM study)

Lars Christian Haugli Bråten 1,2*, Lars Grøvle 3, Ansgar Espeland 4,5, Are Hugo Pripp 6, Margreth Grotle 7,1, Christian Helllum 8, Anne Julsrud Haugen 3, Anne Froholdt 9, Mads Peder Rolfsen 8,2, Øystein Petter Nygaard 10,11,12, Olav Lutro 13, Per Martin Kristoffersen 4,5, Audny Anke 14,15, Elina Iordanova Schistad 16, Jan Sture Skouen 17,18, Jens Ivar Brox 16,2, John-Anker Zwart 1,2, Kjersti Storheim 1,7 and The AIM-study group

Abstract

Background: Randomised trials on antibiotic treatment for patients with chronic low back pain and vertebral endplate changes visible on MRI (Modic changes) have shown mixed results. A possible explanation might be a real treatment effect in subgroups of the study populations. The purpose of the present study was to explore potential clinical effect modifiers of 3-months oral amoxicillin treatment in patients with chronic low back pain and type I or II Modic changes at the level of a previous lumbar disc herniation.

Methods: We performed analyses of effect modifiers on data from AIM, a double-blind parallel-group multicentre trial. One hundred eighty patients with chronic low back pain, previous disc herniation, Modic change type I (n = 118) or type II (n = 62) were randomised to 3-months oral treatment with 750 mg amoxicillin (n = 89) or placebo (n = 91) three times daily. The primary outcome was the Roland-Morris Disability Questionnaire (RMDQ) score (possible values 0–24) at 1-year follow-up in the intention-to-treat population. The predefined minimal clinically important between-group mean difference was 4 RMDQ points (not reached in the primary analysis of AIM).

Predefined baseline characteristics were analysed as potential effect modifiers, four primary (type I Modic changes, previous disc surgery, positive pain provocation test, high CRP) and five exploratory (disturbed sleep, constant low back pain, short duration of low back pain, younger age, and male) using ANCOVA with interaction terms.

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Background
In most patients with chronic low back pain no specific or underlying disease can be found. An efficient management is often difficult and current treatment options for low back pain offer at best only small to moderate reductions in pain and disability [1].

Accordingly, there are ongoing attempts to identify subgroups with specific clinical characteristics that could lead to effective treatments. A suggested subgroup is patients with vertebral bone marrow changes extending from the endplate (Modic changes) visible on magnetic resonance imaging (MRI), which may be associated with low back pain [2]. A prominent hypothesis for the etiology of Modic changes is a low-grade bacterial infection of the adjacent intervertebral disc [3]. A disc herniation is a suggested precondition for the bacteria to enter into the disc.

A randomised placebo controlled trial published in 2013 reported that three months of antibiotic treatment offered substantial improvement of symptoms in patients with chronic low back pain and type I Modic changes [4]. The AIM-study (Antibiotics In Modic changes), a reassessment and replication study of the former trial from 2013, did not find any clinically important difference in outcome between the treatment groups at three or 12 months follow-up [5]. There was however a small difference between the groups and an increased variance in outcome measure in the amoxicillin group compared to the placebo group, that may suggest a possible treatment effect in subgroups [6]. There is also a biological rationale for the heterogeneity of treatment effect, as even positive biopsy studies in patients with Modic changes mostly have a large proportion of negative samples [7]. There have not been any reported attempts so far to find effect modifiers of antibiotic treatment in low back pain based on randomised trials.

The present study was hypothesis-setting [8], meaning that we attempted to find candidate effect modifiers to be verified in further hypothesis-testing studies. We sought subgroups with treatment response, not diagnostic subgroups. The objective of this study was to explore potential clinical effect modifiers of three months oral amoxicillin treatment in patients with chronic low back pain and type I or II Modic changes at the level of a previous lumbar disc herniation included in the AIM-study.

Methods
Our hypothesis was that one or more of nine predefined clinical characteristics (described below) modified the efficacy of three months oral amoxicillin treatment in patients with chronic low back pain and type I or II Modic changes at the level of a previous lumbar disc herniation.

Study design and setting
The present hypothesis-setting analyses were based on data from the AIM-study, a multicentre, randomised, double-blind, placebo-controlled, parallel-group trial with a treatment phase (three months) and a follow-up phase (nine months). Trial methods have been detailed previously [9]. The AIM-study was performed in accordance with the Helsinki Declaration. This included being registered at ClinicalTrials.gov in December 2014 under the identifier: NCT02323412, approved by the Regional Committees for Medical Research Ethics - South East Norway (2014/158/REK sør-ost) before being commenced and that all participants gave written informed consent. This study is reported in accordance with the CONSORT guidelines [10] and recommendations for research method framework for studies of subgroups in low back pain [8].

Study population
Patients were recruited from outpatient clinics at six hospitals in Norway from June 2015 to September 2017. We included patients with age 18 to 65 years, low back pain for > 6 months, and low back pain intensity ≥ 5 on a 0–10 Numerical Rating Scale, a lumbar disc herniation on MRI in the former two years, and type I and/or type II Modic changes (with height ≥ 10% of vertebral height and diameter > 5 mm) at the herniated disc level. Patients were excluded if they had surgery for disc

Results: None of the four primary potential effect modifiers had strong evidence of modifying the treatment effect. In patients younger than 40 years the difference in mean RMDQ score between the treatment groups was −4.0 (95%CI, −6.9 to −1.2), compared to −0.5 (95%CI, −2.3 to 1.3) in patients 40 years or older, both in favour of amoxicillin treatment (exploratory analysis).

Conclusions: We did not find evidence for convincing clinical effect modifiers of antibiotic treatment in patients with chronic low back pain and Modic changes. Our results for younger age in these explorative analyses should not affect clinical treatment decisions without confirmation in future studies.

Trial registration: ClinicalTrials.gov NCT02323412, First registered 23 December 2014.

Keywords: Chronic low back pain, Modic changes, Antibiotic, Effect modifier, Subgroup, Randomised, Infection.
herniation in the last year, or any specific diagnosis that
could explain patient’s low back symptoms (i.e. tumor,
fracture, spondyloarthritis, infection, spinal stenosis) [5].

**Randomisation, masking and procedures**

Patients were allocated to either three months oral
treatment with amoxicillin 750 mg three times daily or pla-

cebo. Allocation was concealed by a computer generated allocation sequence number and stratified by Modic
change type (I or II) and previous disc herniation sur-
gery (yes or no). All care providers, research staff, statisti-
cians, and patients were blinded to group allocation
during the data collection and analysis. Both treatment
groups received identical capsules, containers, and
labels.

**Outcomes and data collection**

The score on the Norwegian version of the Roland Mor-
ris Disability Questionnaire (RMDQ) at 1-year follow-up
was used as primary outcome. Secondary outcomes were
Oswestry Disability Index (ODI) 2.0 and low back pain
intensity (0–10 NRS). Serum concentrations of CRP
were measured with the same method for all study cen-
tres (Roche Diagnostics) detecting levels down to 0.6
mg/L. We defined type I Modic changes as primary
(most extensive) or secondary type I Modic changes. Pa-
tients with type II Modic changes, but not type I Modic
changes, were defined as belonging to the type II Modic
change group. Two experienced radiologists independ-
ently evaluated Modic changes and trial eligibility based
on a standardized baseline 1.5 T MRI, and discussed and
solved all disagreements on eligibility. There was no
change in the trial measurements after trial start.

**Potential effect modifiers**

We preselected, predefined, pre-categorized and ordered
four baseline characteristics as primary potential effect
modifiers and five as explorative potential effect modi-
fiers, based on a biological rationale and previous litera-
ture (Table 1). An additional three variables (NSAIDs
consumption during treatment phase, compliance and
treatment effect at 3 months) described in the Statistical
Analysis Plan were not analysed, as they were measured
after baseline [18].

**Statistical analysis**

We pre-specified all statistical analyses in a Statistical
Analysis Plan in advance of database locking [19]. We
used the same 50 imputed sets as for the original trial,
where missing RMDQ values (13/180) and missing
values in the secondary outcomes were imputed with a
multiple imputation model using predictive mean
matching as described in the Statistical Analysis Plan for
the main results [20]. Missing values of the potential
effect modifiers were not imputed. All analyses were per-
formed and all figures were made using software pack-
age Stata version 15.

The effect of each of the nine potential effect modifiers
was analysed with an ANCOVA model on the intention
to-treat population using RMDQ scores at 1-year follow
up as the dependent variable. Independent variables in-
cluded the baseline RMDQ score, treatment group, the
effect modifier, treatment group multiplied with the ef-
fect modifier (interaction term), and the stratification
variables embedded in the randomisation (Modic change
type and previous disc surgery). The hypothesis of
whether there is a difference in the treatment effect
across levels of the potential effect modifier was assessed
by the interaction term [18, 21]. We also report mean
differences between the antibiotic and the placebo group
for patients in each category of the subgroup by pairwise
comparison of margins in the model with the interaction
term (stratified analysis). Using the analysis of Modic
change type as an example, the stratified analysis com-
pared the predicted mean in the amoxicillin group with
the predicted mean in the placebo group for only those
patients who had type I Modic changes (and then separate-
ly for those who had type II Modic changes). The stratified
analyses intend to answer “what is the effect of
the treatment in each category of the subgroup?” The
significance test of the interaction term intends to an-
swer “was the observed difference in the treatment effect
between the two categories of the subgroup due to a
statistical significant effect modification?” Our analyses
should not be confused with analyses of prognostic fac-
tors, which is another type of subgroup analyses in
which it is not possible to elucidate if the observed sub-
groups are due to the treatment or not [8].

To explore whether any effect modifier was consistent
across related outcomes we repeated the analyses using
ODI and low back pain intensity as dependent variables
[18]. In addition, to assess if any effect modification
remained when adjusted for the other potential effect
modifiers (independency of effect) [18], we performed
ANCOVA with baseline RMDQ score, treatment groups,
after

As in the original trial, we predefined the minimal
clinically important between-group difference in mean
RMDQ score as 4. The AIM-study was powered for
secondary analyses separately for type I and type II Modic changes, in which 66 patients were needed to detect \((\beta = 0.1, \alpha = 0.05)\) a difference of 4 (standard deviation 5) in mean RMDQ score between the two treatment groups. To equally power effect modifier analyses with interaction terms at the identical effect of the modifier as for the between-group difference, a roughly four times larger sample \((66 \times 4 = 264 \text{ patients})\) would be needed [22]. However, since the present sample \((n = 180)\) give a somewhat lower power of about 75% to assess effect modifier analyses (assuming evenly sized groups and an identical effect size of the modifier as for the between-group difference), we focused on the size and direction of the effects, rather than relying only on the statistical significance of the interaction term. The statistical power was likely somewhat enhanced as we included baseline values of the outcome, and the stratification variables, as covariates. We also analysed the potential effect modifiers in a prioritized order. As the analyses were hypothesis-setting only, we did not adjust the significance level due to multiple testing [8].

### Table 1 Predefined potential effect modifiers of interest

| Potential effect modifier | Biological rationale |
|---------------------------|----------------------|
| **Primary analyses**      |                      |
| 1. Modic changes type I   | We expected a larger treatment effect in type I compared to type II. | Type I Modic changes are more strongly associated with low back pain [11]. In animal models, injecting *C. acnes* into intervertebral discs induced type I Modic changes [12, 13]. |
| 2. Previous disc surgery at level with Modic changes | We expected a larger treatment effect in patients with previous disc surgery compared to those without. | Low-grade discitis might be a complication of disc surgery due to introduction of bacteria into the disc during the surgical procedure. The randomised trial from 2013 with a high number of patients with previous surgery found effect of antibiotic treatment [4], while a case series with few patients with previous surgery was negative [14]. |
| 3. Positive pain provocation test | We expected a larger treatment effect in patients with a positive Sparring test (patient reported pain with pressure applied to lumbar transverse processes) compared to those with a negative Sparring test. | Spinal tenderness may indicate regular spondylodiscitis [15]. Sparring test is found to be borderline significant discriminator between patients with and without Modic changes [16]. |
| 4. Elevated CRP (C-reactive protein) | We expected a larger treatment effect in those with higher CRP. The predefined cut-off values for CRP were changed from 3 mg/L and 10 mg/L to 5 mg/L due to too few patients in the predefined categories. | CRP in serum is associated with bacterial infection and inflammation. |
| **Exploratory analyses**  |                      |
| 1. Disturbed sleep        | We expected a larger treatment effect in those with disturbed sleep than in those without. Disturbed sleep was defined as a \(\geq 2\) score on the Oswestry Disability Index item 7 (sleep scale), i.e. less than 6 h sleep to no sleep because of pain. | Night-time pain may indicate infectious spondylodiscitis [15]. |
| 2. Constant low back pain | We expected a larger treatment effect in those patients with constant low back pain compared to those with fluctuating low back pain. | Constant pain may indicate regular spondylodiscitis [15]. |
| 3. Short duration of low back pain | We expected a larger treatment effect in those with short duration of symptoms compared to those with longer duration of symptoms. The predefined categorization (< 1 year, 1–2 years and \(\geq 2\) years) was dichotomized into < 2 years and \(\geq 2\) years due to too few patients with symptoms < 1 year. | Recent disc herniation could have increased perfusion in the disc as part of disc repair, thereby increasing absorption of amoxicillin. |
| 4. Younger age            | We expected a larger treatment effect in patients < 40 years of age compared to those \(\geq 40\) years of age. | *C. acnes* could be more prevalent in discs of young patients [17]. |
| 5. Male gender            | We expected a larger treatment effect in men compared to women. | *C. acnes* could be more prevalent in discs in men than in women [17]. |
**Results**

Of 180 included patients, 89 were randomised to amoxicillin and 91 to placebo. One patient in the amoxicillin group and one patient in the placebo group did not report the baseline RMDQ. Four patients in the amoxicillin group and seven patients in the placebo group did not report RMDQ at 1-year follow up. All randomised patients were included in the intention-to-treat analyses (multiple imputations were used to account for missing values in the primary and secondary outcomes).

The distribution of the potential effect modifiers at baseline is presented in Table 2. Elevated CRP was present in 14/89 (17%) in the amoxicillin group and in 7/91 (8%) in the placebo group. The distribution of baseline characteristics within each potential effect modifier is presented in Table S1 in the Supplementary Appendix.

**Primary analysis**

The treatment effect (the adjusted mean difference in RMDQ score between the amoxicillin group and the placebo group at 1 year) for patients with type 1 Modic changes was $-2.3$ (95% CI, $-4.2$ to $-0.4$), with type 2 Modic changes $-0.1$ (95% CI, $-2.7$ to $2.5$), and with a difference between the two of $2.2$ (95% CI, $-1.0$ to $5.4$) (estimates from the interaction term) (Fig. 1). The similar treatment effect for patients with previous disc surgery was $-3.2$ (95% CI, $-6.6$ to $0.1$), and for patients without previous disc surgery $-1.1$ (95% CI, $-2.8$ to $0.6$; interaction term, $-2.1$; 95% CI, $-5.8$ to $1.6$), for patients with negative pain provocation test $-4.3$ (95% CI, $-8.5$ to $-0.1$), for patients with positive pain provocation test $-1.2$ (95% CI, $-2.8$ to $0.5$; interaction term, $3.1$; 95% CI, $-1.4$ to $7.6$), for patients with low CRP $-2.0$ (95% CI, $-3.7$ to $-0.4$), and for patients with elevated CRP $2.9$ (95% CI, $1.7$ to $7.6$; interaction term, $4.9$; 95% CI, $0.0$ to $9.9$). The direction of effect for pain provocation test and CRP was opposite of the predefined hypothesis.

**Exploratory analysis**

The adjusted mean difference in RMDQ score between the treatment groups for those with disturbed sleep was $0.2$ (95% CI, $-2.0$ to $2.3$), and for those with undisturbed sleep $-3.3$ (95% CI, $-5.5$ to $-1.1$; interaction term, $3.5$; 95% CI, $0.4$ to $6.6$) (opposite direction of the predefined hypothesis) (Fig. 1). In younger patients, i.e. $<40$ years, the adjusted mean difference was $-4.0$ (95% CI, $-6.9$ to $-1.2$), and in those $\geq 40$ years old $-0.5$ (95% CI, $-2.3$ to $1.3$; interaction term, $3.6$; 95% CI, $0.2$ to $6.9$), in favour of amoxicillin (same direction of effect as hypothesised).

In the multivariate analysis including all effect modifiers and their interaction terms the adjusted mean difference in RMDQ score between the treatment groups was $3.5$ (95% CI, $-0.1$ to $7.0$) points larger for those

| Table 2 Distribution of the potential effect modifiers according to treatment groups |
|---------------------------------|-----------------|-----------------|
|                                 | Amoxicillin ($n = 89$) | Placebo ($n = 91$) |
| **Primary effect modifiers**    |                   |                   |
| Modic changes type I             |                   |                   |
| Yes                             | 58               | 60               |
| No                              | 31               | 31               |
| Missing                         | 0                | 0                |
| Previous disc surgery           |                   |                   |
| Yes                             | 18               | 20               |
| No                              | 71               | 71               |
| Missing                         | 0                | 0                |
| Pain provocation test           |                   |                   |
| Negative                        | 15               | 10               |
| Positive                        | 74               | 81               |
| Missing                         | 0                | 0                |
| CRP                             |                   |                   |
| $< 5$ mg/L                      | 70               | 82               |
| $\geq 5$ mg/L                   | 14               | 7                |
| Missing                         | 5                | 2                |
| **Exploratory effect modifiers**|                   |                   |
| Disturbed sleep                 |                   |                   |
| No                              | 42               | 47               |
| Yes                             | 46               | 42               |
| Missing                         | 1                | 2                |
| Pain characteristics            |                   |                   |
| Fluctuating                     | 70               | 63               |
| Constant                        | 19               | 26               |
| Missing                         | 0                | 2                |
| Duration of low back pain       |                   |                   |
| $< 2$ years                     | 31               | 25               |
| $\geq 2$ years                  | 58               | 65               |
| Missing                         | 0                | 1                |
| Age                             |                   |                   |
| $< 40$ years                    | 28               | 27               |
| $\geq 40$ years                 | 61               | 64               |
| Missing                         | 0                | 0                |
| Gender                          |                   |                   |
| Male                            | 36               | 39               |
| Female                          | 53               | 52               |
| Missing                         | 0                | 0                |

CRP C-reactive protein
ODI Oswestry Disability Index. Score from 0 to 100. Higher scores indicate more severe pain and disability
Fig. 1 Forest plot with results for RMDQ (primary outcome). The difference in mean RMDQ score between the treatment groups (size of treatment effect) with 95% confidence interval is shown in black on the right for each of the two categories of each potential effect modifier. The difference in size of treatment effect between the two categories (estimated by the interaction term), with 95% confidence interval and p-values is shown in red. RMDQ Roland-Morris Disability Questionnaire. Score from 0 to 24. Higher scores indicate more severe pain and disability. CRP C-reactive protein. ODI Oswestry Disability Index. Score from 0 to 100. Higher scores indicate more severe pain and disability. LBP Low back pain.
Fig. 2 Forest plot with results for ODI (secondary outcomes). The difference in mean ODI score between the treatment groups (size of treatment effect) with 95% confidence interval is shown in black on the right for each of the two categories of each potential effect modifier. The difference in size of treatment effect between the two categories (estimated by the interaction term), with 95% confidence interval and p-values is shown in red. CRP C-reactive protein. ODI Oswestry Disability Index. Score from 0 to 100. Higher scores indicate more severe pain and disability. LBP Low back pain.
### Fig. 3

Forest plot with results for low back pain intensity (secondary outcome). The difference in mean low back pain intensity score between the treatment groups (size of treatment effect) with 95% confidence interval is shown in black on the right for each of the two categories of each potential effect modifier. The difference in size of treatment effect between the two categories (estimated by the interaction term), with 95% confidence interval and p-values is shown in red. CRP C-reactive protein. ODI Oswestry Disability Index. Score from 0 to 100. Higher scores indicate more severe pain and disability. LBP Low back pain.

| Factor                          | Treatment Effect | 95% Confidence Interval | p-value |
|---------------------------------|------------------|-------------------------|---------|
| **Overall**                     | -0.6 (-1.3 to 0.0) |                         |         |
| **Modic changes**              |                  |                         |         |
| Type I (n=117)                 | 0.5 (-0.9 to 1.8) | p=0.499                 |         |
| Type II (n=62)                 | -0.8 (-1.8 to 0.0) |                         |         |
| **Previous disc surgery**      |                  |                         |         |
| No (n=141)                     | -1.3 (-2.9 to 0.2) | p=0.092                 |         |
| Yes (n=38)                     | -0.3 (-1.1 to 0.4) |                         |         |
| **Pain provocation test**      |                  |                         |         |
| Negative (n=25)                | 1.1 (-0.8 to 2.9) | p=0.252                 |         |
| Positive (n=154)               | -1.6 (-3.3 to 0.1) |                         |         |
| **CRP**                        |                  |                         |         |
| <5 mg/L (n=151)                | 2.7 (0.7 to 4.7) | p=0.006                 |         |
| ≥5 mg/L (n=21)                 | -0.8 (-1.5 to -0.2) |                         |         |
| **Disturbed sleep**            |                  |                         |         |
| No (n=89)                      | 1.5 (0.2 to 2.8) | p=0.020                 |         |
| Yes (n=88)                     | -1.4 (-2.3 to -0.5) |                         |         |
| **Pain characteristic**        |                  |                         |         |
| Fluctuating pain (n=133)       | 0.0 (-1.5 to 1.5) | p=0.997                 |         |
| Constant pain (n=45)           | -0.6 (-1.3 to 0.2) |                         |         |
| **Duration of LBP**            |                  |                         |         |
| <2 years (n=56)                | -1.1 (-2.4 to 0.3) | p=0.121                 |         |
| ≥2 years (n=123)               | 0.2 (-1.0 to 1.3) |                         |         |
| **Age**                        |                  |                         |         |
| <40 years (n=55)               | 0.6 (-0.9 to 2.0) | p=0.437                 |         |
| ≥40 years (n=124)              | -1.0 (-2.2 to -0.2) |                         |         |
| **Gender**                     |                  |                         |         |
| Male (n=75)                    | -0.0 (-1.3 to 1.3) | p=0.961                 |         |
| Female (n=104)                 | -0.6 (-1.5 to 0.4) |                         |         |
The present findings indicating age as an effect modifier may represent a type I error due to multiple testing. The relationship between age and change in RMDQ from baseline to one year is shown in Fig. S1 in the Supplementary Appendix.

The primary potential effect modifiers had no or only a small effect on ODI or low back pain intensity in the hypothesized direction. The treatment effect did not change a great deal across age categories (9.2; 95%CI 1.6 to 16.8) with a moderate treatment effect in younger patients (−11.2; 95%CI −17.6 to 4.8) on ODI (Fig. 2), but not on low back pain intensity (Fig. 3).

Discussion
In this study, none of the four primary potential effect modifiers (type I Modic changes, previous disc surgery, positive pain provocation test, high CRP) had a clinically relevant or statistically significant impact on the effect of antibiotic treatment in patients with chronic low back pain and type I or II Modic changes at the level of a previous lumbar disc herniation. Patients with low CRP had better treatment effect than those with high CRP, opposite of the prespecified direction, and mainly driven by better RMDQ scores in the placebo compared to the amoxicillin group for those with high CRP, which we find biologically implausible. In the exploratory analyses we observed a small effect modification of disturbed sleep in the opposite of the prespecified direction. We observed a modifying effect of age; patients younger than 40 years had a clinically relevant and statistically significant impact on ODI or low back pain intensity, outside our age limits, and with other comorbidities.

Microbiological studies on disc biopsies show mixed results, and it is still uncertain whether the observed C.acnes in such studies are partly or completely explained by contamination. However, proteomic analyses of degenerated discs did find evidence of response to gram positive bacterial infection that is difficult to explain by contamination [27]. Further trials with antibiotic treatment in back pain should preferably be performed on patients with confirmed infection, either microbiologically or other methods.

Conclusions
We did not find evidence for convincing clinical effect modifiers of antibiotic treatment in this secondary analysis of the AIM study. Age may possibly act as an effect modifier, requiring attention in further studies, but the present results should not affect clinical practice without further confirmation.

Supplementary information
Supplementary information accompanies this paper at https://doi.org/10.1186/s12891-020-03422-y.

Additional file 1: Table S1. Baseline characteristics in the antibiotic and placebo group, for each potential effect modifier. Table S2. Multivariate model of primary outcome (RMDQ). Figure S1. Change in RMDQ score (from baseline to 1-year) by age.
Abbreviations
AIM: Antibiotics in Modic changes; MRI: Magnetic Resonance Image; RMDQ: Roland-Morris Disability Questionnaire; CRP: C-reactive protein; ANCOVA: Analysis of covariance; REK: Regionale komite for medisinsk og helsefaglig forskningsetikk (Regional Committees for Medical and Health research Ethics); CONSORT: Consolidated Standards of Reporting Trials; ODI: Oswestry Disability Index; NSAIDs: Non-steroidal anti-inflammatory drugs; Cacnes: C. butyricum

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Authors’ contributions
All authors critically revised the manuscript for important intellectual content. AA, AJH, JSS, MPR, LCB and AF were trial care providers. AE and PMK evaluated MRIs. LCB did the statistical analyses under supervision of AHP. AF, AJH, ON, AA, JSS, LG and JB were Principal Investigators and took part in planning the study with MG, OL, EIS, AE, JAZ and KS. JAZ was the Coordinating Investigator and KS was the project manager. LCB wrote the first draft with input from KS. All authors read and approved the final manuscript.

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Availability of data and materials
Requests to access data should be addressed to kjersti.storheim@medisin.uio.no. De-identified individual participant data (including data dictionary) will be available to medical researchers by request in accordance with local registration and ethical approval, when the article has been published until 1st of July, 2029. All proposals requesting data access will need to specify an analysis plan and will need approval of the scientific board before any data can be released.

Ethics approval and consent to participate
All procedures performed on human participants were in accordance with the ethical standards of the institutional and national research committee (Regional Committees for Medical Research Ethics - South East Norway, 2014/158/REK sør-øst) and with the 1964 Helsinki declaration and its later amendments. All participants gave a written informed consent to take part in the study.

Consent for publication
Not applicable.

Competing interests
Audny Anke, Anne Julsrud Haugen, Jan Sture Skouen, Mads Peder Rolfson, Lars Christian Bråten, Anne Froholtd, Ansgar Espeland, Per Martin Christoffersen, Are Hugo Pripp, Øystein Nygaard, Lars Gravle, Jens Ivar Brox, Margreth Grotle, Olav Lutro, Christian Hellum, Elina Iordanova Schistad, John-Anker Zwart and Kjersti Storheim declare that they have no conflict of interest.

Author details
FORMI, University Hospital HF, Ulleval, Bygg 37b, Postbox 4956, Nydalnen, 0424 Oslo, Norway. 1Faculty of Medicine, University of Oslo, PO Box 1078 Blindern, 0316 Oslo, Norway. 2Department of Rheumatology, Østfold Hospital Trust, PB 300, 1714 Grålum, Norway. 3Department of Radiology, Haukeland University Hospital, Jonas Lievei 65, 5021 Bergen, Norway. 4Department of Clinical Medicine, University of Bergen, Klinisk institutt 1, Postbox 7804, NO-5020 Bergen, Norway. 5Oslo Centre of Biostatistics and Epidemiology, Research Support Services, Oslo University Hospital, Postbox 4950 Nydalnen, 0424 Oslo, Norway. 6Department of Physiotherapy, Oslo Metropolitan University, PO Box 4 St. Olavs plads, NO-0130 Oslo, Norway. 7Department of Orthopaedic surgery, Oslo University Hospital, Postbox 4956, Nydalnen, 0424 Oslo, Norway. 8Department of Physical Medicine and Rehabilitation, Drammen Hospital, Vestre Viken Hospital Trust Drammen, Postbox 800, 3004 Drammen, Norway. 9Department of Neurosurgery, St. Olavs University Hospital, Postbox 3250 Torgarden, NO-7006 Trondheim, Norway. 10Department of Biostatistics and Epidemiology, Research Support Services, Oslo University Hospital, Postbox 4950 Nydalnen, 0424 Oslo, Norway. 11Department of Neurosurgery, St. Olavs University Hospital, Postbox 3250 Torgarden, NO-7006 Trondheim, Norway. 12Department of Neuromedicine and Movement Science, Norwegian University of Science and Technology (NTNU), Faculty of Medicine and Health Sciences, N-7491 Trondheim, Norway. 13National Advisory Unit on Spinal Surgery, St Olavs Hospital, Postbox 3250 Torgarden, 7006 Trondheim, Norway. 14Savanger University Hospital, Helse Stavanger HF, Postbox 8100, 4068 Stavanger, Norway. 15Department of Rehabilitation, University Hospital North Norway, Postbox 100, 9038 Tromsø, Norway. 16Faculty of Health Sciences, Department of Clinical Medicine, UiT The Arctic University of Norway, 9037 Tromsø, Norway. 17Department of Physical Medicine and Rehabilitation, Oslo University Hospital HF, Ulleval, Postbox 4956, Nydalnen, 0424 Oslo, Norway. 18Department of Physical Medicine and Rehabilitation, Haukeland University Hospital, Helse Bergen HF, Box 1, Bergen, Norway. 19Department of Global Public Health and Primary Care, University of Bergen, Postbox 7804, NO-5020 Bergen, Norway.

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