Spinal pain in Danish school children
Epidemiology and manipulative therapy
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List of papers

The thesis is based on the following papers:


III. Dissing KB, Hartvigsen J, Wedderkopp N, Hestbaek L. Conservative care with or without manipulative therapy in the management of back and/or neck pain in Danish children aged 9-15. A randomized controlled trial nested in a school-based cohort. Submitted, August 2017


The papers are reprinted in Appendix 1.

Furthermore I have been co-author on the following papers, which are related to this project but not part of my thesis:


II. Fuglkjaer S, Dissing KB, Hestbaek L. Prevalence and incidence of musculoskeletal extremity complaints in children and adolescents. A systematic review. Accepted for publication BMC Musculoskeletal Disorders July 2017
Preface

This PhD was conducted part time from August 2011 to August 2017 at the research unit of Clinical Biomechanics in the Department of Sports Science and Clinical Biomechanics, University of Southern Denmark (SDU).

This thesis is based on data from a longitudinal open cohort study: The Childhood Health, Activity and Motor Performance School Study (CHAMPS Study-DK), which commenced in 2008 initiated by Professor Niels Wedderkopp. The CHAMPS Study-DK is a school-based study including approximately 1400 children aged 9 to 15 from 13 public schools in Svendborg, Denmark. The main purpose of this study was to evaluate the influence of extra physical education on the amount of musculoskeletal complaints and on childhood health in general.

Nested in the CHAMPS Study-DK was a randomised controlled trial (RCT) aiming to determine the effectiveness of adding manipulative therapy to other types of conservative care (advice, exercises and soft tissue treatment) in relation to the frequency and duration of spinal pain in children. This RCT was initiated February 2012 and ended in June 2014, and was the main focus for my thesis.

I was involved in study planning and data collection in the CHAMPS Study-DK and the RCT from August 2011 until the data collection on musculoskeletal complaints ended in June 2014.

I gratefully acknowledge The Danish Chiropractic Research Foundation and The University of Southern Denmark for funding my salary for this PhD. Furthermore I acknowledge the following for funding the CHAMPS Study-DK: The Nordea Foundation, The TRYG Foundation, The IMK Foundation, The Region of Southern Denmark, The Egmont Foundation, The A.J. Andersen Foundation, The Danish Rheumatism Association, Østifternes Foundation, Brd. Hartmanns Foundation and TEAM Denmark, University College Lillebælt, Department of Physiotherapy, The Svendborg Project by Sport Study Sydfyn, The Municipality of Svendborg, as well as the Nordic Institute of Chiropractic and Clinical Biomechanics for providing office space and support.
Acknowledgements

I am so very grateful to everyone who has stood by me and supported me on this rollercoaster journey through research! Being a clinician for many years, it has been a turbulent ride into the world of unknown. Many times I wondered what I was doing on that trip and could I please go home now. But coming out on the other side, I must say that it was a ride that I would not have been without.

A lot of people has supported me during this study and I owe a huge gratitude to my supervisors who were brave enough to let me in to the academic world: Jan Hartvigsen, Niels Wedderkopp and most of all to my main supervisor Lise Hestbæk - for all your patience with me and the never ending flow of questions going your way and for putting your foot down at the right times.

Warm and thankful thoughts to my very good friend and colleague Susanne Vejsgaard Vesterager for planting the seed in the first place. If it were not for you, I would not have been here.

I would also like to express my gratitude to the whole CHAMPS-Study-DK team for all your effort and great work: Signe Fuglkjær, Dorthe Brandborg Olsen, Tina Junge, Lisbeth Runge, Mathilde Jensen, Lene Kaysen, Henrik Eshøj, Kirstine Bay Hoyer and Eva Jespersen. This was a big ship to sail, but we managed together.

Furthermore, I would like to thank all the chiropractors taking out time of their daily life to participate in this project: Henrik Mazanti, Christian Castella, Sine Kiilerich Andresen, Marianne Christoffersen and Ulla Brøgger. You have made a huge contribution.

Thanks to all my fellow PhD students in the research unit of Clinical Biomechanics. It has been good knowing we were all in the same boat, especially at times with too much rocking.
A special thanks to Signe Fuglkjær, with whom I have shared office space, frustrations, joyful moments and lots of coffee!

Thanks to Eleanor Boyle for always taking your time to answer all sorts of questions and helping me survive the world of statistics, and for offering Canadian sweets at all times. Thanks to Werner Wach for statistical advice throughout the process.

Thanks to Inge Ris for taking your time to read this thesis through and giving constructive feedback on whether it made sense at all.

To Christopher Williams from the University of Newcastle, Australia, thank you for giving me the opportunity to have a study period abroad and for introducing me to a different research environment and to lots of nice people.

And a very big thank you to all the children and parents from Svendborg, who have made a great contribution by participating in this project for such a long time and to ‘Sport og Uddannelse, Svendborg Kommune’ for supporting the project.

Most importantly: to my husband Hans Peder and our lovely daughters Benedikte and Elisabeth – thank you for supporting me in this crazy decision going into this challenging world. For always being there for me, your patience and shoulders to cry on and arms to hold in joy. Love you to the moon!
Summary English

There is increasing evidence that spinal pain (i.e. back- and/or neck pain) in children and adolescents is a common condition but usually transient and inconsequential for most children and rarely associated with serious pathology. However, there seems to be a considerable subgroup of children with recurrent and bothersome spinal pain that is in need of more attention. This is especially important considering the fact that the lifetime prevalence increases steadily to reach adult levels around the age of 18 and that children with spinal pain are more likely to become adults with spinal pain. Despite increasing knowledge, there is still a lack of research, both in relation to occurrence and to efficient treatment strategies, necessitating longitudinal studies in this area.

Today, no ‘gold standard’ treatment for spinal pain in children exists, but manipulative therapy is increasingly being used in spite of a lack of evidence of its effectiveness. Instead, management of children’s health relies to a large extent on parents’ values, preferences and experience, and healthcare professionals have to depend on guidelines developed for adults.

The overall aims of this thesis were to explore the magnitude of spinal pain in Danish school children, particularly duration and frequency, and to evaluate the effectiveness of manipulative therapy in addition to other types of conservative care in the treatment of this spinal pain. In addition, the effect of potentially modifying factors was explored.

This thesis is based on data from a 3-year longitudinal school-based open cohort study, the CHAMPS Study-DK. The outcomes were based on weekly text messages (SMS) to one of the parents inquiring about the child’s musculoskeletal pain, and on clinical data from examinations of the children. A two-arm pragmatic randomised controlled trial was conducted to determine the effectiveness of manipulative therapy when added to other types of conservative care. Interventions included either 1) advice, exercises, and soft tissue treatment (control), or 2) advice, exercises, and soft tissue treatment plus manipulative therapy (intervention).
This study demonstrated that spinal pain is a rather substantial problem. Most episodes are brief, but there are a vast number of children with frequent and long-lasting episodes of spinal pain. In at least a quarter of those with spinal pain, the episodes lasted for more than four weeks and/or occurred three times or more during a school year.

We found no significant difference in the number of recurrences of episodes of spinal pain when adding manipulative therapy to other conservative treatment, but children in the manipulative therapy group had a higher Global Perceived Effect. In the subgroup analyses, we found weak tendencies supporting our hypotheses about a greater chance of improvement in response to manipulative therapy in the most affected children regarding duration and frequency, whereas the least affected children showed no or even negative response if they were randomised to manipulative therapy.

Future research should focus on evidence-based prevention and efficient treatment regimes for the most affected children. Furthermore, a more qualitative approach should be incorporated into future trials and self-reported outcomes measuring improvement in children should be validated.

Det overordnede formål med denne afhandling var at beskrive omfanget af ryg- og nakkesmerter hos danske skolebørn, især i forhold til varighed og hyppighed, samt at vurdere den additive effekt af manipulationsbehandling til anden konservativ behandling heraf. Derudover ville vi undersøge effekten af potentielle modificerende faktorer.

Denne afhandling er baseret på data fra et 3-årigt longitudinelt skolebaseret åbent kohortestudie, CHAMPS-Study DK. Effektmålene var baseret på ugentlige SMS spørgsmål sendt til en af forældrene, hvor de blev spurt om barnet havde haft nogen muskuloskeletale gener i den forgangne uge, samt på data fra kliniske undersøgelser af barnet. En pragmatisk randomiseret kontrolleret undersøgelse blev gennemført for at vurdere effekten af manipulationsbehandling tilføjet til anden konservativ behandling. Interventionen inkluderede enten 1) rådgivning, træning og bløddelsbehandling (kontrol gruppe) eller 2) rådgivning, træning og bløddelsbehandling plus manipulationsbehandling (interventions gruppe).

Vi fandt ingen signifikant forskel i antallet af tilbagefald med ryg- og nakkesmerter ved at tilføje manipulationsbehandling til anden konservativ behandling, men børnene i manipulationsgruppen havde bedre 'Global Perceived Effect'.

Subgruppe-analyserne viste svage tendenser til understøtning af vores hypotese; at de mest påvirkede børn ville have større effekt af manipulationsbehandling, hvorimod de mindst påvirkede børn havde enten ingen eller dårligere effekt hvis de fik manipulationsbehandling.

Fremtidig forskning bør fokusere på at øge vores viden omkring evidens baseret forebyggelse og effektive behandlings strategier de mest påvirkede børn for. Endvidere bør der inkorporeres en mere kvalitativ tilgang i kommende undersøgelser og effektmål omkring forbedring bør valideres på børn.
### Abbreviations and definitions

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>CHAMPS Study-DK</td>
<td>The Childhood Health, Activity and Motor Performance School Study</td>
</tr>
<tr>
<td>EoCC</td>
<td>Expectations of the Clinical Course</td>
</tr>
<tr>
<td>GPE</td>
<td>Global Perceived Effect</td>
</tr>
<tr>
<td>IQR</td>
<td>Interquartile range</td>
</tr>
<tr>
<td>IRR</td>
<td>Incidence rate ratio</td>
</tr>
<tr>
<td>KIDScreen</td>
<td>Quality of life questionnaire developed for children aged 8-18</td>
</tr>
<tr>
<td>MT</td>
<td>Manipulative therapy</td>
</tr>
<tr>
<td>Non-MT</td>
<td>Non-manipulative therapy</td>
</tr>
<tr>
<td>NRS</td>
<td>Numerical rating scale ranging from 0-10</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>PE</td>
<td>Physical education</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised controlled trial</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SMS</td>
<td>Short Message Service (text message)</td>
</tr>
<tr>
<td>SP</td>
<td>Spinal pain: neck, mid back and/or low back pain</td>
</tr>
</tbody>
</table>
1. Introduction

1.1. Spinal pain and epidemiology

The focus of this thesis is spinal pain defined as pain in the back and/or neck region. There is increasing evidence that spinal pain in children and adolescents is a common condition but usually transient and inconsequential for most children and rarely associated with serious pathology\(^1\)\(^-\)\(^3\). However, there seems to be a subgroup of children with recurrent and bothersome spinal pain that is in need of more attention\(^3\)\(^,\)\(^4\). This is especially important considering the fact that the lifetime prevalence increases steadily to reach adult levels around the age of 18\(^1\)\(^,\)\(^2\) and that children with spinal pain are more likely to become adults with spinal pain\(^2\)\(^,\)\(^5\). Furthermore, spinal pain ranks third among reasons for years lived with disability for individuals within the range of 15-19 years\(^6\).

It is difficult to obtain a comprehensive picture of the extent of spinal pain in children due to great heterogeneity in which spinal pain is measured and reported across different studies\(^1\)\(^-\)\(^7\)\(^,\)\(^8\). Prevalence ranges from 1\% - 89\%, including point, period and lifetime prevalence, with period prevalence being the most frequently reported\(^3\)\(^,\)\(^8\)\(^,\)\(^9\). The most commonly used type of data collection are questionnaires, followed by physical examinations and interviews\(^8\). There is considerable variation in how spinal pain is defined; some define spinal pain as one region and some as three different regions (cervical, thoracic and lumbar pain), and there is no consensus on what is the most appropriate definition to use\(^3\)\(^,\)\(^7\)\(^,\)\(^10\). Furthermore, the definition on the different regions are not always consistent, e.g. sometimes the definition of lumbar pain includes pelvic pain and sometimes not\(^6\).

Another important issue to consider regarding reporting of spinal pain, is length of recall period, which varies from 1 week to lifetime, which makes comparison of studies rather difficult\(^6\)\(^,\)\(^11\). Additionally, it is often unclear, whether the parent assisted the child in pain estimation or if it was a self-report by the child itself\(^1\), which may impact the results obtained\(^12\). Parents seem to under report compared to the child when the pain is low, whereas the concordance is better when the pain is more severe\(^12\). There is limited research on memory for pain in children. The most reliable period for recall in adolescents
seems to be up to 1 month, but results are unclear if the period is longer, which is the case in spinal pain studies with recall periods up to one year. The use of prospective studies has therefore been recommended to improve pain assessment and diminish recall bias.

Therefore, there is still a wide gap in our understanding of duration and frequency, necessitating longitudinal studies in this area. Reliable understanding of prevalence and course of spinal pain is essential for further research into the development of effective prevention and treatment strategies. Knowledge about recurrent events of spinal pain for adolescents is sparse and broad definitions of an ‘episode’ of pain are often used. It seems that spinal problems usually are of a shorter duration and self-limiting, but for some children spinal pain is recurrent in nature, and this group should be given more attention, especially considering the fact that the more days with low back pain in adolescence, the higher the risk of future low back pain in adulthood.

The etiology of spinal pain in children is still unclear, and associations with different physical, psychological and social factors have been explored but the direction of these associations is unclear, whether spinal pain is the chicken or the egg. Age and sex are regarded as important predictors of spinal pain. Discrepancies regarding the association to sex have been found, but most studies report higher prevalence for girls. We know, that age is an important factor as prevalence increase with age, particularly around the age of 12. This age group (or earlier) could be a window of opportunity in terms of exploring conditions surrounding the initial onset, which could give a better chance of developing preventive approaches and/or efficient treatment regimes.

Physical activity has been investigated in a number of studies, as it seems logical that this could be associated to spinal pain. Wedderkopp et al. demonstrated that a higher level of physical activity seemed to protect against low back and mid back pain, and Timpka reported that particularly girls with a low level of physical activity had a higher risk of getting musculoskeletal diagnoses. In contrast to these results, Aartun found no overall association between physical activity and spinal pain, but that the most active adolescents were at higher risk of developing spinal pain.
Various psychosocial factors have been investigated in children and adolescents: a recent study by Stallknecht et al.\textsuperscript{23} showed that spinal pain in adolescents co-occurs with stress and poor general well-being. Furthermore, children with high level of psychosocial difficulties are more likely to develop back pain\textsuperscript{24} and high levels of psychosomatic symptoms and depression were associated with higher odds of having spinal pain\textsuperscript{25}. These results indicate the importance of incorporating a psychosocial approach to the management of children with spinal pain, and not only focus on the physical aspects.

Stinson et al.\textsuperscript{26} explored this in children with chronic musculoskeletal pain, and her results emphasized that children cannot be viewed as little adults in terms of prevention and treatment, and therefore other models should be developed.

1.2. Consequences

Why is this area so important, what are the consequences? Most importantly, experiencing pain in childhood should be avoided, because of the pain in itself. Furthermore, pain can be a barrier to physical activities, which could potentially have an impact on both physical and psychological health in terms of e.g. higher chance of comorbidity\textsuperscript{27, 28}, skipping school\textsuperscript{29}, inability to participate in hobbies or relate with friends\textsuperscript{29, 30}, or disturbed sleep\textsuperscript{29}.

Maintaining ability to be physically active is especially important in this age group, since the level of physical activity decreases during adolescence\textsuperscript{31, 32}. Several studies have shown that there seems to be a relationship between musculoskeletal pain and other adverse health risk factors, e.g. overweight, poor mental health and smoking\textsuperscript{14}. This could have immense consequences on adult health, as poor lifestyle habits in adolescence are known to continue into adulthood. Another consequence is the strong association between pain medication and recurrent low back pain\textsuperscript{33}, which is an important issue to address, considering insufficient knowledge of appropriate use and potential risk associated with intake\textsuperscript{34}. In particular regarding adolescents with recurrent pain, who are more likely to use medication for non-pain conditions too, e.g. for sleep difficulties\textsuperscript{33}.

Furthermore, previous episodes of spinal pain or widespread body pain and combined musculoskeletal pain appear to be predictive of future low back pain in children\textsuperscript{35, 36}. Balague et al. reported that low back pain affects health-related quality of life marginally, but a subgroup of children with both low back pain and whole body pain had significantly impaired quality of life. This implies that complaints may cluster in some children.
Considering the association between low back pain in adolescence and low back pain in adulthood\textsuperscript{2-5}, and the association between spinal pain and other lifestyle disorders, recurrent spinal pain in children and adolescents also presents a potentially significant health challenge in their adult years. Musculoskeletal problems in childhood can lead to not only other musculoskeletal problems in adulthood, but also lifestyle diseases like diabetes or cardiovascular diseases\textsuperscript{29,37}, which in both a personal and a socioeconomic perspective can be comprehensive. Additionally, the economic burden on society is substantial\textsuperscript{38,39}; in Denmark annual direct and indirect costs are around 13 billion kroner\textsuperscript{40,41}.

1.3. Potential solutions

\textit{Epidemiology}

Since evidence is so sparse and the knowledge so limited, it is important to gain reliable understanding of the magnitude of spinal pain in children and adolescents, which applies to both duration and frequency. Hence, prospective studies as longitudinal research is warranted with frequent follow ups, to provide more detailed information about course and consequences, especially regarding identification of those at high risk of long-term pain and disability.

\textit{Manipulative therapy}

A focused effort is needed towards early prevention and effective treatment strategies of spinal problems in childhood, especially if we want to maintain physical activity and limit long-term weakness and reduced function in the population caused by spinal pain. Today, no 'gold standard' treatment for spinal pain in children exists\textsuperscript{14,42,43}, but manipulative therapy is increasingly being used in spite of a lack of evidence of its effectiveness\textsuperscript{30,44}. Management of children's health relies to a large extent on parents' values, preferences and experience, and healthcare professionals have to rely on guidelines developed for adults\textsuperscript{45-47}, which primarily recommends patient education including advice on staying active, manual therapy and supervised exercise. One review found only four RCTs dealing with conservative interventions for low back pain in children and they all had a high risk of bias\textsuperscript{43}. One of the studies included manual therapy combined with exercise, but it had only
45 participants, and the final conclusion was that further research was needed and that no conclusion regarding preventive interventions could be drawn. In recent years there has been an increasing focus on identifying subgroups of patients who are likely to respond to a particular type of treatment and it is highly likely, that certain subgroups exists, as clinicians already consider and treat adult patients differently for low back pain. To our knowledge this has not been investigated in children, and it is unclear if there are subgroups of children who respond better or worse to manipulative therapy than others. Since manipulative therapy is being widely used, and no clear evidence is present, we believe that further research in this area is warranted including potential subgroup effect.
2. Aim

The overall aims of this thesis were to explore the magnitude of spinal pain in Danish school children, particularly regarding duration and frequency, and to evaluate the relative clinical effectiveness of manipulative therapy in addition to other types of conservative care in the treatment of this spinal pain. In addition, the effect of potentially modifying factors was explored.

Paper I (Prevalence)

The purpose of this paper was to describe the characteristics of spinal pain episodes in 8-15-year-old Danish school children during three school years. Specifically we aimed to:

1. Report the proportion of individuals reporting any type of spinal pain during a school year
2. Report the prevalence, frequency and duration of spinal pain per school year by means of:
   a. The proportion of weeks with spinal pain per child
   b. The number of spinal pain episodes per child
   c. The length of spinal pain episodes
   d. The relationship between number of episodes and episode length per child
3. Determine the relationship between the episode length and pain site (cervical, thoracic or lumbopelvic), and between episode length and complaint severity.

Paper II (RCT protocol)

The purpose of this paper was to describe the background and methodology (study protocol) of a randomised controlled trial. The aim was to determine the effectiveness of adding manipulative therapy to other conservative care (advice, exercises and soft tissue treatment) in Danish children aged 9 to 15 years who were participating in a school-based open cohort study.

Paper III (RCT primary analyses)

The purpose of this paper was to report the results of the randomised controlled trial described in Paper II, using following outcomes:

1. Primary outcome: number of recurrences of spinal pain during the follow-up period (3-27 months).
2. Secondary outcomes:
   a. Average duration of spinal pain episodes
   b. Total duration of complaint time
   c. Change in pain intensity after 2 weeks
   d. Global Perceived Effect after 2 weeks

**Paper IV (RCT effect modification)**

The purpose of this paper was to explore whether potential treatment effect modifiers, i.e. baseline variables, may be associated with difference in outcomes between the two intervention groups from the RCT described in Paper II and III. Outcomes from the main analysis being explored were:

   1. Number of recurrences of spinal pain during the follow-up period (3-27 months)
   2. Average duration of spinal pain episode
   3. Total duration of complaint time

Potential effect modifiers being explored:

   1. Spinal pain 6 months prior to inclusion
   2. Co-occurring musculoskeletal pain 6 months prior to inclusion
   3. Expectations of the clinical course of spinal pain
   4. Pain intensity
   5. Quality of life
3. Method

3.1. Design
This project is based on data from The Childhood Health, Activity and Motor Performance School Study (CHAMPS Study-DK), which is a Danish longitudinal school-based open cohort study\(^{50}\). Due to the open cohort design, children could enter or leave the project at any time during the study period. Nested in this study was a pragmatic parallel two-armed randomised controlled trial (RCT).

3.2. Participants and setting
Participants in the CHAMPS Study-DK were children aged 8 to 15 years from 13 public schools in the municipality of Svendborg, which is considered representative of the Danish population\(^{50}\). The main purpose of the CHAMPS Study-DK was to evaluate the influence of extra physical education (PE) lessons on general childhood health including musculoskeletal complaints. The schools were divided into two groups: one group receiving the normal amount of two PE lessons per week and the other receiving six PE lessons per week. At baseline, the children and their parents completed a questionnaire addressing age, gender, health status, social class, work and leisure time activities. Schools were matched according to size and socio-economic status within the uptake areas. The study was initiated in 2008 and the data collection regarding musculoskeletal complaints and physical activity ended in 2014. Data from 2011 to 2014 were used for this thesis.

In January 2012, all children enrolled in the CHAMPS Study-DK were invited to participate in the RCT, determining the effectiveness of adding manipulative therapy to other conservative care, if they experienced spinal pain during the study period. There was a pilot phase from February to March 2012 to test procedures and logistics, where no problems were encountered. No adaptations were made, so the RCT continued unaltered. All examinations and treatments took place at the schools.

3.3. Data collection
All the children in the CHAMPS Study-DK have been followed with different kinds of testing throughout the study, e.g. physical tests, blood samples and DEXA scans. However, for this project only reports of musculoskeletal pain were relevant. These were obtained through
weekly text messages (SMS) and clinical examinations. Different teams were responsible for different aspects of the study.

3.3.1. The teams

The research team
The research team consisted of researchers with different professional backgrounds, e.g. medical doctors, chiropractors, physiotherapists, investigating diverse aspects of childhood health. This team was responsible for planning, funding and administration of the study, and for the research questions being explored.

The clinical team
The clinical team consisted of experienced chiropractors and physiotherapist with extensive knowledge in managing children. This team was responsible for the data collection (telephone interviews, examinations of musculoskeletal complaints and SMS data checking) and the daily logistics, as well as communication to parents, schools and Svendborg municipality.

The RCT team
The RCT team consisted of seven experienced chiropractors from private practice, who were responsible for all the treatments provided in the RCT (control and intervention), as well as communication to the parents regarding treatment planning.

3.3.2. SMS
The basis for the analyses on musculoskeletal complaints in this thesis was the text messaging system, the SMS Track. Weekly text messages (SMS) to one of the parents of participating children, inquired about any musculoskeletal complaints, and the amount and type of leisure time sports activity during the past week (see Appendix 2). Hence, the parents were used as proxy on behalf of their child. Answers were automatically registered, entered and stored in a database. If the parent did not reply, he or she automatically received up to two SMS reminders within a week. If the answers were invalid, e.g. text or incorrect numbers, a research assistant would telephone the parents to clarify the reply. The SMS-response is a very efficient way to obtain information on a frequent basis\textsuperscript{51,52}. There were no text messages during the summer and Christmas
holidays because there was no possibility of pursuing positive pain reports in that time span.

In the first SMS question, parents were asked if their child had any musculoskeletal pain in the previous week. Response options were: ‘1’ for spinal pain, ‘2’ for upper extremity pain, ‘3’ for lower extremity pain, or a response containing any combination of the three numbers, or ‘4’ if there was no pain. Parents were instructed to continue answering (e.g. ‘1’) as long as the child was experiencing musculoskeletal pain. Thus we were able to identify how often and how long a child was affected by pain. With every new positive reply on the SMS to the presence of musculoskeletal pain after a pain free period, a member of the clinical team telephoned the parent and conducted a standardised interview about the complaint, in order to determine the severity. Complaint severity was classified as trivial or non-trivial by the interviewer based on anamnestic information about the history of the complaint, the duration, the potential cause, and the nature of the pain. If the complaint was considered to be non-trivial, an appointment for an examination was scheduled.

3.3.3. Clinical procedures
The examinations of all non-trivial musculoskeletal complaints took place at the child’s school within the subsequent two weeks of the first report. A member of the clinical team performed the examination. Subsequently, the child received a tentative diagnosis and advice on how to handle his/her problem. Complaints were categorized according to the International Classification of Diseases (ICD-10), and the parents were informed about the result and any possible actions following the examination, either by telephone or letter. All data were filed in an electronical journal system established specifically for this project and stored on a secure server.

RCT
If a parent answered positively on the SMS to the presence of spinal pain on behalf of their child, the telephone interview was conducted in order to determine whether the child was eligible for inclusion in the RCT. Initial eligibility was based on: 1) the pain was spinal and still present at the time of the interview, 2) the parent had agreed, on behalf of the child, to
join the RCT, and 3) the child had not had any manual therapy of the spine during the previous 2 months. If these eligibility criteria were fulfilled, the child was evaluated for inclusion into the trial within the subsequent two weeks at the school by a chiropractor from the RCT team. The flow can be seen Figure 1.

**Figure 1 Flow from SMS to RCT**

![Diagram showing the flow from SMS to RCT](attachment://diagram.png)

**RCT**: randomised controlled trial. **SMS**: text message. **MT group**: manipulative therapy group. **Non-MT group**: non-manipulative therapy group

**First consultation in the RCT**

At the first consultation, the chiropractor obtained a case history, including pain intensity on an 11-box Numerical Rating Scale (NRS)\(^53\), performed a clinical examination, and acquired various baseline data (Table 1).
Table 1 Baseline data and definitions

<table>
<thead>
<tr>
<th>Baseline data</th>
<th>Definitions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KIDSCREEN 27 questionnaire</strong></td>
<td>Quality of life measured from 27 questions covering the following five domains. Values vary from 10-70 with population norm mean=50, high value equals better QOL</td>
</tr>
<tr>
<td><strong>KID Physical</strong></td>
<td>Physical wellbeing domain</td>
</tr>
<tr>
<td><strong>KID Psych</strong></td>
<td>Psychological wellbeing domain</td>
</tr>
<tr>
<td><strong>KID Autonomy</strong></td>
<td>Autonomy and parent relation domain</td>
</tr>
<tr>
<td><strong>KID Social</strong></td>
<td>Social support and peers domain</td>
</tr>
<tr>
<td><strong>KID School</strong></td>
<td>School domain</td>
</tr>
<tr>
<td><strong>Expectations of the Clinical Course (EoCC)</strong></td>
<td>The child was asked before the treatment: “What do you expect the outcome of your spinal pain will be compared with how it is now?” Rated on a 5-point scale (‘1’ being ‘much worse’ and ‘5’ being ‘much better’)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>9-15 years</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>Boy/girl</td>
</tr>
<tr>
<td><strong>Intervention group</strong></td>
<td>Manipulative group (MT)/non-manipulative group (non-MT)</td>
</tr>
<tr>
<td><strong>School</strong></td>
<td>13 schools included</td>
</tr>
<tr>
<td><strong>Class</strong></td>
<td>4th to 9th grade</td>
</tr>
</tbody>
</table>

Based on this evaluation, it was determined whether the child fulfilled the inclusion criteria (Table 2). After the evaluation, both the parents and the child were informed about the results and if included, the child was randomised to one of two intervention groups and treatment was initiated. Two weeks after inclusion, the child was asked about Global Perceived Effect (GPE) and pain intensity (NRS).

**Randomization**

A computer-generated block randomization was made with block sizes alternating between two and six at the time of inclusion, using a 1:1 allocation to the two groups. The consecutive designations of the two groups were written on separate pieces of paper and given to the chiropractors in the RCT team in sealed opaque envelopes. A research assistant, who was not otherwise connected to the study, performed the procedure.

Table 2 Inclusion and exclusion criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Pain in neck or back equal to or greater than 3 on an 11-box numerical rating scale for more than 3 days</td>
<td>• Serious pathology (cancer, inflammatory diseases, vertebral fractures, cauda equina syndrome)</td>
</tr>
<tr>
<td></td>
<td>• Manual treatment for the past 2 months (for this particular complaint)</td>
</tr>
<tr>
<td></td>
<td>• Handicaps preventing normal physical activity</td>
</tr>
</tbody>
</table>
**Interventions**
The non-manipulative therapy group received advice, exercises and, soft tissue treatment, and the manipulative therapy group received the same plus manipulative therapy (Table 3).

<table>
<thead>
<tr>
<th>The non-manipulative group</th>
<th>The manipulative group received</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Pragmatic advice (activity level, ergonomics, cold packs etc.)</td>
<td>• Advice, exercises and soft tissue treatment</td>
</tr>
<tr>
<td>• Exercises (stretching and/or strengthening exercises)</td>
<td>• Manipulative therapy: joint manipulation and/or mobilization</td>
</tr>
<tr>
<td>• Soft tissue treatment (manual trigger point therapy or massage)</td>
<td></td>
</tr>
</tbody>
</table>

Manipulative therapy was delivered at the discretion of the chiropractor from the RCT team and applied on the basis of an evaluation from the clinical examination of the child’s spine and extremities. Due to the pragmatic nature of the study, the frequency and content of treatments in both groups was determined by the chiropractor at each consultation, similar to normal procedure in clinical practice and treatments continued until the child was asymptomatic regarding the musculoskeletal complaint, or until the chiropractor or parent decided that further treatment was not indicated.

**Blinding**
Due to the nature of the intervention, blinding of the treating chiropractors was not possible, however, neither parents nor children were informed about group allocation, parents did not attend consultations and they answered the SMS independent of clinicians or researchers. The coding of the intervention group was not revealed to the primary investigator or the statisticians until after completion of analyses.

**3.4 Ethics**
All parents gave written informed consent to participation on behalf of their child and the children gave oral consent. Before every clinical examination, the parents gave verbal...
consent and the child assented. All participation was voluntary and the parent or child could withdraw from the study or parts of it at any time during the study period. All participants were treated according to the Helsinki declaration. The project was approved by the Regional Committee on Health Research Ethics (#S-20110042) and data are being handled according to regulations by the Danish Data Protection Agency (#2013-41-1738).

Temporary reddening and soreness in the treated area is common after both soft-tissue and manipulative therapy. To our knowledge, no serious harms following manipulative therapy have been reported in children of this age group and no compensation claims have ever been made for this age group in Denmark.

3.5. Data analysis

3.5.1. Paper I (Prevalence)

To avoid break in data continuity due to the six week Summer holiday, we chose to report by school year rather than for three full calendar years, e.g. school year 1 representing the school year starting in August 2011 and ending in June 2012. Outcomes, definitions and statistical methods presented in Table 4. Significance level was set to 5%.
Table 4 Outcomes, definitions and statistical methods (Paper I)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Definition</th>
<th>Statistical method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of individuals reporting any type of spinal pain during a school year</td>
<td>A positive answer on the weekly SMS for spinal pain (‘1’)</td>
<td>Prevalences (%) with 95% confidence intervals (CI), including sex- and age specific prevalences. Wilcoxon-type test for trend used for relationship with age</td>
</tr>
<tr>
<td>Proportion of weeks with spinal pain per school year per child</td>
<td>Calculated by dividing all answers that included a ‘1’ by the total weeks of observation within that school year</td>
<td>Histograms including medians with interquartile ranges, and means with standard deviations</td>
</tr>
<tr>
<td>Number of spinal pain episodes per school year per child</td>
<td>A new episode was defined as an episode occurring after at least one week without spinal pain (‘1’)</td>
<td>Numbers and percentages, described with medians with interquartile ranges and means with standard deviations</td>
</tr>
<tr>
<td>Length of spinal pain episodes per school year</td>
<td>Number of weeks of continuous reporting of spinal pain (‘1’)</td>
<td>Numbers and percentages, medians with interquartile ranges and means with standard deviations</td>
</tr>
<tr>
<td>Relationship between number of episodes and episode length per school year per child</td>
<td></td>
<td>Wilcoxon-type test for trend</td>
</tr>
<tr>
<td>Relationship between episode length and pain site (cervical, thoracic or lumbopelvic pain), and between episode length and complaint severity</td>
<td>Non-trivial spinal pain was coded into pain sites, i.e. cervical, thoracic, lumbopelvic or multisite pain (defined as pain in more than one spinal region) (clinical examination data)</td>
<td>Prevalences with 95% CI and episode length (medians with interquartile ranges and means with standard deviations). Differences between groups evaluated using One-way analysis of variance for complaint type and t-test for pain site</td>
</tr>
</tbody>
</table>

3.5.2. Paper III and IV (RCT)

The analyses followed intention-to-treat principles. The study had continuous inclusion hence we were able to recruit participants until 3 months prior to the end of data collection in summer 2014, to include as many participants as possible. This resulted in children having varying follow-up times. Class and school were evaluated and included in the
models as random effects if their effect was statistically significant. Outcomes, definitions and statistical methods presented in Table 5. Significance level was set to 5%.

Table 5 Outcomes, definitions and statistical methods (Paper III and IV)

<table>
<thead>
<tr>
<th><strong>Primary outcome</strong></th>
<th><strong>Definition</strong></th>
<th><strong>Statistical method</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of recurrences of spinal pain (3-27 months follow up)</strong></td>
<td>i) A positive answer on the weekly SMS for spinal pain ii) Minimum of 1 week without report of spinal pain prior to the recurrence</td>
<td>To estimate level of statistical significance, a hierarchical negative binomial regression model was used. Intervention effects were expressed as incidence rate ratio</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Average duration of spinal pain episodes</strong></td>
<td>The number of consecutive weeks the child was affected by spinal pain (response option ‘1’)</td>
<td>To estimate level of statistical significance, a mixed effects linear regression model with subject as random effect and outcome log transformed was used. Intervention effects were expressed as the difference in median length</td>
</tr>
<tr>
<td><strong>Total duration of complaint time in relation to individual follow-up time</strong></td>
<td>Total number of weeks a child was affected by spinal pain (response option ‘1’) in the entire follow-up period</td>
<td>To estimate level of statistical significance, a hierarchical negative binomial regression model was used. Intervention effects were expressed as incidence rate ratio</td>
</tr>
<tr>
<td><strong>Global Perceived Effect after 2 weeks</strong></td>
<td>Dichotomized into two groups: “Much better” and “The same or worse”</td>
<td>To estimate level of statistical significance, a logistic regression model was used. Intervention effects were expressed as odds ratios</td>
</tr>
<tr>
<td><strong>Change in pain intensity after 2 weeks</strong></td>
<td>Rated on an 11-point Numerical Rating Scale with ‘0’ being ‘no pain’ and ‘10’ being ‘worst pain’</td>
<td>To estimate level of statistical significance, a linear regression model was used. Intervention effects were expressed as the difference in mean length</td>
</tr>
</tbody>
</table>
3.5.3. Paper IV (RCT Effect modification)

Baseline variables measured before randomization were dichotomized and used as potential effect modifiers (Table 6). We hypothesized that the most affected children would gain the most benefit from manipulative therapy when compared to the least affected. To make this comparison, we chose to dichotomize the variables by using the upper 10% as the cut point, thereby assessing the most affected children. Potential effects were explored by comparing the outcome between the two intervention groups in each of the two strata, e.g. high versus low level of pain at baseline. Interaction tests were conducted for each of the potential modifiers using the original regression models for the three first outcomes from the primary analysis (Table 5) including intervention group, the potential modifier and the interaction between intervention group and modifier. Forest plots were made for graphical interpretation and confidence intervals and p-values were inspected for significance.

Table 6 Potential effect modifiers and definitions

<table>
<thead>
<tr>
<th>Effect modifier</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal pain (SP)</td>
<td>Defined by number of weeks with spinal pain during the 6 months prior to inclusion. SP&gt;20% of time = considerable amount of pain. Six months was chosen because we considered this to be an adequate time span for experiencing persistent or recurring pain.</td>
</tr>
<tr>
<td>Co-occurring musculoskeletal pain (CMP)</td>
<td>Defined by number of weeks having pain in more than one region (spine, upper and/or lower extremity) more than 20% of the time during the 6 months prior to inclusion. CMP &gt;20% of time = considerable amount of pain.</td>
</tr>
<tr>
<td>Expectations of the clinical course (EoCC)</td>
<td>Rated on a 5-point scale with ‘1’ being much worse and ‘5’ being much better. Dichotomized into ‘Much better’ (value=5) and ‘The same or worse’ (value&lt;5) (Due to a very small number of children in the most extreme category, we were not able to use the 10% percentile.)</td>
</tr>
<tr>
<td>Pain intensity (NRS)</td>
<td>Rated on an 11-point Numerical Rating Scale (NRS) with ‘0’ being ‘no pain’ and ‘10’ being ‘worst pain’. The upper 10% chosen as the cut point, hence dichotomized into (high &gt;7 vs. low ≤7)</td>
</tr>
<tr>
<td>Quality of life (QoL)</td>
<td>Each domain was dichotomized into high vs. low quality of life using the 10% threshold from our own population as cut points.</td>
</tr>
</tbody>
</table>
3.5.4. Missing data

Missing SMS responses could potentially impact the determination of the numbers and length of an episode because it was not possible to establish if the child still experienced spinal pain or was pain-free in the week with the missing answer. We therefore developed two decisions rules for defining the end of an episode. The first was if there were four or fewer consecutive missing answers, preceded and followed by a ‘1’, then this was considered as one continuous episode and the missing values were imputed as ‘1’. The second was if there were more than four consecutive missing answers, or the next answer after missing was ‘2’, ‘3’ or ‘4’, we considered the episode of spinal pain as terminated by the last report of ‘1’.

No literature was found to validate this decision, thus a sensitivity analysis was conducted to estimate the influence of this decision, in paper I and III. The missing weeks were imputed in two different ways: first, we imputed the missing answers to be the same as the last answer, regardless of the number in the next answer. This would potentially inflate the episode lengths and reduce the number of episodes. Second, we imputed an answer of ‘4’ (no pain) for all the weeks with missing answers, which would do the opposite. Thereby, we determined the range within which the correct answer would probably lie.

3.5.5. Statistical software

Data were analysed using STATA 14.0, 14.2 and 15.0 (Papers I, III, IV) (StataCorp, College Station, Texas, USA) and Excel 2011 (Paper I) (Microsoft Corporation, Redmond, WA, USA).
4. Summary of results

4.1. Baseline characteristics of the included cohort
In total, 1917 children were invited to participate in the study and 421 either declined to participate or never answered. Thus, the cohort included 1465 children (766 girls, (52%)) who were followed for up to 3 years, ranging from 1 to 137 weeks (median 137, IQR 110-137). The average weekly SMS response rate for all three years was 96.4% (ranging from 93.7% to 98.3%). Dropouts occurred when children moved away from their school or for personal reasons (Figure 2).

Figure 2 Participant flow CHAMPS 2011-2014

*Yes (drop-ins): change of school or wish to enter the project, **Dropouts: change of school or personal reasons
4.3. Paper I (Prevalence)

To gain a satisfactory observation period, we excluded the children for whom the observation period (from the first SMS to the last SMS) was less than a school year minus 1 week, e.g. less than 43 possible answer weeks in school year 1. Within this period there was the possibility of missing answers, and thus we also excluded children with less than 50% answers within that period to ensure reliable estimates. This resulted in 27% of the participants being excluded in school year 1, 8% in school year 2, and 8% in school year 3 because the SMS participation period was too short, and five children were excluded due to low response rate (<50%)(Figure 3). The response rates for the included children ranged from 50 to 98%, with 84%, 86% and 89% of the children having a response rate higher than 95% for school year 1, 2 and 3 respectively.

Figure 3 Participant flow SMS track

*Children participating less than maximum possible number of weeks minus one. **Children answering less than 50% of participation time
In total, 1327 children (690 girls, 52\%) were in the cohort over the 3 years (2011-2014), and of these, 794 children (416 girls, (52\%)) participated for all 3 years. The 3-year prevalence for spinal pain was 55.5\% [95\% CI: 52.1-59.0\%] for the children who participated in all 3 school years. No difference was found according to sex or number of PE lessons.

A summary of results is provided in Table 7 and Figure 4. Full details can be seen in Paper I (Appendix 1).

Figure 4 Prevalence of spinal pain by age and school year

The test for trend confirmed the general increase of spinal pain with age (p<0.05).
Table 7 Summary of Results prevalence study

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Results</th>
</tr>
</thead>
</table>
| **Proportion of individuals reporting any type of spinal pain during a school year** (by age see Figure 3) | **School year 1** 29.2% [95% CI: 26.4-32.0%]  
**School year 2** 33.3% [95% CI: 30.7-36.1%]  
**School year 3** 31.2% [95% CI: 28.5-34.0%] |
| **Proportion of weeks with spinal pain per school year per child**       | Median 4.5% (IQR 2.3-13.6)  
Mean 13.1% (SD 20.0%)  
Median 4.3% (IQR 2.2-15.2)  
Mean 14.5% (SD 21.0%)  
Median 6.5% (IQR 2.2-17.4)  
Mean 15.6% (SD 21.6%) |
| **Number of spinal pain episodes per school year per child**             | Median 1 (IQR 1-2)  
Mean 1.9 (SD 1.4)  
Median 1 (IQR 1-2)  
Mean 1.9 (SD 1.6)  
Median 1 (IQR 1-2.5)  
Mean 1.9 (SD 1.4) |
| **Length of spinal pain episodes per school year**                      | Median 1 (IQR 1-3)  
Mean 2.6 (SD 2.9)  
Median 1 (IQR 1-3)  
Mean 2.9 (SD 3.3)  
Median 1 (IQR 1-3)  
Mean 3 (SD 3.3) |
| **Relationship between number of episodes and episode length per school year per child** | Majority of children had one episode by school year (55.7-60.1%).  
Most episodes lasted one week (51.2-59.1%).  
16-17% of episodes lasted for five or more weeks.  
The more episodes, the longer the episodes (Test for trend: p<0.0001). |
| **Relationship between episode length and pain site**                   | The length of episodes varied little according to pain site.  
There was a tendency for multisite pain to last longer (median 3.7, IQR 1-13) and thoracic pain episodes to be shorter (median 2.5, IQR 1-5).  
Approximately 2/3 of the complaints were of a trivial character in all three school years.  
The episodes were longer for the non-trivial complaints in all three school years (p<0.001). |
| **Sensitivity analysis on missing data**                                 | Only small differences according to imputation method and school year.  
No impact on the number and the length of the episodes of spinal pain |
4.4. Paper II and III (RCT primary analyses)

The inclusion period ran from February 1st 2012 to April 1st 2014, and the follow-up period ended on June 27th 2014 (the end of the school year) resulting in between 1 and 868 follow-up days, (mean 477 days; SD 233). A total of 770 children reported spinal pain on SMS in this period, 483 children were excluded based on telephone interviews and additional 44 individuals reported pain less than 3 on the Numerical Rating Scale (NRS) on the day of examination, leaving 243 children randomised and included in the study. During data cleaning, we found five participants had been wrongly included, i.e. the SMS answer indicated no spinal pain, and they were excluded from the analyses. Thus, the final cohort for analysis contained 238 children with a mean age of 12.6 years: 116 in the non-manipulative therapy group (49%) and 122 in the manipulative therapy group (51%) (Figure 5). Full details can be seen in Paper III (Appendix 1).
The baseline covariates are presented in Table 8, and as seen there was no difference between the groups for any of the covariates and therefore univariate analyses were conducted for all analyses. Regarding expectations of the clinical course, the amount of missing data was approximately 34%, and for the KIDScreen domains between 1-5%, but equally distributed between intervention groups.
### Table 8 Baseline covariates by control and intervention group

<table>
<thead>
<tr>
<th></th>
<th>Non-MT group (n=116)</th>
<th>MT group (n=122)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, Female, No (%)</td>
<td>73 (63)</td>
<td>78 (64)</td>
</tr>
<tr>
<td>Age at inclusion (years)</td>
<td>12.6 (12.4-12.9)</td>
<td>12.6 (12.3-12.9)</td>
</tr>
<tr>
<td>Follow-up time (days)</td>
<td>492 (448-536)</td>
<td>463 (423-504)</td>
</tr>
<tr>
<td>Pain intensity at baseline (NRS)</td>
<td>5.3 (5.1-5.6)</td>
<td>5.2 (4.9-5.5)</td>
</tr>
<tr>
<td>Expectations of the Clinical Course (EoCC)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EoCC (&quot;Much worse&quot;)</td>
<td>0%</td>
<td>1.3% (0.2-8.7)</td>
</tr>
<tr>
<td>EoCC (&quot;Little worse&quot;)</td>
<td>1.2% (0.2-8.7)</td>
<td>2.8% (1.2-11.3)</td>
</tr>
<tr>
<td>EoCC (&quot;The same&quot;)</td>
<td>6.3% (2.6-14.5)</td>
<td>2.5% (0.6-9.7)</td>
</tr>
<tr>
<td>EoCC (&quot;Little better&quot;)</td>
<td>64.6% (53.3-74.4)</td>
<td>62.0% (50.7-72.1)</td>
</tr>
<tr>
<td>EoCC (&quot;Much better&quot;)</td>
<td>27.8% (19.0-38.9)</td>
<td>30.4% (21.2-41.5)</td>
</tr>
<tr>
<td>KIDScreen questionnaire</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KID Physical wellbeing</td>
<td>44.7 (38.5-49.6)</td>
<td>43.8 (40.5-49.6)</td>
</tr>
<tr>
<td>KID Psychological wellbeing</td>
<td>49.5 (44.8-56.0)</td>
<td>48.5 (44.8-56.0)</td>
</tr>
<tr>
<td>KID Autonomy and relation</td>
<td>49.5 (45.2-55.8)</td>
<td>49.5 (45.2-55.8)</td>
</tr>
<tr>
<td>KID Social support and peers</td>
<td>53.2 (46.9-57.8)</td>
<td>53.2 (46.9-57.8)</td>
</tr>
<tr>
<td>KID School</td>
<td>51.1 (45.4-58.2)</td>
<td>51.1 (45.4-58.4)</td>
</tr>
</tbody>
</table>

Non-MT: non-manipulative therapy; MT: manipulative therapy; CI: confidence intervals; NRS: Numerical Rating Scale; IQR: interquartile range; KID: KIDScreen domains

During the follow-up period, 175 (74%) of the children had a total of 592 recurrences, ranging from 1 to 21 recurrences per child. The median number of recurrences was 2 (IQR 0-4) for the manipulative therapy group and 1 (IQR 1-3) for the non-manipulative therapy group, revealing no statistically significant difference between groups, incidence rate ratio (IRR) 1.26 (95% CI 0.98-1.61), p=0.07. Children in the group receiving manipulative therapy reported a statistically significant higher Global Perceived Effect: odds ratio (OR) 2.22 (95% CI 1.19-4.15), p=0.01. Results for all secondary outcomes are displayed in Table 9. The sensitivity analysis did not change the between-group difference on either the primary outcome or most of the secondary outcomes, but it did result in a statistically significant increased length of episode for the manipulative therapy group, median 2 weeks (1-5) vs. 2 weeks (1-4) for the non-manipulative therapy group p=0.045.
Table 8 Results on secondary outcomes

<table>
<thead>
<tr>
<th></th>
<th>MT group</th>
<th>Non-MT group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Length of spinal pain episode</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number of episodes</td>
<td>456 (55%)</td>
<td>374 (45%)</td>
</tr>
<tr>
<td>Median (IQR) (number of weeks)</td>
<td>2 (1-6)</td>
<td>2 (1-5)</td>
</tr>
<tr>
<td>β-coefficient (95% CI)</td>
<td>0.11 (-0.07; 0.29)</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.21</td>
<td></td>
</tr>
<tr>
<td><strong>Total duration of complaint time per child</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number of pain weeks</td>
<td>1-114</td>
<td>1-111</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>9 (IQR 4-22)</td>
<td>7 (IQR 4-18)</td>
</tr>
<tr>
<td>IRR (95 % CI)</td>
<td>1.16 (0.92; 1.48)</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.22</td>
<td></td>
</tr>
<tr>
<td><strong>Global Perceived Effect</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of children in analysis*</td>
<td>96 (52%)</td>
<td>86 (48%)</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>2.22 (1.19; 4.15)</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td><strong>Change in pain intensity (NRS)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of children in analysis*</td>
<td>112 (50%)</td>
<td>111 (50%)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>2.2 (2.5)</td>
<td>2.3 (2.7)</td>
</tr>
<tr>
<td>β-coefficient (95% CI)</td>
<td>0.10 (-0.57; 0.78)</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.76</td>
<td></td>
</tr>
</tbody>
</table>

MT: manipulative therapy; Non-MT: non-manipulative therapy; IQR: Inter quartile range; IRR: Incidence rate ratio; OR: Odds ratio; NRS: Numerical Rating Scale; SD: Standard deviation. *Number of children in analysis of the first episode due to missing data

Adverse events

No serious adverse events to manipulative therapy have to our knowledge been reported in children of this age group57, 59, and we did not encounter reports of serious adverse events in our trial. Treating chiropractors should record treatment-related harms if the child stated these at the consultation, but none were reported and no child was referred to other health care providers because of adverse events or harms.

4.4. Paper IV (RCT effect modification)

Data from 238 children was available from the original RCT and used in the analysis of number of recurrences. Regarding the variables spinal pain and co-occurring musculoskeletal pain prior to inclusion, 211 children fulfilled the criterion of half a year of text message answers before inclusion.

Overall, we found tendencies supporting our hypotheses about improvement in response to manipulative therapy in the most affected children, whereas the least affected children
showed no or even negative response if they were allocated to the manipulative therapy group. This trend was seen primarily for the variables spinal pain prior to inclusion, the expectations of the clinical course and quality of life and to a lesser extent for co-occurring musculoskeletal pain prior to inclusion. Graphical presentation of the results can be seen in Figure 6.

For the outcome number of recurrences, the regression analyses showed statistical significant interactions between treatment allocation and the psychological domain of quality of life. For the lengths of episodes, statistical significant interactions were found between treatment allocation and the expectations of the clinical course and pain intensity. For total number of pain weeks, the regression analyses showed statistical significant interactions between treatment allocation and the expectations of the clinical course, pain intensity and the psychological domain. However, this trial was clearly underpowered for this type of analysis and therefore our results can at best be regarded as hypothesis-generating. Full details can be seen in Paper IV (Appendix 1).
Figure 6 Results on effect modification

**Number of recurrences**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>IRR (95% CI)</th>
<th>n</th>
<th>Interaction</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>SP before inclusion (&lt;20%)</td>
<td>1.32 (0.99, 1.75)</td>
<td>189</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SP before inclusion (≥20%)</td>
<td>0.75 (0.34, 1.68)</td>
<td>22</td>
<td>0.57 (0.24, 1.34)</td>
<td>0.20</td>
</tr>
<tr>
<td>CMP before inclusion (&lt;20%)</td>
<td>1.24 (0.93, 1.65)</td>
<td>188</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMP before inclusion (≥20%)</td>
<td>0.69 (0.45, 1.78)</td>
<td>25</td>
<td>0.72 (0.34, 1.50)</td>
<td>0.38</td>
</tr>
<tr>
<td>EsC (Better)</td>
<td>1.48 (0.73, 2.94)</td>
<td>46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EsC (Worse or same)</td>
<td>1.04 (0.70, 1.53)</td>
<td>112</td>
<td>0.70 (0.31, 1.57)</td>
<td>0.39</td>
</tr>
<tr>
<td>NRS (≥7)</td>
<td>1.27 (0.98, 1.65)</td>
<td>219</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NRS (&gt;7)</td>
<td>1.09 (0.45, 2.63)</td>
<td>19</td>
<td>0.85 (0.34, 2.15)</td>
<td>0.74</td>
</tr>
<tr>
<td>KID physical (High)</td>
<td>1.25 (0.67, 1.82)</td>
<td>218</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KID physical (Low)</td>
<td>0.96 (0.36, 2.57)</td>
<td>20</td>
<td>0.77 (0.28, 2.12)</td>
<td>0.61</td>
</tr>
<tr>
<td>KID psychological (High)</td>
<td>1.34 (1.03, 1.73)</td>
<td>207</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KID psychological (Low)</td>
<td>0.48 (0.19, 1.12)</td>
<td>22</td>
<td>0.34 (0.14, 0.87)</td>
<td>0.02</td>
</tr>
<tr>
<td>KID autonomy (High)</td>
<td>1.29 (0.99, 1.69)</td>
<td>200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KID autonomy (Low)</td>
<td>0.69 (0.41, 1.86)</td>
<td>30</td>
<td>0.69 (0.32, 1.45)</td>
<td>0.32</td>
</tr>
<tr>
<td>KID social (High)</td>
<td>1.31 (1.00, 1.72)</td>
<td>200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KID social (Low)</td>
<td>0.87 (0.45, 1.69)</td>
<td>32</td>
<td>0.66 (0.33, 1.36)</td>
<td>0.26</td>
</tr>
<tr>
<td>KID school (High)</td>
<td>1.22 (0.93, 1.61)</td>
<td>189</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KID school (Low)</td>
<td>0.15 (0.04, 0.64)</td>
<td>207</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Length of episodes**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>ES (99% CI)</th>
<th>n</th>
<th>Interaction</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>SP before inclusion (&lt;20%)</td>
<td>1.20 (0.69, 1.84)</td>
<td>570</td>
<td>0.88 (0.48, 1.62)</td>
<td>0.68</td>
</tr>
<tr>
<td>SP before inclusion (≥20%)</td>
<td>1.06 (0.59, 1.89)</td>
<td>118</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMP before inclusion (&lt;20%)</td>
<td>1.17 (0.96, 1.42)</td>
<td>666</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMP before inclusion (≥20%)</td>
<td>1.10 (0.68, 1.79)</td>
<td>120</td>
<td>0.94 (0.56, 1.59)</td>
<td>0.83</td>
</tr>
<tr>
<td>EsC (Better)</td>
<td>1.48 (0.99, 2.22)</td>
<td>105</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EsC (Worse or same)</td>
<td>0.94 (0.74, 1.19)</td>
<td>338</td>
<td>0.63 (0.40, 1.00)</td>
<td>0.05</td>
</tr>
<tr>
<td>NRS (≥7)</td>
<td>1.06 (0.88, 1.27)</td>
<td>764</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NRS (&gt;7)</td>
<td>2.27 (1.21, 4.16)</td>
<td>66</td>
<td>2.15 (1.12, 4.13)</td>
<td>0.02</td>
</tr>
<tr>
<td>KID physical (High)</td>
<td>0.94 (0.48, 1.64)</td>
<td>54</td>
<td>0.85 (0.42, 1.70)</td>
<td>0.64</td>
</tr>
<tr>
<td>KID physical (Low)</td>
<td>1.16 (0.56, 2.09)</td>
<td>77</td>
<td>0.92 (0.47, 1.81)</td>
<td>0.82</td>
</tr>
<tr>
<td>KID psychological (High)</td>
<td>1.16 (0.65, 1.81)</td>
<td>723</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KID psychological (Low)</td>
<td>1.09 (0.50, 2.39)</td>
<td>713</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KID autonomy (High)</td>
<td>1.24 (0.75, 2.00)</td>
<td>99</td>
<td>1.14 (0.66, 1.95)</td>
<td>0.64</td>
</tr>
<tr>
<td>KID autonomy (Low)</td>
<td>1.06 (0.89, 1.31)</td>
<td>695</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KID social (High)</td>
<td>1.61 (1.00, 2.58)</td>
<td>121</td>
<td>1.48 (0.89, 2.46)</td>
<td>0.13</td>
</tr>
<tr>
<td>KID social (Low)</td>
<td>1.08 (0.87, 1.30)</td>
<td>658</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KID school (High)</td>
<td>1.27 (0.84, 1.92)</td>
<td>158</td>
<td>1.19 (0.75, 1.89)</td>
<td>0.46</td>
</tr>
</tbody>
</table>

**Total number of painweeks**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>IRR (95% CI)</th>
<th>n</th>
<th>Interaction</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>SP before inclusion (&lt;20%)</td>
<td>1.31 (1.01, 1.70)</td>
<td>189</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SP before inclusion (≥20%)</td>
<td>0.75 (0.54, 1.07)</td>
<td>22</td>
<td>0.59 (0.25, 1.40)</td>
<td>0.23</td>
</tr>
<tr>
<td>CMP before inclusion (&lt;20%)</td>
<td>1.18 (0.91, 1.54)</td>
<td>186</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMP before inclusion (≥20%)</td>
<td>1.16 (0.87, 1.57)</td>
<td>25</td>
<td>0.98 (0.64, 2.10)</td>
<td>0.97</td>
</tr>
<tr>
<td>EsC (Better)</td>
<td>1.67 (0.97, 2.87)</td>
<td>46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EsC (Worse or same)</td>
<td>0.66 (0.46, 1.21)</td>
<td>112</td>
<td>0.52 (0.27, 0.98)</td>
<td>0.04</td>
</tr>
<tr>
<td>NRS (≥7)</td>
<td>1.05 (0.89, 1.26)</td>
<td>219</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NRS (&gt;7)</td>
<td>3.35 (1.41, 5.10)</td>
<td>19</td>
<td>3.10 (1.28, 7.86)</td>
<td>0.01</td>
</tr>
<tr>
<td>KID physical (High)</td>
<td>1.16 (0.60, 1.94)</td>
<td>212</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KID physical (Low)</td>
<td>0.80 (0.54, 1.18)</td>
<td>20</td>
<td>0.69 (0.39, 1.26)</td>
<td>0.42</td>
</tr>
<tr>
<td>KID psychological (High)</td>
<td>1.36 (1.06, 1.75)</td>
<td>207</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KID psychological (Low)</td>
<td>0.43 (0.19, 0.99)</td>
<td>22</td>
<td>0.32 (0.14, 0.75)</td>
<td>0.01</td>
</tr>
<tr>
<td>KID autonomy (High)</td>
<td>1.22 (0.84, 1.96)</td>
<td>200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KID autonomy (Low)</td>
<td>0.80 (0.41, 1.56)</td>
<td>30</td>
<td>0.66 (0.32, 1.34)</td>
<td>0.25</td>
</tr>
<tr>
<td>KID social (High)</td>
<td>1.23 (0.95, 1.59)</td>
<td>200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KID social (Low)</td>
<td>0.95 (0.60, 1.53)</td>
<td>32</td>
<td>0.78 (0.43, 1.41)</td>
<td>0.49</td>
</tr>
<tr>
<td>KID school (High)</td>
<td>1.13 (0.87, 1.48)</td>
<td>189</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KID school (Low)</td>
<td>1.08 (0.83, 1.37)</td>
<td>43</td>
<td>0.96 (0.52, 1.75)</td>
<td>0.89</td>
</tr>
</tbody>
</table>

5. Discussion

5.1. Knowledge gained

5.1.1. Epidemiology
Spinal pain in children is rather frequent: approximately half of the children experienced spinal pain at some point during the 3 year follow up period, and one third of the children within a school year. For most children the pain was short-lived and infrequent, but there were a quite considerable number of children who experienced more frequent and persistent pain. In at least a quarter of those with spinal pain, the episodes lasted for more than four weeks and/or occurred three times or more during a school year. Additionally, the more episodes a child had the longer they were, with the most severe episodes being of longer duration. Furthermore, prevalence increased significantly with age, with a peak in increase around the age of 12.

5.1.2. Manipulative therapy
To our knowledge, this is the first RCT to assess the potential benefit of adding manipulative therapy to other conservative care in this age group. Only four other RCT’s have looked into conservative interventions on low back pain in children, and they had a high risk of bias. In our study, the addition of manipulative therapy to other conservative care for children with spinal pain did not reveal any overall increased effectiveness regarding frequency and duration of spinal pain. Neither did we find any change in pain intensity between the groups, but children in the manipulative therapy group reported statistically significantly higher Global Perceived Effect. We explored if it was possible to identify certain subgroups of children who would respond better to manipulative therapy than others. The study was not powered for this type of analyses, so no conclusions could be drawn, but we did see a trend that children being worse off at baseline seemed to gain the most benefit from manipulative therapy; that is, children who had a high number of spinal pain episodes prior to inclusion, with low expectations of the clinical course and low quality of life.
5.2. Methodological qualities

5.2.1. Design
The main strength in relation to the prevalence study is the prospective school-based open cohort design enabling us to follow many participants over a long period and thereby providing a very reliable and complete picture of spinal pain. All examinations and treatments took place at the school, thus there was little logistic burden for the parents. Furthermore, social bias was not likely because everybody was invited to join the study and there was equal access because there was no fee for examinations or treatments. Further benefit of being part of a large on-going project, initiated 3 years before the beginning of this study, was the well-incorporated logistics. Municipality as well as schools, parents and children were all very well integrated in the project and how things were done, and the commitment was immense.

5.2.2. SMS track
The use of text messages (SMS) in data collection has been utilised in several studies by now, and is a very efficient way of collecting frequent data over a long time. Most people in Denmark have a cell phone, it is easy to use for most age groups, real time data are available in databases immediately and compliance is usually good. In our study the average weekly response rate was 96.4% for all 3 years (ranging from 93.7-98.3%). The weekly inquiries minimized the possibility of recall bias, because the parents reported complaints from the preceding seven days. Missing responses from the SMS track system did not appear to be a problem. We used different strategies to impute the missing data, and there were only very small differences according to imputation method, and it did not have an impact on number and length of episodes.

5.3. Methodological considerations

5.3.1. Setting and trial
The study population of the CHAMPS Study-DK may be different from a normal care seeking population and therefore we should be careful about extrapolating the results. In our study, 65% of the total cohort reported any musculoskeletal complaint on the SMS, i.e. spinal and/or extremity complaints, between 2011 and 2014. In comparison, only 5.4% of Danish children in the same age group consulted a chiropractor or a physiotherapist in the
same time period\textsuperscript{61}. This huge difference is probably due to a lower threshold for reporting complaints and for examining a child in this project because of the overall research setting.

The main purpose of the CHAMPS Study-DK was to explore the health related effects of extra physical education (PE) lessons in school and it could have been enlightening to include this in our analyses. However, the municipality of Svendborg found it to be such a success, that they enrolled extra PE on all schools and furthermore they changed the school districts in the middle of the study period. That led to change of status for approximately half of the included children during the follow-up period, meaning that a child could change status from being on a school with normal PE to extra PE or the opposite, which made it impossible to include it in our analyses.

The inclusion criteria for the RCT of 3 or more on the Numerical Rating Scale might have been low compared with when a parent would normally have sought care on behalf of their child. This could have the implication, that some of the children included in the RCT may have improved without treatment or even got worse after treatment, and thus should not have been included at all. This could be one of the reasons why the results from the RCT are very vague, due to the very broad inclusion criteria, and this should be considered in future trials. Another issue of being part of an on-going project is that we could not prolong the follow-up period and hence could not include more children into the trial, which might have provided more robustness to the results.

\textbf{5.3.2. Parent-generated data (SMS)}

Albeit the efficiency and many benefits of the SMS track system, there are certain issues to consider. In this study, parents reported musculoskeletal complaints on behalf of their child, i.e. being a proxy for the child, and this may not have been the true answer. We know from other studies, that there is a discrepancy between child and parent reporting on spinal pain\textsuperscript{12, 62, 63}. Parents seem to under report compared to the child when the pain is low, whereas the concordance is better when the pain is more severe. Hence it is possible, that parents would stop reporting if they believed the complaint to be minor, even though the child may still be bothered by the complaint. The true answer probably lies somewhere in between, but it is possible that the prevalences found in our study may have been higher
if they only relied on the child’s answer, but on the other hand we avoided getting minor complaints, e.g. bruises. However, this discrepancy might explain some of the difference found between the child report (Global Perceived Effect) and the parent report (SMS). An additional consideration is that parents may have been worn out by answering SMS questions every week for up to six years, but the high response rate does not support this. In addition, the number of missing answers did not increase by school year, indicating continued dedication. Another potential source of error could be that parents report ‘no pain’ on the SMS in order to avoid a phone call from a clinician, but this can only be speculative. This could potentially have caused an under-reporting of pain. It has also been suggested that children and parents may have changed their behaviour in reporting due to answering questions weekly for a long time and that there is a possibility of ‘medicalization’ of the children. However, comparing our results to another Danish project on school children (aged 11-15)³, where they simply filled out a questionnaire, the prevalences found seemed to be comparable to our results indicating that this was not the case.

5.3.3. Clinician-generated data
Combining the parent-generated data with the clinician-generated data gave a very complete picture of spinal pain, but some considerations arose during data collection. Having several practitioners participating in the RCT is considered a strength, since this may have prevented a potential patient-practitioner relationship. However, the more people involved, the more mistakes and irregularities are likely to happen. Examples of this are the rather substantial amount of missing data on the measures collected by the clinicians, e.g. pain intensity measured with the Numerical Rating Scale scores and expectations of the clinical course. This had the consequence, that we could not use these measures to say whether there is a learning effect over time or whether the expectations would change over time between the two treatment groups. Hence, we only analysed data from the first spinal pain episode including follow-up measures from week 2. However, there was no difference between intervention groups and it was assumed that data were missing completely at random. Different approaches have been made to prevent irregularities: a standardised protocol for data collection was written and disclosed, regular meetings were held with the
practitioners to ensure everybody was on track and keeping up with the protocol, and the
primary investigator checked the files regularly.
An electronical file system was developed and used for this study, and there was a short
period of time, where the system failed on saving data, which also could be a reason for
missing data, but we do not know how massive that problem was. For future projects, it is
advisable to establish the system in such a way, that it would be impossible to go any
further unless certain fields are filled out, which should diminish the amount of missing
data.

5.3.4. Spinal pain regions
As already mentioned, the SMS track system gives a comprehensive picture on frequency
and duration of spinal pain. Nevertheless, we do not get any specific details about the exact
region of spinal pain, i.e. cervical, thoracic or lumbopelvic pain, unless a practitioner saw
the child. Parents were instructed to keep on answering ‘1’ as long as the child experienced
spinal pain, but this is rather undetailed information. There is a possibility that the
complaint would change over time from e.g. cervical to lumbar pain due to new problems
arising, but this is not necessarily captured from the SMS, if there was no break in between
the two complaints (i.e. an answer of ‘not 1’ for ‘no spinal pain’). Hence, it would look like
one continuous episode of e.g. cervical pain. It is also not possible to capture if the pain is in
several regions at the same time. However, this is not necessarily a problem, depending on
the research question and the information needed. Other studies have suggested various
approaches to the definition of spinal pain as one region or as three different regions.
Aartun et al. showed that localised spinal pain in early adolescence appears to spread to
other regions of the spine over time and that pain in more regions was more common than
in one region only. A study on adults by Leboeuf et al., concluded that spinal pain should
be regarded as the same condition regardless of which region the pain was localised, since
proportions of people with pain and consequences thereof was the same no matter in which
region the pain was manifest. This supports our decision, that spinal pain should be
regarded as one region. In contrast, Kjaer et al. concluded in their study, that the patterns
and onset of spinal pain vary for different regions of the spine, and they recommended
reporting separately for the three regions in future research. However, it is not known, if
there is a difference in disability between those who have pain in all three regions at the
same time or those who have fluctuating pain from one region to another. But it is known, that multiple pain sites are associated to disability in adolescents\(^{64}\), which underlines the importance of focusing on early prevention and/or treatment regardless of definition.

5.3.5. Reflections on the RCT

It is probably not that surprising that we did not find any large differences between the two intervention groups, due to the two-armed design with extensive treatment (exercises, advice, soft tissue treatment) in both groups with manipulative therapy as the only addition in one of the groups.

Another reason for not finding any differences could be the outcomes chosen. As mentioned earlier, the parent SMS reports are maybe not in full agreement with the child’s own perception of recovering, which could reflect the lack of differences between the two groups. It is also possible that parents are more inclined to report positive for spinal pain on the SMS, knowing an efficient treatment is available.

Another issue of concern are the self-reported responses to treatment from the children (pain intensity measured on the Numerical Rating Scale and Global Perceived Effect), which may not reflect the true improvement.

Treatment - when and how

It may be that adding manipulative therapy simply does not benefit any extra to other conservative care, and that it does not really matter which kind of manual treatment is provided, or that specific subgroups benefit more than others. The subgroup analysis indicated that the most affected children might benefit more from manipulative therapy than the least affected. This gives rise to considerations on when or not to intervene and how. It may be, that the type of treatment and what we do is not so important compared to doing something at all, considering the fact that both intervention groups had a decrease in pain intensity rated on the Numerical Rating Scale. The same pattern was seen in a study concerning manual therapy on adults with neck pain\(^{65}\): both groups improved, but there was no statistically significant difference between groups and they reached the conclusion, that choice of treatment should be based on personal preferences and experience.

So which intervention to choose? As health professionals it is crucial to help our patients to an understanding of their situation, and maybe not consider spinal pain as a “disease”, but a “condition”. It is now well recognised that spinal pain is often fluctuating and episodic in
nature and as such should probably be recognised as a normal part of life\textsuperscript{66, 67}. This is important to emphasize to the patients in order to avoid beliefs about having a 'non-curable disease', e.g. patients reporting that “I have a bad back” or “I have a skewed back”, and thereby consider themselves as chronic patients, despite the fact that they probably do not have pain continuously. This implies that treatment should be more than just manipulative therapy, possibly incorporating the biopsychosocial model\textsuperscript{68} on an individual level. It is particularly important to educate and help children and their parents to take care of themselves and to make good choices regarding their musculoskeletal health, and not maintain them in long and costly treatment regimes. This does not imply that we should not use manipulative therapy in children with spinal pain, but considerations should be made regarding the expected prognosis and on whom to intervene.

\textit{Numerical Rating Scale}

The choice of the Numerical Rating Scale as an outcome was based on prior validations\textsuperscript{53, 69} and the practical usability, although the use of a number for pain may be an oversimplification, but very useful in research to inform, evaluate and improve management\textsuperscript{70}. Furthermore, we had the experience from the study that children could quite easily state their pain when asked, but it became apparent at follow ups that it was not congruent with their actual state as expected, when compared to their rating on Global Perceived Effect; a child could say he/she felt better rated on Global Perceived Effect even though the pain intensity on the Numerical Rating Scale report was higher than the first time. Voepel-Lewis et al.\textsuperscript{71} found the same discrepancy between the Numerical Rating Scale and Global Perceived Effect, where 27% of the children studied had a higher pain score though they said they felt better. The reason for this is unclear, but some of the reason may be explained by social influences: the rating of pain could be influenced by who is asking and/or the expected consequences hereof. For instance, a child may want to please a practitioner and rate a lower pain on the Numerical Rating Scale than actually felt, or rate a higher pain on the Numerical Rating Scale in order to keep getting treatments. This truly emphasizes the complexity of evaluating pain outcomes in the individual child. No statistically significant differences was found in our study between groups according to change in pain intensity on the Numerical Rating Scale. However, both groups reached a mean change of 2.3, which could be regarded as clinically meaningful, indicating that both
groups got equally better. This is underlined by other studies, showing a minimally clinically important change to be +/- 171,72.

**Global Perceived Effect**

We wanted to have a measure of the child’s own perception of improvement, and therefore included the Global Perceived Effect, which have been validated to be a good measure in adults73,74, but to our knowledge no studies have been conducted on children. We expected it to follow the same direction as the Numerical Rating Scale, but this was not apparent. In a study on adults concerning recovery, the Numerical Rating Scale was found to be a good measure on recovery when related to the self-rating on Global Perceived Effect, and that both measures should be considered when determining the complex construct of recovery. In general, the concept of improvement or recovery is not well defined. There is a great heterogeneity in outcomes used for recovery75, and therefore a need for more standardised measures, both to advance the field of research but also to improve the work of clinicians. One crucial problem is, that Global Perceived Effect is not just an estimate on pain recovery, but several factors may contribute to the notion feeling ‘much better’, e.g. being able to participate in normal activities and better sleep73. This implies that different people may have different perceptions on what Global Perceived Effect is to them, and that change in recovery may be independent of change in pain75 and that there is no such thing as a perfect measure.

Consensus was made in the PedIMMPACT group regarding recommendations on six core outcome domains to be included in clinical trials on paediatric pain76, e.g. pain intensity and global judgement on satisfaction with treatment. Considering global satisfaction, they recommended asking a global question with indications of what should be considered in the answer, i.e. a more open question: “Considering pain relief, side effects, physical recovery, emotional recovery, and economic considerations (if appropriate), how satisfied were you with the intervention your child received?”76 This was addressed to the parents, but regarded as appropriate for adolescents too. These recommendations were not made specifically for musculoskeletal conditions, but could easily be transferred to clinical trials in this area. Regardless, this underlines our assumption, that it is necessary to incorporate a more qualitative approach to get a reliable measure on pain and improvement. Twycross et al.77 have suggested a bundled pain assessment approach (CARES approach) for clinical
judgement making, that besides self-reporting is taking a group of other elements into account (biological, psychological and socio-cultural factors), which could be one way of helping in decision making. The challenge is to have something that is simple enough to use in practice, still be detailed enough to reflect the outcome measured.

**Effect modification**

To our knowledge, no other studies have tried to explore treatment effect modifiers associated with the outcome of manual treatment for spinal pain in children. According to Pincus\(^78\), most trials in back pain are under-analysed and this could support the decision of conducting a post-hoc analysis regarding effect modification. Our trial was without doubt underpowered for this, but due to the immense lack of evidence about treatment of spinal pain in children, data from existing studies should be fully exploited. The overall hypothesis was, that the most affected children would improve more with manipulative therapy than the least affected. We found weak tendencies supporting this hypothesis, primarily for children with high number of weeks with spinal pain 6 months prior to inclusion and with low expectations of the clinical course.

The same tendencies regarding previous spinal pain were found in studies on adults. Gurung et al. reviewed analyses from 4 RCT’s including 5514 participants, and they identified previous back pain as a potential effect modifier, showing strong evidence for greater improvement to therapist-delivered interventions for those who had longer duration of back pain prior to inclusion\(^79\). Similarly, another study on acupuncture for back pain, reported that patients with more severe back pain prior to treatment had a greater benefit\(^80\). Several studies on adults have looked at the importance of taking expectations into account, when assessing improvement, and most often high expectations predict a better outcome\(^81\)-\(^83\). We hypothesized, that children with low expectations of the clinical course would have the greatest benefit of manipulative therapy, as we believe they are the children being worse off with the potential to improve the most, which seemed to be the case in our study.
6. Conclusion

Following a school-based cohort of Danish children aged 8-15 years for three years we have gained good insight into duration, frequency and characteristics of spinal pain and the effect of adding manipulative therapy to other conservative treatment for spinal pain, including potential effect modifications.

Paper I (Prevalence)
This study demonstrated that spinal pain is a rather substantial problem. Most episodes are brief, but nevertheless there is a substantial number of children with frequent and long-lasting episodes of spinal pain. In at least a quarter of those with spinal pain, the episodes lasted for more than four weeks and/or occurred three times or more during a school year. It is towards this group that a concerted research effort should be directed to inform evidence-based prevention and management.

Paper II and III (RCT primary analyses)
This study demonstrated no significant difference in the number of recurrences of episodes of spinal pain in a school-based cohort of children when adding manipulative therapy to advice, exercises, and soft tissue therapy, but children in the manipulative therapy group reported a higher Global Perceived Effect. The choice of treatment therefore relies on personal preferences, and could include conservative care with and without manipulative therapy. The study population is not comparable to a normal care-seeking population and therefore the results may not be directly transferrable.

Paper IV (RCT effect modification)
This study demonstrated weak tendencies supporting our hypotheses about a greater chance of improvement in response to manipulative therapy in the most affected children, whereas the least affected children showed no or even negative responses if they were randomised to the manipulative therapy group. Considering the hypothesis-generating nature of this study, we believe that we have provided insight into potential effect modifiers worthy of being considered in future larger trials.
7. Perspectives

**Epidemiology**
This study has shown, fortunately, that most children are rarely affected by spinal pain, but a substantial number of children reported having persistent or recurring episodes of spinal pain. Furthermore prevalence increased with age, especially around the age of 12. This age group (or earlier) could be a window of opportunity in terms of exploring conditions surrounding the initial onset. Future research should focus on this and hereby increase our knowledge in these areas, hence providing a better chance of developing preventive approaches and/or efficient treatment regimes, which is highly needed.

**Manipulative therapy**
We saw in the subgroup analysis that the most affected children might have benefited from manipulative therapy and that the least affected had no or even negative responses. In a clinical perspective, this could indicate that we maybe should refrain from treating the least affected children. In a research perspective, we believe that future trials on manipulative therapy should probably include only children with longer lasting and more intense spinal pain and not children with mild pain.
We will recommend including an untreated group in a future trial to elucidate the effect of treating these children, whether manipulative therapy is included or not.

**Future trials**
It would be of great value to conduct a mixed methods study with a qualitative approach. Incorporating interviews with parents and children during and after the trial could provide us with better insight into their perceptions on different issues in the study, e.g. change of behaviour on seeking health care after being part of the trial or if they pay more or less attention to musculoskeletal complaints than before the study.
It would also be beneficial to incorporate the practitioners’ expectations of the clinical course on behalf of the child. Most practitioners will probably, more or less deliberate, define who will improve or not to treatment, at the first consultation. If we could combine that with the actual course, we might be able to predict the change of recovery by a few questions, and thereby have a better foundation for deciding who gets which treatment or
not. Additionally, the child’s own expectation of the treatment could be of benefit, since this is highly indicative of future course.

Future trials incorporating subgroup analyses on effect modification, should consider exploring prior spinal pain, expectations of the clinical course and quality of life as potential candidates for effect modification.

**Improving outcomes**

There is a great heterogeneity in outcomes used for improvement in spinal pain in children, and therefore a great need for more standardised measures, both to advance the field of research but also to improve the work of clinicians. Especially regarding the use of Global Perceived Effect, which has never been validated in children.

Inconsistencies exist regarding which cut points to use for improvement. For one person ‘1’ on the Numerical Rating Scale equals improved, whereas for another person ‘4’ equals improvement. One solution could be to combine it with simply asking questions: “what level of pain means ‘better’ to you? What is your goal (playing football, better sleep etc.)?”

This could also help clinicians in making realistic treatment plans.

So is it even worthwhile using the presently available scales, e.g. the Numerical Rating Scale and Global Perceived Effect? We do believe that these self-report measures are a good starting point for evaluation, although further validation is needed for the use in children, but they should be used in conjunction with clinical judgement and not stand alone.

Qualitative research could also help to develop better outcomes for the future.
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References


[73] Evans R, Bronfort G, Maiers M, Schulz C, Hartvigsen J. "I know it's changed": a mixed-methods study of the meaning of Global Perceived Effect in chronic neck pain patients. European spine journal : official publication of the European Spine Society, the


Appendix 1: Papers I-IV
Paper I

Spinal pain in Danish school children – how often and how long? The CHAMPS Study-DK
Dissing KB, Hestbaek L, Hartvigsen J, Williams C, Kamper S, Boyle E, Wedderkopp N
BMC Musculoskeletal Disorders 2017 18:67
Background: Spinal pain in children and adolescents is a common condition, usually transitory, but the picture of spinal pain still needs elucidation, mainly due to variation in measurement methods. The aim of this study was to describe the occurrence of spinal pain in 8–15 year-old Danish school children, over a 3-year period. Specifically determining the characteristics of spinal pain in terms of frequency and duration.

Methods: The study was a 3-year prospective longitudinal cohort study including 1400 school children. The outcomes were based on weekly text messages (SMS) to the parents inquiring about the child’s musculoskeletal pain, and on clinical data from examinations of the children.

Results: The 3-year prevalence was 55%. The prevalence was 29%, 33% and 31% for each of the three study years respectively, and increased statistically significantly with age, especially for lumbopelvic pain. Most children had few and short-lasting episodes with spinal pain, but more than one out of five children had three or more episodes during a study year and 17% of all episodes lasted for more than 4 weeks.

Conclusion: This study demonstrates that spinal pain is a substantial problem. Most episodes are brief, but there are a vast number of children with frequent and long-lasting episodes of spinal pain indicating a need for action regarding evidence-based prevention and management.

Keywords: Spinal pain, Children, Adolescents, Prevalence
appear to have recurrent and more painful spinal pain events [2, 3], especially considering that the teenagers with the most frequent back pain seemed to have the highest risk of back pain in adulthood [2–4, 12]. Reliable understanding of prevalence and course of spinal pain is essential for further research into the development of effective prevention and treatment strategies [11]. This study will extend our understanding in the area by capturing accurate estimates of prevalence, number of episodes and length of episodes with spinal pain in children and adolescents aged 8 to 15 years.

The overall aim of this study was to describe the characteristics of spinal pain episodes in 8–15 year-old Danish school children followed for three study years. Specifically we aimed to:

1. Calculate the proportion of individuals reporting any type of spinal pain during a study year
2. Report the prevalence, frequency and duration of spinal pain by means of:
   a. The proportion of weeks with spinal pain per study year per child
   b. The number of spinal pain episodes per study year per child
   c. The length of spinal pain episodes per study year
   d. The relationship between number of episodes and episode length per study year per child
3. Determine the relationship between episode length and pain site (cervical, thoracic or lumbopelvic pain), and episode length and complaint severity

**Method**

**Overview of design**

This study was a 3-year prospective longitudinal cohort study of school children who took part in the Childhood Health, Activity and Motor Performance School Study (CHAMPS Study-DK). The protocol for CHAMPS Study-DK has been published elsewhere (14). The main purpose of the CHAMPS Study-DK was to evaluate the influence of extra physical education (PE) on general childhood health including musculoskeletal complaints. The schools were divided into two groups: one receiving the normal amount of two PE lessons per week (control) and the other receiving six PE lessons per week (intervention). The study involved researchers with a range of professional backgrounds, all investigating different aspects of childhood health.

The CHAMPS Study-DK commenced in 2008 and the data collection regarding injuries and back problems ended in summer 2014. The study was an open cohort study and children could enter or leave the study at any time during the study period. Originally, the study was designed to last for 3 years (2008–2011), but additional funding made it possible to continue for 3 more years. Another team of researchers were responsible for the additional 3 years, which constitutes the basis for this study.

**Participants and setting**

Participants in this study included children aged 8–15 from 13 primary schools in the municipality of Svendborg, Denmark. Svendborg consists of approximately 58,000 inhabitants and is considered representative of the Danish population [13]. The schools were matched according to the size and distribution of the socio-economic groups within the uptake area. The clinical team responsible for the follow-up consisted of experienced chiropractors, physiotherapists and a medical doctor.

At baseline, the children and their parents filled out a questionnaire with information on age, sex, health status, parental educational level, work and leisure time activities.

**Outcome measurement**

Outcomes were captured via weekly text messages (SMS) to one of the parents of participating children, inquiring about the child’s musculoskeletal complaints, and the amount and type of leisure time sports activity during the past week (see Additional file 1). It was only possible to connect one telephone number to the SMS system and as the phone number was a personal mobile it was generally the same parent answering throughout the study period. Answers were automatically registered, entered and stored in a database. If the parent did not reply, the parent automatically received up to two SMS reminders within the week. The SMS-response is a very efficient way to obtain information on a frequent basis [14, 15]. There were no text messages during the summer and Christmas holidays to reduce the parent’s burden and because there was no possibility of following-up on positive reports of pain.

To avoid break in data continuity due to the long summer break, we chose to report by study year rather than for three full calendar years, i.e. year 1 representing the school year starting in August 2011 and ending in June 2012, year 2 representing the school year starting in August 2012 and ending in June 2013 and year 3 representing the school year starting in August 2013 and ending in June 2014.

In the first SMS question, parents were asked if their child had any musculoskeletal pain in the previous week. Response options were: ‘1’ for spinal pain, ‘2’ for upper extremity pain, ‘3’ for lower extremity pain, any combination of the three numbers or ‘4’ if there was no pain.

If musculoskeletal pain was reported (response options 1, 2, 3 or any combination of the three numbers), the parents were interviewed by telephone by a member of
the screening team. This team was composed of experienced chiropractors and physiotherapists. They administered a standardized interview that included information about the duration of the complaint, the mode of onset, the nature of the pain and any interventions that have been tried (e.g. treatments, drugs used). Based on this interview, complaint severity was classified as trivial or non-trivial.

If the complaint was considered to be non-trivial, an appointment for an examination was made. The examination of non-trivial complaints took place at the child’s school within 2 weeks of first reporting. A member of the clinical team consisting of chiropractors and physiotherapists with extensive experience in examining children performed the examination. Following the examination, complaints were categorized according to the International Classification of Diseases (ICD-10). The child was offered advice on how to handle his/her problem and the parents were notified about the result and any potential action following the examination either by telephone or letter. All data were filed in an electronic journal system established specifically for this project and stored on a secure server.

Data analysis
STATA 14.0 (StataCorp, College Station, Texas, USA) was used for data analyses. Data for these analyses were collected over 44 weeks in study year 1, 47 weeks in study year 2, and 46 weeks in study year 3, giving a total of 137 weeks.

To obtain a satisfactory observation period, we excluded the children for whom the observation period was less than a study year minus 1 week (from the first SMS to the last SMS), e.g. less than 43 possible answer weeks in study year 1. Within this period there was the possibility of missing answers, and thus we also excluded cases with less than 50% answers within that period to ensure reliable estimates.

1) A 3-year prevalence with 95% confidence intervals (CI) was calculated for the children that participated for the entire study period, including sex-specific prevalences. We calculated the study year specific prevalences for each study year, including sex-specific prevalences. Finally, we calculated the age-specific prevalences for each age from 8 to 15 years old. The relationship between age and prevalence of spinal pain was assessed using test for trend as described by Cuzick [16].

2) The characteristics of spinal pain were described as a) the proportion of weeks with spinal pain, b) the number of episodes, c) the duration of episodes per child and d) relationship between number of episodes and episode length.

3) Region specific spinal pain diagnoses were made by the clinicians in the subset of children with non-trivial spinal pain. These were coded into painsites, i.e. cervical, thoracic, lumbopelvic or multisite pain (defined as pain in more than one spinal region).

If one continuous episode consisted of pain from different spinal regions at different timepoints, the whole episode was considered as multisite. Prevalences with 95% CI and episode length (medians with interquartile ranges and means with standard deviations) were reported for the different painsites as well as for trivial vs. non-trivial complaints. Any differences between groups in relation to episode length were evaluated using One-way analysis of variance for complaint type and t-test for pain site. Significance level was set to 5%.

a. Proportion of weeks with spinal pain
The proportion of weeks a child experienced spinal pain was calculated by dividing all answers that included a ‘1’ by the total weeks of observation within a study year. This is illustrated graphically with histograms including medians with interquartile ranges, and means with standard deviations.

b. Number of episodes per child
A new episode was defined as an episode occurring after at least 1 week without spinal pain. It was reported using numbers and percentages, described with medians with interquartile ranges and means with standard deviations.

A sensitivity analysis was conducted to assess the effect of the recovery definition, i.e. recovery was defined as 4 weeks of ‘no pain’ [17, 18], instead of 1 week, before a subsequent episode was considered to be a new episode.

c. Duration of episodes
The length of an episode was calculated as the number of weeks of continuous reporting ‘1’ (i.e. spinal pain). Because a small number of the children had very long episodes, we chose to truncate episode length at 13 weeks, as this is a commonly used definition of chronic pain [19], and to prevent these few individuals from skewing the results disproportionately. We reported numbers and percentages, medians with interquartile ranges and means with standard deviations. A sensitivity analysis was conducted to assess the effect of the recovery definition, i.e. recovery was defined as 4 weeks of ‘no pain’, instead of 1 week, before a subsequent episode was considered to be a new episode.

d. Relationship between number of episodes and episode length
The relationship between number of episodes and episode length was assessed using test for trend.
Missing data
Missing SMS responses had an impact on how to determine the length of an episode because it was impossible to determine if the child still had spinal pain or was pain-free in the week with the missing answer. We therefore formulated two decision rules for defining the end of an episode. The first was if there were four or fewer consecutive missing answers, preceded and followed by a ‘1’, then this was considered as one continuous episode and the missing values were imputed as ‘1’. The second was if there were more than four consecutive missing answers, or the next answer after missing was ‘2’, ‘3’ or ‘4’, we considered the episode of spinal pain as terminated by the last report of ‘1’.

Because there is no literature to support this decision, a sensitivity analyses was performed to estimate the impact of this decision. For that purpose, the missing weeks were treated in two extreme ways: first, we imputed the missing answers to be the same as the last answer, regardless of the value of the next report. This would potentially inflate the episode lengths and diminish the number of episodes. Second, we imputed an answer of ‘4’ (no pain) for all the weeks with missing answers, which would do the opposite. Thereby, we determined the range within which the correct answer would likely lie.

Results
In total, 1917 children were invited to participate in the study and 421 either refused to participate or never answered. Thus, the cohort included 1465 children (766 girls, (52%)) who were followed for up to 3 years, ranging from 1 to 137 weeks (median 137, IQR 110–137). There was a statistically significant difference among schools according to the 3-year prevalence ($p<0.001$). However, this difference was only driven by study year 2 ($p=0.01$). There were no differences in study year 1 ($p=0.35$) and study year 3 ($p=0.19$). The difference found in study year 2 was based on a high prevalence from two schools, but the same schools did not have high prevalences in the other two study years, and therefore, we consider this to be a chance finding. There was a statistically significant difference ($p<0.05$) between participants and non-participants in the study according to which school they were attending, but not according to sex. The average weekly SMS response rate for all schools for all 3 years was 96.4% (ranging from 93.7 to 98.3%) with a total of 158,478 observations. Dropouts occurred when children moved away from their school or for personal reasons (Fig. 1a).

Twenty Seven percent of the participants were excluded in study year 1, 8% in study year 2, and 8% in study year 3 because the SMS participation period was too short, and five children were excluded due to low response rate (<50%) (Fig 1b). There were a higher number of children excluded in year 1 because of an administrative change of the school districts. This resulted in new schools being enrolled in the project, and during the first half year the parents gradually consented to let their children participate in the study. Furthermore, the older children from some schools were joined in a special school class on a school that was not part of the project.

After exclusion of those participants, the cohorts used for analyses consisted of 1015 participants in study year 1, 1179 in study year 2, and 1,077 in study year 3 (Table 1). In total, 1327 children (690 girls, 52%), over the 3 years (2011–2014) were in the cohort and of these, 794 children (416 girls, (52%)) participated for all years.

Prevalence
The 3-year prevalence for spinal pain was 55.5% [95% CI: 52.1–59.0%] for the children who participated in all three study years. No statistically significant difference was found for spinal pain according to sex (girls 58.2% [95% CI: 53.4–62.8%] vs boys 52.6% [95% CI: 47.6–57.6%], $p=0.12$). There was no statistically significant difference in the prevalence of spinal pain between the children having more PE lessons compared to those with a standard amount of PE lessons. We therefore chose to report on the children as one cohort throughout this study and not take the number of PE lessons into account.

In study year 1, the prevalence for spinal pain was 29.2% [95% CI: 26.4–32.0%], in study year 2 it was 33.3% [95% CI: 30.7–36.1%], and in study year 3 the prevalence was 31.2% [95% CI: 28.5–34.0%]. Girls more often reported neck- and back pain than boys in all 3 years, but the difference was only statistically significant in study year 1 ($p=0.01$).

Prevalence of spinal pain by age and study year can be seen in Fig. 2, ranging from 16.0% at age eight in study year 1 to 40.2% at age 14 in study year 2. The prevalences generally increased with age, and this was confirmed in the trend test looking at all three study years ($p<0.05$). The largest increase appeared at age 12 (Fig. 2).

Proportion of painweeks, number of episodes and lengths of episodes
Most children had few weeks with spinal pain during the 3-year study (Fig. 3). Forty-seven to 54% of the affected children had pain for less than 5% of the weeks reported. A small proportion of children had pain for more than 50% of the time (7%, 7% and 8% for study years 1, 2 and 3, respectively).

The majority of the children had one episode by study year (Table 2), but up to one fourth of the children had three or more episodes during a study year (21%, 20% and 25%, respectively for the three study years). In
addition, there seemed to be a slight increase in the number of episodes over the 3-year study period.

Most of the episodes were short with 51–59% lasting for 1 week, but 16–17% of the episodes lasted for 5 or more weeks by study year (Table 3). Furthermore, for a significant number of children (10%, 13% and 10%, respectively for the three study years) all episodes were long lasting (5 or more weeks).

The relationship between number of episodes and mean episode length showed that for the children with only one episode in a study year, 57%, 58% and 64% (respectively for the three study years) of these episodes lasted only 1 week. However, for the children with three or more episodes in a study year, only 38%, 51% and 39% of these episodes lasted for 1 week or less. The test for trend by study year showed a statistical significant
difference \( (p < 0.001) \) indicating that the more episodes a child had, the longer the episodes were.

**Regional spinal pain and episodes**

In total, 185 different ICD-10 diagnoses were given for the non-trivial spinal pain episodes (e.g. cervicalgia, lumbar facet syndrome, unspecific back pain) and these were classified into mutually exclusive pain sites: 42% lumbopelvic, 31% cervical, 14% thoracic and 13% multisite. Because the data were not normally distributed, a log transformation was performed before the analyses. There was a decreasing number of cervical pain episodes (27.7−22.4%) and an increasing number of lumbopelvic pain episodes (38.5−48.9%) over the 3-year period, but this was not statistically significant, whereas the number of thoracic and multisite pain episodes varied non-systematically (Table 4). The length of episodes did not vary much according to type of regional pain (Table 4), although there was a tendency for multisite pain to last longer (median 3.7, IQR 1−13) and thoracic pain episodes to be shorter (median 2.5, IQR 1−5). The results were only statistically significant for study year 3 \( (p = 0.05) \).

### Table 1 Age, sex and type of school for the children participating by study year

<table>
<thead>
<tr>
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<tbody>
<tr>
<td></td>
<td>Number of children</td>
<td>% girls</td>
<td>Number of children</td>
</tr>
<tr>
<td>Age 8</td>
<td>50</td>
<td>54%</td>
<td>–</td>
</tr>
<tr>
<td>Age 9</td>
<td>197</td>
<td>61%</td>
<td>69</td>
</tr>
<tr>
<td>Age 10</td>
<td>213</td>
<td>50%</td>
<td>236</td>
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<td>Age 11</td>
<td>224</td>
<td>50%</td>
<td>271</td>
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<td>Age 12</td>
<td>225</td>
<td>52%</td>
<td>270</td>
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<tr>
<td>Age 13</td>
<td>103</td>
<td>49%</td>
<td>218</td>
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<tr>
<td>Age 14</td>
<td>3</td>
<td>33%</td>
<td>112</td>
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<tr>
<td>Age 15</td>
<td>–</td>
<td>–</td>
<td>3</td>
</tr>
<tr>
<td>Age 16</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>I-school/c-school(^a)</td>
<td>602/413</td>
<td>56%/47%</td>
<td>800/518</td>
</tr>
</tbody>
</table>

\(^a\)I-school: intervention school, 6 h PE per week  
C-school: control school, 2 h PE per week

**Fig. 2** Prevalence by age and study year
Trivial vs. non-trivial complaints and episodes

The majority of complaints (approximately 2/3) were of a trivial character, i.e. without a diagnosis, in all three study years (Table 5), but the tendency shifted towards more non-trivial complaints in study year three. Because the data were not normally distributed, a log transformation was performed before the analyses. The episodes were statistically significantly longer for the non-trivial complaints when compared to the trivial complaints in all three study years ($p < 0.001$), but medians and means did not change according to study year (Table 5).

Sensitivity analyses

Results of the sensitivity analysis assessing the impact of missing data showed no differences between the three different types of imputation in relation to number and lengths of episodes (Table 6).

- Primary data: up till 4 missing weeks after a ‘1’ is imputed with ‘1’
- v1: all missing weeks after a ‘1’ is imputed with ‘1’
- v2: all missing weeks after a ‘1’ is imputed with ‘4’

Defining a new episode as starting after 4 weeks of ‘no pain’ instead of 1 week, resulted in a reduction of number of episodes by 20.0%, 18.8% and 18.0% in study years 1, 2 and 3 respectively, and the maximum number of episodes decreased from 8 to 5, 12 to 6 and 9 to 6 in study years 1, 2 and 3 respectively. No difference in the median number of episodes was found and the mean number was only slightly smaller (1.9 to 1.5), with a higher proportion of children having 1 or 2 episodes.

Finally, we found somewhat higher proportion of episodes lasting for 1 week, (62.0%, 59.1% and 53.2% vs 59.1%, 56.6% and 51.2% for study year 1, 2 and 3 respectively), but overall, the distribution between the different lengths of episodes was almost the same.

Discussion

This study reports weekly spinal pain in children and adolescents with up to 3 years of follow-up in a large cohort. Spinal pain was experienced by approximately half of the children at some point throughout the 3-year study period and the 1-year prevalence approximated 30%. Most children had few and short episodes of pain, but a rather substantial number of children had more frequent and longer lasting episodes. The prevalence of spinal pain increased significantly with age. There was no statistically significant difference in spinal pain prevalence between children having two or six PE lessons. This was indeed an interesting finding, but not the aim of this study and therefore we did not analyse this further, but will probably include it in a future manuscript.

This study reported a slightly higher 1-year prevalence than a study using the same cohort (30% vs. 25%) 3 years earlier [1]. This confirms the finding of increasing prevalence with age as found in the current study. Likewise, it is consistent with the observations in a meta-analysis by Calvo-Munoz [7] (mean overall prevalence 33%), who also reported an increase in prevalence with increasing age despite considerably different methodologies in studies and potential recall bias from studies commonly reporting 1-year prevalence recalls. The
increase from around age 12, which has also been shown in other studies [9, 20], indicates that this could be an important age regarding prevention and/or treatment.

We do not know much about the impact of adolescent spinal pain on general health, but Gobina et al. showed a strong association between the use of pain medication and recurrent low back pain in adolescents [8]. In addition, Hestbaek et al. reported that adolescents with low back pain have more comorbidity than adolescents without low back pain [21]. We are unable to determine if these issues are present in our cohort or the impact that spinal pain may have on our adolescents’ general health. However, these issues should give rise to extra concern about recurrent spinal pain in this age group. Considering the association between low back pain in adolescence and low back pain in adulthood, recurrent spinal pain in this age group also presents a potentially significant health challenge in their adult years [3].

Similar to other studies, we found that most children had a few short episodes of pain [1, 2]; however, a significant number of children did have pain more often and for longer periods of time. Of those with spinal pain, 20–25% in our study had three or more episodes during a study year and 16–17% of all episodes lasted for more than 4 weeks, indicating that recurrent or persistent spinal pain is not uncommon in this age group. This is similar to previous studies that reported rates of persistent low back pain in adolescents (14–26%) [2, 8, 12, 22, 23].

Defining episode length based on 1 or 4 weeks of ‘no pain’ between episodes resulted in only minor differences

Table 2 Number of episodes per child by study year

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<tbody>
<tr>
<td>1</td>
<td>60.1%</td>
<td>59.5%</td>
<td>55.7%</td>
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<tr>
<td>2</td>
<td>18.6%</td>
<td>20.6%</td>
<td>19.3%</td>
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<tr>
<td>3</td>
<td>8.8%</td>
<td>7.9%</td>
<td>11.3%</td>
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<tr>
<td>4</td>
<td>5.4%</td>
<td>4.8%</td>
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<td>5</td>
<td>4.0%</td>
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<td>3.9%</td>
</tr>
<tr>
<td>6</td>
<td>1.7%</td>
<td>1.5%</td>
<td>2.4%</td>
</tr>
<tr>
<td>≥7</td>
<td>1.4%</td>
<td>2.4%</td>
<td>1.2%</td>
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<td></td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Median # episodes (IQR)</td>
<td>1 (1–2)</td>
<td>1 (1–2)</td>
<td>1 (1–2.5)</td>
</tr>
<tr>
<td>Mean # episodes (SD)</td>
<td>1.9 (1.4)</td>
<td>1.9 (1.6)</td>
<td>1.9 (1.4)</td>
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*N = Number of children per school year

Table 3 Length of episodes

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<tr>
<td>1</td>
<td>59.1%</td>
<td>56.6%</td>
<td>51.2%</td>
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<tr>
<td>2</td>
<td>13.1%</td>
<td>14.7%</td>
<td>17.9%</td>
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<tr>
<td>3</td>
<td>7.4%</td>
<td>6.7%</td>
<td>7.3%</td>
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<tr>
<td>4</td>
<td>4.4%</td>
<td>4.9%</td>
<td>6.2%</td>
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<tr>
<td>5</td>
<td>3.6%</td>
<td>3.1%</td>
<td>2.9%</td>
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<td>2.2%</td>
<td>1.5%</td>
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<td>7</td>
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<tr>
<td>8</td>
<td>1.1%</td>
<td>1.5%</td>
<td>0.3%</td>
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<tr>
<td>9</td>
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<td>0.7%</td>
<td>0.4%</td>
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<tr>
<td>10</td>
<td>1.1%</td>
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<td>1.2%</td>
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<tr>
<td>11</td>
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<td>0.5%</td>
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<tr>
<td>12</td>
<td>0.7%</td>
<td>0.4%</td>
<td>0.6%</td>
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<tr>
<td>≥13</td>
<td>2.9%</td>
<td>6.6%</td>
<td>6.5%</td>
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<td></td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
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<tr>
<td>Median # weeks (IQR)</td>
<td>1 (1–3)</td>
<td>1 (1–3)</td>
<td>1 (1–3)</td>
</tr>
<tr>
<td>Mean # weeks (SD)</td>
<td>2.6 (2.9)</td>
<td>2.9 (3.3)</td>
<td>3 (3.3)</td>
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</table>

*N = Number of episodes per school year
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<tbody>
<tr>
<td></td>
<td>Episode length (median, IQR)</td>
<td>Episode length (mean, SD)</td>
</tr>
<tr>
<td>n % (CI)</td>
<td>Episode length (median, IQR)</td>
<td>Episode length (mean, SD)</td>
</tr>
<tr>
<td>Cervical pain</td>
<td>41 27.7% [21.0–35.5%] 3 (2–7)</td>
<td>63 25.4% [20.3–31.2%] 3 (1–6)</td>
</tr>
<tr>
<td>Thoracic pain</td>
<td>25 16.9% [11.6–23.9%] 3 (1–5)</td>
<td>49 19.8% [15.2–25.2%] 2 (1–4)</td>
</tr>
<tr>
<td>Lumbopelvic pain</td>
<td>57 38.5% [30.9–46.7%] 3 (2–7)</td>
<td>107 43.1% [37.1–49.4] 2 (1–6)</td>
</tr>
</tbody>
</table>

*Number of diagnosed spinal pain episodes per study year*
Table 5 Complaint type according to episode length

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<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>CI</td>
</tr>
<tr>
<td>Trivial pain</td>
<td>405</td>
<td>73.1%</td>
<td>[69.2–76.6%]</td>
</tr>
<tr>
<td>Non-trivial pain</td>
<td>148</td>
<td>26.9%</td>
<td>[23.3–30.8%]</td>
</tr>
</tbody>
</table>

\(^a\) Total number of spinal complaints per year
in the median and mean episode lengths and thus did not introduce a systematic bias to the results. These findings are in line with other studies suggesting, that 1-month without back pain would be an appropriate cutpoint [17, 18].

Due to the subjective judgement of the telephone interviewers, there is a potential risk for misclassification of the complaints. Fortunately this only relates to a small part of the study (last part of objective 3) and therefore does not affect our primary objective of prevalence.

Another potential source or error could have been the parents’ response to the SMS question. In order to avoid a phone call from a clinician following a pain report, parents may have reported ‘no pain’ despite actual pain reports from the child, which would have caused an under-reporting of spinal pain. Furthermore, it could be a concern that the children and their parents might have changed their behaviour of reporting pain during the study period, since they have answered SMS-questions continuously for up to 6 years. However, when comparing to another Danish project with school children (aged 11–15) who were not followed with SMS, but simply answered one questionnaire, the prevalences (lifetime prevalence 86%, 1-week prevalence 36% and point prevalence 17%) seem to be comparable with our results [2]. In addition, the proportion of missing weeks did not increase by study year, indicating continued dedication to the project.

Finally, nested in this cohort was a randomised clinical trial, which compared two different kinds of manual treatment, and all of the children enrolled in the trial received more clinical care than usual [24]. We do not know how this might have impacted the overall prevalence and characteristics of the spinal pain episodes. We have little knowledge (sex and school only) about the children that refused to participate in the study. We did find that the refusal rate differed across schools, and therefore bias is likely to be non-differential in relation to back pain, but the generalizability might be compromised.

The parents’ answer may not have been a good proxy for the child’s true health status, especially in the context of the development from child to adolescent. Kamper et al.[25] did a study on the same cohort investigating the agreement between the child’s own assessment of their pain and the parents’ report of their child’s pain, and found that the child expressed pain more often than the parents. However, when the parents did report pain, the child also reported pain, which indicated that the parents did not over-report pain. The same pattern was found by Sundblad et al.[26]. For our study, these findings imply that the actual prevalence of spinal pain and the length of spinal pain episodes might have been higher if the children had self-reported, but on the other hand we avoided reports on minor complaints e.g. bruises.

The major strength of this study was the 3-year weekly follow-up in the same cohort using the SMS-track system to collect the outcome measures. The SMS-track system is a very efficient method, providing a very easy way of collecting frequent follow-up. It minimized the recall bias because the parents reported events of the last 7 days; everybody in Denmark has a cell phone; it was easy for everybody to answer; and the response rate was very high. Furthermore, missing responses from the SMS-track system was not an issue. We imputed the missing data using different strategies, and we only found a small difference according to imputation method and study year. These differences did not have an impact on the number and the length of the episodes of spinal pain.

Finally, we combined the SMS track data from the parents with data from the clinicians, which gave us a very complete picture of the frequency, the duration and the localisation of spinal pain.

**Conclusion**

Although rates of spinal pain report were high, for most children the pain was short-lived and did not recur frequently. Of concern though, was the rather substantial number of children who reported either persistent or recurrent pain. In at least a quarter of those with spinal pain, the episodes lasted for more than 4 weeks.

<table>
<thead>
<tr>
<th>Table 6 Sensitivity analyses on missing data</th>
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<tr>
<td>Primary data</td>
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<tr>
<td>Median number of episodes (IQR)</td>
</tr>
<tr>
<td>Study year 1</td>
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<tr>
<td>Study year 2</td>
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<tr>
<td>Study year 3</td>
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</table>
and/or occurred three times or more during a study year. It is towards this group that a concerted research effort is needed to inform evidence-based prevention and management.

Additional file

**Additional file 1**: SMS questions. (DOCX 41 kb)

Abbreviations

CHAMPS: The childhood health, activity and motor performance school study; PE: Physical education; SMS: Short message system (text messages)

Acknowledgements

We acknowledge all the members of the CHAMPS Study DK and the clinicians taking part in this study and making it possible. Finally we would like to thank the participants and their parents and the participating schools.

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Availability of data and materials

The data that support the findings of this study are available from Niels Wedderkopp but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Niels Wedderkopp.

Authors' contributions

NW was responsible for the concept and design of the CHAMPS Study DK. KBD, LH and JH participated in the design of this study. KBD was responsible for the data management and wrote the first draft for this manuscript. All authors took part in a critical revision and have read and approved the final manuscript.

Competing interests

LH is a member of the Editorial Board of BMC Musculoskeletal Disorders. The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

Ethics committee approval was obtained before the start of the project; ID S20080047, and registration in the Danish Data Protection Agency was made, as stipulated by Danish law Jnr. 2008-41-2240. Written informed consent was obtained from parents for the child to join the study. Before every clinical examination, the parents gave verbal consent and the child assented. All participation was voluntary and the parent or child could drop out of the study or parts of it at any time during the study period.

Author details

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References

Paper II

Conservative care with or without manipulative therapy in the management of back and neck pain in Danish children aged 9-15. Study protocol for a randomized controlled trial.
Dissing KB, Hartvigsen J, Wedderkopp N, Hestbaek L
Chiropractic & Manual Therapies 2016 24:5
Conservative care with or without manipulative therapy in the management of back and neck pain in Danish children aged 9–15. Study protocol for a randomized controlled trial

Kristina Boe Dissing¹*, Jan Hartvigsen¹,², Niels Wedderkopp³,⁴ and Lise Hestbaek¹,²

Abstract

Background: Complaints in the musculoskeletal system often start early in life and back and neck pain in children are well-established predictors for similar problems in adulthood. Despite lack of evidence of effectiveness, manipulative therapy is one of the most commonly used treatment modalities for back and neck pain in children. The primary objective of this study is to evaluate the effectiveness of manipulative therapy when added to an approach consisting of manual soft tissue treatment, exercises and advice as needed, in children aged 9–15 complaining of back and neck pain.

Method: The project is nested in the Childhood Health, Activity and Motor Performance School Study, which includes around 1200 children aged 9–15, who were all invited to participate in this randomized controlled trial in case they experienced back and/or neck pain during the two year inclusion period. Parents received text messages (SMS) on a weekly basis inquiring about the child’s musculoskeletal pain. If pain was reported, the child was evaluated for inclusion into the trial and, if eligible, randomized into one of two intervention groups:

1. Pragmatic advice, manual soft tissue treatment and exercises
2. The above plus manipulative therapy

By the end of data collection 237 children were included in the study. The primary outcome measure is number of recurrences of back and neck pain during the follow-up period (3–27 months). Secondary outcome measures are average duration of complaint time for each episode, total duration of complaint time, global perceived effect after two weeks, and change in pain intensity after 2 weeks. Baseline information includes quality of life, expectations to treatment, expectations to future course, age, gender, social class and physical education at school.

(Continued on next page)
Discussion: For most common non-traumatic musculoskeletal complaints no standardized and evidence based treatment strategy exists. We want to evaluate the effectiveness of manipulative therapy in addition to an approach consisting of manual soft tissue treatment, exercises and advice as needed, in children aged 9–15 complaining of back and neck pain.

To our knowledge this is the first large scale randomized controlled trial investigating the effectiveness of commonly used treatments for back and neck pain in children.

Trial registration: ClinicalTrials NCT01504698

Keywords: Randomized controlled trial, Children, Adolescents, Spinal pain, Manipulative therapy, Neck pain, Back pain

Background

Complaints in the musculoskeletal system often start during childhood and adolescence [1–4], and back and neck pain in children and young people are well-established predictors for similar problems in adulthood [5–8]. Besides the complaints directly related to pain or reduced mobility, these problems can also be a barrier to children's physical activities, which may influence both physical and psychological health [9, 10]. Therefore, limitations caused by musculoskeletal pain in childhood can lead to musculoskeletal problems as well as potentially other lifestyle diseases like diabetes or cardiovascular diseases in adult life [11].

Low back pain is the most important of the musculoskeletal complaints from a socioeconomic perspective and is now ranked as the leading cause of years lived with disability in the world while neck pain is ranked fourth [12]. Back and neck pain has also been shown to be common in children, but for many children, the pain is mild in nature and of low intensity [13, 14]. However, some children are more severely affected, and this group is of particular interest in terms of prevention and treatment. Furthermore, it has been shown, that back and neck pain in children may progress; both to more locations in the spine, to higher frequency of pain, and to a higher pain intensity [13].

Thus, a focused effort directed towards early effective treatment of musculoskeletal problems in childhood to reduce recurrences, i.e. secondary prevention, appears justified. In fact this may be necessary if we want to maintain physical activity and limit long-term weakness and reduced function in the population caused by back and neck pain and other musculoskeletal disorders.

A positive effect of manipulative therapy (MT) in adults with various musculoskeletal problems is well-documented [15–18], e.g. for low back pain, where the effect is equally as good or better than usual care [18], and for several extremity joint conditions too [15, 19]. However, the evidence of effect in children is very sparse [20–23] and none of the studies relate to spinal pain. The choice of using MT on children can therefore only be based on tradition as well as on indirect evidence from trials and clinical guidelines for adults. The implications of using untested treatments on children are uncertain. Since they may not respond similarly to adults, they may require different dosages and experience different frequencies of side effects. Presently, MT is the most frequently used treatment of musculoskeletal complaints in children [24, 25], and in Denmark alone chiropractors treat around 17,000 children under the age of 18 every year, with musculoskeletal complaints being the most common one [10]. Therefore, it is of absolute importance to investigate the effect of this commonly used treatment strategy, which is actually considered to be best practice at the moment, despite lack of scientific evidence [21, 24, 25].

The purpose of this paper is to describe the methodology of a randomized controlled trial examining the effectiveness of MT when added to an approach consisting of manual soft tissue treatment, exercises and advice as needed, in children aged 9–15 complaining of back and neck pain. We hypothesize that the addition of manipulative therapy will decrease the risk of future episodes as well as the duration of episodes.

Method

Study design

Randomized controlled trial

Participants and setting The project is a sub-study of The Childhood Health, Activity and Motor Performance School Study (CHAMPS). The CHAMPS study is a longitudinal cohort study that includes app. 1200 children aged 9–15 from 13 primary schools in the municipality of Svendborg, which is considered to be representative of the Danish population [26]. The main purpose of the overarching study is to evaluate the influence of extra physical education on the amount of musculoskeletal injuries and on childhood health in general. The schools were divided into two groups: one receiving the normal amount of two physical education lessons per week and the other one receiving six lessons per week.

The CHAMPS study started in 2008 and the data collection on injuries and back problems ended in summer 2014. The research team consisted of researchers with a range of professional backgrounds and from different
departments all investigating different aspects of childhood health. At baseline, the children and their parents filled out a questionnaire addressing age, gender, health status, social class, work and leisure time activities. Social class was derived from parental educational level. The children have been followed with different kinds of testing throughout the study, e.g. physical tests, blood samples, DEXA scans, and, most importantly, three weekly text messages (SMS) sent to their parents inquiring about the child’s musculoskeletal complaints and the amount and type of leisure time sports activity during the past week (Additional file 1: Appendix 1). Parents answered using the reply function, and these were automatically registered and stored in a database. If they did not reply, they automatically got a SMS reminder two times during the following week. The SMS-response is a very efficient way to obtain frequent information and has been proven effective [27], and the response rate has been above 92 % in the CHAMPS study.

When a parent responded that the child had experienced pain during the previous week, a member of a screening team, consisting of three chiropractors and two physiotherapists, phoned the parents and administered a standardized interview regarding the complaint. Based on this, the interviewer determined whether the complaint was negligible or whether the child should be seen by a member of a clinical team that consists of five chiropractors with at least 3 years of clinical experience. The decision was made from anamnestic information about the history of the complaint, the duration and possible cause of complaint, the nature of the pain and if the pain seemed to be self-limiting or of a more prolonged nature. The examination took place at the child’s school, and following the examination the child received a diagnosis if possible, and was offered advice on how to handle his or her problem too. The same information was given to the parents either by phone or letter.

**RCT Recruitment**

In 2012, all enrolled children (see Fig. 1) were invited to join this randomized controlled trial if they experienced back and neck pain during the study period (2 years), i.e. they accepted participation pending a future episode of back and neck pain. Children not enrolled and new coming children had the possibility to join the study throughout the study period. There was a start-up period from February to March 2012 where procedures and logistics were tested as well as the feasibility of the self-reported outcome measures, i.e. the NRS scale and the KIDDS screen questionnaires. Because no problems were encountered and no alterations were made, the trial continued unaltered. The children were followed until the end of school in the summer of 2014.

**Ethics**

Temporary reddening and soreness in the treated area is common after both soft-tissue and manipulative treatment. No serious or lasting side effects have ever been reported in children aged 9–12 following the types of treatment used in this trial and no compensation claims have ever been made for this age group in Denmark [28]. Because there is no experimental treatment involved, but only treatments, which are usually performed in clinical practice, no interim analyses were made.

All parents have given written informed consent for their child to participate in the study. Participation in this trial is voluntary and the parents could withdraw their child from the study at any time with no negative consequences for the child. All participants were treated according to the Helsinki declaration [29].

The project has been approved by The Regional Committee on Health Research Ethics (#S-20110042) and data are being handled according to regulations by the Danish Data Protection Agency (#2013-41-1738).

**Procedure**

If a parent answered positively for back and neck pain on the weekly SMS and the telephone interviewer found that the child possibly was eligible for the trial, a member of the clinical team would evaluate the child at his or her school for inclusion or exclusion criteria (see Table 1).

At the first visit, the chiropractor took down a thorough history that included the rating of pain on a numerical 11-box rating scale. If the child fulfilled the inclusion criteria of NRS (3 or more on a numerical rating scale) [30, 31], he or she was randomized to treatment in either group A or B (see Fig. 2).

At baseline, the children filled in the KIDDS screen questionnaire that is a quality of life measure specifically designed for children [32] and answered a question about their expectations to the course of their treatment. In addition, they underwent an objective clinical examination including relevant neurologic and orthopedic examination as well as general and segmental movement palpation of the spine. General movement palpation is defined by the practitioner moving the spine in all directions and noticing the potential lack of movement, e.g. diminished forward bending of the neck. They then received a working diagnosis and were treated according to the randomization group. If the children did not fulfill the inclusion criteria, they were advised to remain active, and if necessary they were referred to examination and/or treatment elsewhere. If a child enrolled in the study experienced a recurrence of the original complaint or a new complaint during the remaining project period, the whole procedure was repeated starting with the phone interview and judgment of severity as defined
Flowchart CHAMPS/RCT

Year 2011 Children CHAMPS (N=1344)*

Children with MSK complaints reported by SMS 2011-2014 (N=1485)

Children with MSK complaints examined at school (N=1013)

Children with back- and neck complaints (N=448)

Excluded NRS<3 (N=57)

Excluded other reasons** (N=9)

Refused to participate in RCT*** (N=146)

Year 2014 Children CHAMPS (N=1147)*

*Number of children getting text messages (SMS). Number in 2014 lower because of children moving away, leaving the project, moving to other schools.

**Other reasons: Parents or child refused on day of examination, child had other manual treatment, pain was not neck- or back related.

***Refused to participate in RCT: refusal was given at the beginning of the project.

MSK: musculoskeletal

Fig. 1 Flowchart CHAMPS/RCT
previously. The only exception was randomization, as the child stayed in the original randomization group throughout the whole study period regardless of the number of recurrences or new complaints (incl. complaints in the extremities).

All clinical information was filed in a web-based register (Clinic Care Web), the KIDDS screen questionnaire, was paper-based and entered manually into Epidata, and data from the SMS were automatically stored in a secure database. Back up of all data were stored on a secure server at the University of Southern Denmark.

Data was monitored by an employed data manager throughout the project period.

Randomization
A research assistant, not otherwise associated with the study, performed a computer generated block randomization with block sizes randomly changing between 2 and 6 at the time of inclusion using a 1:1 allocation to one of two intervention groups A or B. He then wrote the consecutive letters of the two groups on separate pieces of paper and placed them in sealed opaque envelopes. These were given to the treating chiropractors. The intervention group was not revealed to the child or parents.

Interventions
The non-manipulative group received

- Pragmatic advice such as the use of cold or hot packs, braces, taping, suitable activities, ergonomics etc.
- Exercises including self-stretching and/or strengthening exercises
- Soft tissue treatment in the form of manual trigger point therapy and/or massage. Assisted stretching was not allowed in this group, as this would approach mobilization

The manipulative group received

- The items mentioned above
- Manipulative therapy: joint manipulation consisting of high-velocity, low-amplitude manipulation and/or joint mobilization without a high-velocity impulse to the spine and/or the extremities where indicated based on movement restriction and/or pain response during movement palpation

Thus, manipulative therapy was administered when there was a perceived biomechanical dysfunction of one or more joints that the treating clinician related to the child’s symptoms. The purpose of MT is to eliminate or relieve the pain as well as to reestablish better mobility and enhance the biomechanics of the joint, thus creating a basis for normalization of muscle activity around the joint [33–35].

In both groups, the frequency and content of treatments was determined on a pragmatic basis by the treating chiropractor. The treatment was intended to resemble pragmatic daily clinical practice in order to make the results more generalizable and implementable. The treatment continued until cessation of symptoms as determined by the child or parent or until the treating chiropractor decided that no further treatment was warranted. After 2 weeks of treatment, or earlier if the treatment was terminated, the child was questioned about global perceived effect, NRS and satisfaction with treatment. If there was no improvement in symptoms after 4–6 weeks of treatment, the child was referred to a secondary care spine center for a second opinion and further diagnostic work-up and/or imaging. The child and/or parents could stop the treatment at any time and still participate in other parts of the CHAMPS study.

Blinding
The interventions used in this trial make blinding of care providers impossible. The children were somewhat blinded because they were not told which group they were allocated to and the two groups would more or less have the same amount of treatment in terms of number of visits and time spent per visit. However, concealment of treatment group was difficult and some children might have detected the difference between the groups by comparing with their friends or by talking to their parents; or some may have had manipulative therapy before.

The parents filled in the weekly SMS-track at home independent of clinicians or researchers. For the analyses, the coding of treatment groups will be unknown to the primary investigator (KBD) and the statisticians performing the analyses, and the primary investigator is not involved in the treatments. The code will not be broken until the analyses are completed.

Outcome measures
Primary outcome measure
Number of recurrences during the follow-up period (3–27 months). A recurrence was defined as: i) a positive answer

Table 1 Inclusion and exclusion criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain in neck or back equal to or greater than 3 on an 11-box numerical rating scale for more than three days</td>
<td>Serious pathology (cancer, inflammatory diseases, vertebral fractures, cauda equina)</td>
</tr>
<tr>
<td>Manual treatment for the past 2 months (for this particular complaint)</td>
<td>Handicaps preventing normal physical activity</td>
</tr>
<tr>
<td>Contraindications to manipulative therapy</td>
<td></td>
</tr>
</tbody>
</table>
for back and/or neck pain on the weekly SMS question "Has [name of child] had any pain during the past week?"; ii) at least one pain free week prior to the recurrence; iii) pain location in the same region as initial episode.

Back and neck pain was defined as three spinal regions: cervical pain, thoracic pain and lumbopelvic pain. The reason for combining lumbar and pelvic pain is that prior experience in the study showed that children often tended to define pelvic pain as lumbar pain and did not differentiate between the two.

**Secondary outcome measures**

- The average complaint time for each episode (measured in weeks).
- Information on pain site was collected from interviews and examinations and subsequently from the SMS-track. The number of recurrences and complaint time was collected by using data from the SMS-track (Additional file 1: appendix 1).
- Total duration of complaint time (measured in weeks). This was extracted from the SMS data (continuous variables).
- Global perceived effect after two weeks. The child was asked: how will you describe your general wellbeing now in your neck/back (and any extremities) as opposed to 2 weeks ago before treatment was started? This was rated on a 7-point Likert scale with 1 being much better and 7 being much worse.
- Change in pain intensity after two weeks. This was rated on an 11-point numerical rating scale where 0 is no pain and 10 is worst pain (continuous variable).

Finally, any side effects to the treatment were recorded at each clinical visit, if reported by the child.

In addition the following information was collected at baseline for descriptive purposes:

- Quality of life (KIDDS screen) (At baseline and at recurrent or new episodes).
- Expectations to treatment. The child was asked prior to treatment: how do you expect the course of your problem will be? This was rated on a 5-point scale with 1 being much worse and 5 being much better.
- Expectations to future course: if your problem goes away, do you expect it to recur? Answer: yes/no. (At baseline and at recurrent or new episodes).

Age (9–15 year), gender (boy, girl), educational level (1 = No qualification, 2 = Vocational training, 3 = Higher education < 3 years, 4 = Higher education 3–4 years, 5 = Higher education >4 years), intervention group (A, B), school (11 schools), grade (4th to 9th grade), physical education at school (extra physical education, normal physical education).

**Power considerations**

The power of this study does not only depend on the treatment effects, but also on the average values of the primary outcomes and their inter-individual variation. To obtain a realistic judgment of the power of the study, a formal power calculation was postponed until the data collection was finished. Only information from each child regarding spinal pain or not for each week, and its school and class membership was used for the power calculation. Actually, we used this data to determine the power of the analyses for the primary outcome and the two outcomes based on the weekly SMS data in a small simulation study. In each simulation step we split the children randomly into two groups and removed randomly 20 % of all episodes in the simulated manipulative group, and shortened 50 % of all episodes of two or more weeks duration by 50 %. In this scenario, we observed a power of 76 % for the primary outcome (number of recurrences), of 20 % for the average length and of 87 % for the overall complaint time.

The lack of power for the average length is due to the fact that more than 40 % of all episodes have a length of one week. Removal of these short episodes results in an increase of the average length, counterbalancing the shortening of long episodes.

**Statistical analyses**

The primary outcome of the study is the number of recurrences in a child.

The definition and analysis of this outcome is based on the following considerations:

For each weekly SMS sent after randomization a child is regarded as being affected by the original complaint, i.e. experiencing a recurrence, if there is a positive answer to the question "Has ... had any pain during the last week?" and if the pain is located in the same region. The child is regarded as experiencing a recurrence, if the child was unaffected the previous X weeks (with X ≥ 1 in the main analysis and X ≥ 3 in later sensitivity analyses). The corresponding time at risk for a recurrence is the number of weeks the child is not affected prior to the recurrence. The treatment effect on the number of recurrences is assessed by a hierarchical negative binomial regression model with the number of recurrences as outcome and the time at risk as exposure time variable. School and classes will enter as random effects. Robust standard errors will be used to take a violation of the distributional assumption into account. Intervention effects will be expressed as incidence rate ratio.
Secondary outcomes:

1. Average length of an episode
2. Average complaint time

The definition and analyses of these two outcomes are based on the following considerations:

An episode starts directly after randomization and with each new recurrence there starts a new episode. The length of an episode is the number of consecutive weeks where the child is affected in the same region. For the episode starting with the randomization, one additional week prior to randomization is assumed. The treatment effect on the average length of episode is analyzed by using a hierarchical linear model with the length of each episode as outcome, the treatment indicator as covariate and school, class and subject as random effects. If the child is affected at the end of the follow up period, this (censored) episode is not included in the analysis. Interventions effects will be expressed as the difference in mean length. Since more than 40 % of all episodes have a length of more than one week, we will also compare the histograms of the length of episodes between the two groups to get a better understanding of the effect on the length of the episodes.

The overall complaint time is the number of weeks a child is affected. The treatment effect on the overall complaint time will be analyzed using a hierarchical negative binomial regression model with the overall complaint time as outcome and the time in study as exposure time variable. School and classes will enter as random effects. Robust standard errors will be used to take a violation of the distributional assumption into account. Intervention effects will be expressed as incidence ratios, which correspond here to ratios of the average complaint time per year.

Two further secondary outcomes:

1. Global perceived effect
This outcome on a 7-point scale will be analyzed using a hierarchical linear model with the treatment indicator as covariate and school and class as random effects. Robust standard errors will be used to take a violation of the distributional assumption into account. Treatment effects will be expressed as difference in mean perception.

2. Change in pain intensity
This will be analyzed in the same manner as the global perceived effect. Treatment effects will be expressed as difference in mean change.

All analyses will be repeated separately for cervical complaints, thoracic complaints and lumbopelvic complaints. For all analyses, the covariates quality of life, expectations to treatment, expectations to future course, age, gender, social class, intervention group and

Discussion

Severe traumatic musculoskeletal injuries in children are treated in the emergency department by a specific treatment strategy, but for most common non-traumatic musculoskeletal complaints no standardized and evidence based treatment strategy exists. To our knowledge, this is the first randomized controlled trial investigating the effect of MT on children complaining of back and neck pain. This is important due to the potential long-term consequences of musculoskeletal complaints in children and the lack of evidence based treatments. It is necessary to focus research efforts on how to best treat and prevent these complaints at an early age.

Many adults experience complaints in more than one region of the spine and therefore it is increasingly common to investigate the effect of manipulative therapy on complaints involving the whole spine rather than region-specific complaints [36, 37]. Symptoms from the various regions are very similar [38, 39], and pain in different regions of the spine may be closely interrelated. Furthermore, new research have shown that in children pain is likely to progress to more locations [13]. Therefore it is an important aspect of this study that the spine is treated both as one entity and as three separate regions.

The strengths of this study are that it is school based and nested in a large longitudinal cohort study where the children were monitored every week for two and a half years, and the pragmatic design makes the interventions easy to implement in daily practice. During the study period both groups received optimal pragmatic usual care with MT as the only difference. Therefore any difference in the results obtained between the two groups can be attributed to MT alone. For ethical reasons, we did not have a control group receiving no treatment, and we did not compare with “real life” usual care, which often is probably less than our pragmatic usual care. Because of the pragmatic setup, we did not have standardization on number or duration of treatment. However, in the analyses, we will determine if the number of visits differed between groups and if that is the case, the number of visits will be included in the explanatory models.
Blinding of the children and the practitioners was not possible due to the nature of the treatment. The results might be influenced by the interaction between the children and the practitioners; that includes verbal communication, physical contact and empathy between the two parts. These non-specific factors cannot be measured and we do not know the full influence of them in this trial. All children were however treated by more than one clinician, which will enhance generalizability, and choice of treatment in the individual consultation depended on the treating chiropractor.

A limitation of the study is, that we did not systematically ask for side effects to the treatment; it was only recorded if told by the child or if the practitioner occasionally asked for it. A systematic recording of side effects should be implemented in future studies.

If it is possible to develop efficient treatment for back and neck pain in children and adolescents, a life course of recurring problems may be altered with potential positive implications for both individuals and society. And because it is very rare to have serious side effects to manipulative therapy in children, potentially just mild side effects as soreness or reddening [40], the possible implications in terms of improved spinal health and wellbeing may be considerable.

Furthermore, fast and complete recovery from back and neck pain will minimize the restrictive impact of the pain on the level of physical activity and thus potentially have a positive influence on general health. This is exceedingly important in this age group where the level of physical activity tends to decrease [41–43], which might have a significant impact on future health [44, 45], and where lifetime habits are being developed [43, 46].

Acknowledgement
The authors gratefully acknowledge the following for funding individual researchers and for funding the CHAMPS Study Denmark part II: The Nordoe Foundation, The TRYF Foundation, The IMK Foundation, The Region of Southern Denmark, The Egmont Foundation, The A.J. Andersen Foundation, The Danish Reumatism Association, Østfynes Foundation, Bd. Hartmanns Foundation and TEAM Denmark. University College Lillebaelt Department of Physiotherapy, University of Southern Denmark, The Danish Chiropractic Research Foundation, The Svendborg Project by Sport Study Sydfyn, The Municipality of Svendborg as well as the Nordic Institute of Chiropractic and Clinical Biomechanics for providing office space and support. Finally we would like to thank the participants and their parents and the participating schools, and Professor Werner Yoch and Associate Professor Eleanor Boyle for advice in matters relating to sample size calculations and description of the analysis.

In addition we acknowledge all the members of the CHAMPS study and the clinicians taking part in this study and making it possible.

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Trial status
Patient recruitment ended in summer 2014.

Trial registration
ClinicalTrials NCT01504698

Additional file

Additional file 1: Appendix1. (DOCX 40 kb)

Abbreviations
MT: Manipulative therapy; CHAMPS: The Childhood Health, Activity and Motor Performance School Study; SMS: Text messages.

Competing interest
The authors declare that they have no competing interests.

Authors’ contributions
All authors participated in the design of this study. KBD was project manager for the trial and wrote the first draft for this manuscript. All authors have read and approved the manuscript.

References


Paper III

Conservative care with or without manipulative therapy in the management of back and/or neck pain in Danish children aged 9-15. A randomized controlled trial nested in a school-based cohort.

Dissing KB, Hartvigsen J, Wedderkopp N, Hestbaek L
Submitted, August 2017
Title
Conservative care with or without manipulative therapy in the management of back and/or neck pain in Danish children aged 9-15. A randomized controlled trial nested in a school-based cohort
Short title: Manipulative therapy and children

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* Corresponding author

Word count: 3053
Author summary
Why was this study done?
What is the effect of adding manipulative therapy to other conservative care in a school-based cohort of children aged 9-15 years reporting spinal pain, i.e. back and/or neck pain?
What did the researchers find?
In this randomized controlled trial that included 238 children, we found no effect on the number of recurrences of spinal pain when adding manipulative therapy to information, advice, and soft tissue treatment, but children in the manipulative therapy group had a higher Global Perceived Effect.
What do these findings mean?
Adding manipulative therapy to other conservative care in school children reporting spinal pain does not result in fewer recurrences of pain. The choice of treatment therefore relies on personal preferences, and could include conservative care with and without manipulative therapy.

Abstract
Background
A substantial number of children experience spinal pain, i.e. back and/or neck pain. Today, no 'gold standard' treatment for spinal pain in children exists, but manipulative therapy is increasingly being used in spite of a lack of evidence of its effectiveness. This study investigates the effectiveness of adding manipulative therapy to other conservative care for spinal pain in a school-based cohort of Danish children aged 9-15 years.
Methods and Findings.
The design was a two-arm pragmatic randomized controlled trial, nested in a longitudinal open cohort study in Danish public schools. 238 children from 13 public schools were randomized individually from February 2012 to April 2014. A text message system and clinical examinations were used for data collection. Interventions included either 1) advice, exercises, and soft tissue treatment, or 2) the same plus manipulative therapy. The primary outcome was number of recurrences of spinal pain. Secondary outcomes were duration of spinal pain, change in pain intensity, and Global Perceived Effect.
We found no significant difference between groups in the primary outcome (control group median 1 (IQR 1-3) and intervention group 2 (IQR 0-4), p=0.07). Children in the group receiving manipulative therapy reported a higher Global Perceived Effect: OR 2.22, (95% CI 1.19-4.15). No adverse events were reported. Main limitations are the potential discrepancy between parental and child reporting and that the study population may not be comparable to a normal care-seeking population.

Conclusions
Adding manipulative therapy to other conservative care in school children with spinal pain did not result in fewer recurrent episodes. The choice of treatment – if any – for spinal pain in children therefore relies on personal preferences, and could include conservative care with and without manipulative therapy. Participants in this trial may differ from a normal care-seeking population.

Trial registration: ClinicalTrials NCT01504698
Introduction

Today, no ‘gold standard’ treatment exists for children with spinal pain, i.e. back and/or neck pain, but manipulative therapy (i.e. joint manipulation and/or mobilization) is increasingly being used despite a lack of evidence of its effectiveness. Manipulative therapy is generally recommended as a treatment option for adults with spinal pain, and is delivered by various health professions, both on its own and in combination with other types of therapy, such as advice, exercises, and soft tissue treatment. Management of children's health relies to a large extent on parents' values, preferences and experience, and in the absence of guidelines for the treatment of spinal pain in children, healthcare professionals have to rely on guidelines developed for adults. Although spinal pain is transient and inconsequential for most children, some have frequent and bothersome complaints and the prevalence increases with age. Furthermore, spinal pain is recurrent in some children and spinal pain in adolescence is a strong predictor for similar problems in adulthood.

The aim of this pragmatic randomized controlled trial (RCT) was to determine the effectiveness of adding manipulative therapy to other conservative care (advice, exercises and soft tissue treatment) on the number of recurrences of spinal pain in children aged 9 to 15 years who were participating in a school-based open cohort study. Secondary outcomes included the short-term effect on duration of spinal pain episodes, pain intensity, and Global Perceived Effect.

Method

Study design

A pragmatic parallel observer-blinded RCT nested in a school-based open cohort.

Participants and setting

This study was nested in The Childhood Health, Activity and Motor Performance School Study (CHAMPS Study-DK), which is a Danish longitudinal school-based open cohort study including approximately 1,400 children aged 9 to 15 years from 13 public schools. As it was an open cohort study, children could enter or leave the cohort at any time during the study period. The children were followed weekly with text messages (SMS) to one of their parents inquiring, amongst other things, about any musculoskeletal pain the child might have had during the past week (Questions in S1 text). Data collection on musculoskeletal complaints for this RCT began in February 2012 and ended at the end of June 2014.
Eligibility determination

All children enrolled in the CHAMPS Study-DK were invited to participate in the RCT. The complete protocol for the RCT is described in detail elsewhere. Briefly, when a parent answered positively on the SMS to the presence of spinal pain in their child, a member of a screening team (licensed chiropractors and physiotherapists) telephoned the parent and conducted a standardized interview about the complaint, in order to determine whether the child was eligible for inclusion in the RCT. Initial eligibility was based on: 1) the pain was spinal and still present at the time of the interview, 2) the parent had agreed, on behalf of the child, to join the RCT, and 3) the child had not had any manual treatment of the spine during the previous 2 months. Within 2 weeks, the child was evaluated at the school by a chiropractor from the RCT team (seven licensed chiropractors) to determine whether he or she fulfilled the inclusion criteria (Table 1). After the evaluation, both the child and his/her parents were informed about the results and treatment was initiated.

<table>
<thead>
<tr>
<th>Eligibility criteria</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
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<tbody>
<tr>
<td>Pain in neck or back equal to or greater than 3 on an 11-box numerical rating scale for more than three days</td>
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<td>Manual treatment for the past 2 months (for this particular complaint)</td>
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<td>Contraindications to manipulative therapy</td>
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</table>

**Intervention groups**

<table>
<thead>
<tr>
<th>The non-manipulative group (Non-MT group)</th>
<th>The manipulative group received (MT group)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Pragmatic advice (activity level, ergonomics, cold packs etc.)</td>
<td>• Advice, exercises and soft tissue treatment</td>
</tr>
<tr>
<td>• Exercises (stretching and/or strengthening exercises)</td>
<td>• Manipulative therapy: joint manipulation and/or mobilization</td>
</tr>
<tr>
<td>• Soft tissue treatment (manual trigger point therapy or massage)</td>
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</tr>
</tbody>
</table>

First consultation

At the first consultation, the chiropractor obtained a case history, including pain intensity on an 11-box Numerical Rating Scale, performed a clinical examination, and various baseline data were acquired (S1 Table). Two weeks after inclusion, the child was asked
about Global Perceived Effect (S2 Text) and pain intensity.

If a child experienced a recurrence of spinal pain or a musculoskeletal complaint in the extremities during the study period (i.e. the parent reported pain on the weekly SMS), the procedure was repeated except for randomization, which was carried forward throughout the study period regardless of the body location in which the complaint occurred. All data were filed in electronic data storage systems established specifically for this project and stored on secure servers.

Interventions
The non-manipulative therapy group (non-MT group) received advice, exercises and, soft tissue treatment, and the manipulative therapy group (MT group) received the same plus manipulative therapy (Table 1). Manipulative therapy was delivered at the discretion of the chiropractor and applied on the basis of an assessment of biomechanical dysfunction and pain provocation found during clinical examination of the child’s spine and extremities. Because of the pragmatic nature of the study, the frequency and content of treatments in both groups was determined by the treating chiropractor at each visit, similar to what is normal in clinical practice. Because the treatment team consisted of seven chiropractors, a child could be treated by different chiropractors during different appointments. Treatments continued until the child no longer had any symptoms related to the musculoskeletal complaint, or until the chiropractor or parent decided that further treatment was not warranted. The child and/or parents could terminate the treatments or drop out of the RCT at any time during the study period, but still stay in the cohort of the CHAMPS Study-DK.

Outcomes
The primary outcome was the number of recurrences as measured via the weekly SMS messages. A recurrence was defined as a new episode of spinal pain (i.e. back and/or neck pain) occurring after at least 1 week without spinal pain following the end of the previous episode. (See secondary outcomes, Table 2).
Table 10 Outcomes, definitions and statistical methods

<table>
<thead>
<tr>
<th>Primary outcome</th>
<th>Definition</th>
<th>Statistical method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of recurrences of spinal pain (3-27 months follow up)</td>
<td>i) A positive answer on the weekly SMS for spinal pain ii) Minimum of 1 week without report of spinal pain prior to the recurrence</td>
<td>A hierarchical negative binomial regression model. Intervention effects were expressed as incidence rate ratio</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average duration of spinal pain episodes</td>
<td>The number of consecutive weeks the child was affected by spinal pain (response option ‘1’)</td>
<td>A mixed effects linear regression model with subject as random effect, outcome log transformed. Intervention effects were expressed as the difference in median length</td>
</tr>
<tr>
<td>Total duration of complaint time in relation to individual follow-up time</td>
<td>Total number of weeks a child was affected by spinal pain (response option ‘1’) in the entire follow-up period</td>
<td>A hierarchical negative binomial regression model. Intervention effects were expressed as incidence rate ratio</td>
</tr>
<tr>
<td>Global Perceived Effect after 2 weeks</td>
<td>Dichotomized into two groups: “Much better” and “The same or worse”</td>
<td>A logistic regression model. Intervention effects were expressed as odds ratios</td>
</tr>
<tr>
<td>Change in pain intensity after 2 weeks</td>
<td>Rated on an 11-point Numerical Rating Scale with ‘0’ being ‘no pain’ and ‘10’ being ‘worst pain’</td>
<td>A linear regression model. Intervention effects were expressed as the difference in mean length</td>
</tr>
</tbody>
</table>

Sample size
As it was an open cohort study, we continued to recruit participants until 3 months prior to the end of data collection in summer 2014, to include as many participants as possible with varying follow-up times. Based on preliminary analyses, this resulted in a power of 76% for the number of recurrences, 20% for episode length and 87% for overall complaint time92.

Randomization
A computer-generated block randomization was made with block sizes alternating between two and six at the time of inclusion, using a 1:1 allocation to the two groups. The consecutive designations of the two groups were written on separate pieces of paper and given to the chiropractors in the RCT team in sealed opaque envelopes. A research assistant, who was not otherwise connected to the study, performed the procedure.
**Blinding**
Due to the nature of the intervention, blinding of the treating chiropractors was not possible, however, neither parents nor children were informed about group allocation and parents did not attend treatment sessions and answered the SMS without contact with clinicians or researchers. The coding of the intervention group was not revealed to the primary investigator or the statisticians until after the analyses had been completed.

**Statistical methods**
All analyses used an intention-to-treat approach. Various types of regression analyses were used depending on the type of outcome; follow-up time was included as an exposure time variable; and class, school and subject were evaluated and included in the models as random effects if their effect was statistically significant (see details, Table 2). No effect was seen on any of the outcomes and hence, cluster was not included in the models. For linear models, means and standard deviations (SD) were used if data were normally distributed; otherwise medians and interquartile ranges (IQR) were reported. All methods were checked according to fulfillment of other assumptions and changed where appropriate. Due to some missing SMS answers, we imputed missing data as follows: if four or fewer consecutive missing answers were preceded and followed by a ‘1’, this was considered as one continuous episode and the missing values were imputed as ‘1’.

A sensitivity analysis was conducted to assess the effect of the choice of definitions in relation to recurrence and duration. Hence, in this analysis, a new episode was defined to occur after 4 weeks of ‘no pain’ instead of 1 week before it was considered a new episode. STATA 14.2 (StataCorp, College Station, Texas, USA) was used for data analyses.
Significance level was set to 5%.

**Ethics**
All parents gave written consent to participation on behalf of the child and the children gave oral consent. A child could be withdrawn from the study at any time during the study period and the study was conducted according to the Declaration of Helsinki. The project was approved by The Regional Committee on Health Research Ethics (#S-20110042) and data were handled according to the regulations set by the Danish Data Protection Agency (#2013-41-1738).
Results
The inclusion period ran from February 1\textsuperscript{st} 2012 to April 1\textsuperscript{st} 2014, and the follow-up period ended on June 27\textsuperscript{th} 2014 (the end of the school year) resulting in between 1 and 868 follow-up days, (mean 477 days; SD 233). A total of 770 children reported spinal pain on SMS, and after telephone interviews, 483 children were evaluated for eligibility but did not fulfill the inclusion criteria. Additionally, 44 individuals reported pain less than 3 on the Numerical Rating Scale on the day of examination, leaving 243 children randomized and enrolled in the study. During data cleaning, we found five participants had been wrongly included, i.e. the SMS answer indicated no spinal pain, and they were excluded from the analyses. Thus, the final cohort for analysis consisted of 238 children with a mean age of 12.6 years: 116 in the non-MT group (49\%) and 122 in the MT group (51\%), (CONSORT Flow Diagram Fig 1). Baseline covariates can be seen in Table 3, which also reports the amount of missing data for each variable. There was no difference between the groups for any of the covariates indicating randomization was successful and therefore univariate analyses were performed for all analyses.

Table 11 Baseline data. Baseline covariates by intervention group

<table>
<thead>
<tr>
<th></th>
<th>Non-MT group (n=116)</th>
<th>MT group (n=122)</th>
<th>Missing non-MT group***</th>
<th>Missing MT group***</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, Female, No (%)</td>
<td>73 (63)</td>
<td>78 (64)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at inclusion</td>
<td>12.6 (12.4-12.9)</td>
<td>12.6 (12.3-12.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow up time (days)</td>
<td>492 (448-536)</td>
<td>463 (423-504)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NRS baseline</td>
<td>5.3 (5.1-5.6)</td>
<td>5.2 (4.9-5.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Expectations to clinical course (&quot;Worse&quot;)</td>
<td>7.6% (3.4-16.1)</td>
<td>7.6% (3.4-16.1)</td>
<td>32% (37)</td>
<td>35% (43)</td>
</tr>
<tr>
<td>Expectations to future clinical course (&quot;Negative&quot;)</td>
<td>56.4% (45.1-67.1)</td>
<td>52.6% (41.3-63.7)</td>
<td>33% (38)</td>
<td>38% (46)</td>
</tr>
<tr>
<td>KID Physical wellbeing</td>
<td>44.7 (38.5-49.6)</td>
<td>43.8 (40.5-49.6)</td>
<td>4% (5)</td>
<td>1% (1)</td>
</tr>
<tr>
<td>KID Psychological wellbeing</td>
<td>49.5 (44.8-56.0)</td>
<td>48.5 (44.8-56.0)</td>
<td>5% (6)</td>
<td>2% (3)</td>
</tr>
<tr>
<td>KID Autonomy and relation</td>
<td>49.5 (45.2-55.8)</td>
<td>49.5 (45.2-55.8)</td>
<td>4% (5)</td>
<td>2% (3)</td>
</tr>
<tr>
<td>KID Social support and peers</td>
<td>53.2 (46.9-57.8)</td>
<td>53.2 (46.9-57.8)</td>
<td>4% (5)</td>
<td>1% (1)</td>
</tr>
<tr>
<td>KID School</td>
<td>51.1 (45.4-58.2)</td>
<td>51.1 (45.4-54.4)</td>
<td>4% (5)</td>
<td>1% (1)</td>
</tr>
</tbody>
</table>
Primary outcome
During the follow-up period, 175 (74%) of the children had a total of 592 recurrences, ranging from 1 to 21 times per child. The median number of recurrences was 1 (IQR 1-3) for the non-MT group and 2 (IQR 0-4) for the MT group. There was no significant difference in the number of recurrences between groups, incidence rate ratio 1.26 (95% CI 0.98-1.61), P=.07.

Secondary outcomes
We found no significant difference in the average episode length, total number of pain weeks or change in pain intensity between the two groups. Children in the group receiving manipulative therapy reported a higher Global Perceived Effect: odds ratio 2.22, (95% CI 1.19-4.15), that was statistically significant. All results are displayed in Table 4.

Table 12 Results on secondary outcomes

<table>
<thead>
<tr>
<th></th>
<th>MT group</th>
<th>Non-MT group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Length of spinal pain episode</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number of episodes</td>
<td>456 (55%)</td>
<td>374 (45%)</td>
</tr>
<tr>
<td>Median (IQR) (number of weeks)</td>
<td>2 (1-6)</td>
<td>2 (1-5)</td>
</tr>
<tr>
<td>P value</td>
<td>.21</td>
<td></td>
</tr>
<tr>
<td><strong>Total duration of complaint time per child</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number of pain weeks</td>
<td>1-114</td>
<td>1-111</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>9 (IQR 4-22)</td>
<td>7 (IQR 4-18)</td>
</tr>
<tr>
<td>IRR (95% CI)</td>
<td>1.16 (0.92-1.48)</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>.22</td>
<td></td>
</tr>
<tr>
<td><strong>Global Perceived Effect</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of children in analysis*</td>
<td>96 (52%)</td>
<td>86 (48%)</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>2.22 (1.19-4.15)</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>.01</td>
<td></td>
</tr>
<tr>
<td><strong>NRS change</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of children in analysis*</td>
<td>112 (50%)</td>
<td>111 (50%)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>2.2 (2.5)</td>
<td>2.3 (2.7)</td>
</tr>
<tr>
<td>P value</td>
<td>.76</td>
<td></td>
</tr>
</tbody>
</table>

IQR= Inter Quartile Range; IRR=Incidence Rate Ratio; OR= Odds Ratio; NRS=Numerical Rating Scale; SD=Standard Deviation; *Number of children in analysis of the first episode due to missing data

Sensitivity analysis on number of pain free weeks
The number of recurrences declined from a total of 592 to 259 when we defined a new episode to occur after 4 weeks of ‘no pain’ instead of 1 week. This, however, did not change
the between-group difference on either the primary outcome or most of the secondary outcomes, but it did result in a statistically significant increased length of episode for the MT group, mean 3.5 (3.0-4.0) vs. 4.4 weeks (3.8-5.0) and median 2 (1-5) vs. 2 (1-4), P=.045.

Harms
To our knowledge, no serious harms following manipulative therapy have been reported in children of this age group\textsuperscript{57, 58}. However, it is common to experience temporary reddening or soreness in the area being treated after both soft tissue treatment and manipulative therapy\textsuperscript{56}. Treating chiropractors recorded treatment-related harms if the child stated these at the consultation, but none were reported and no child was referred to other health care providers, including general practitioners, because of side effects or harms.

Discussion
Adding manipulative therapy to other conservative care for children reporting spinal pain did not result in fewer recurrences in a school-based cohort of Danish children aged 9-15 years. Furthermore, the average episode length, total number of pain weeks, and change in pain intensity were no different between the groups. However, in the sensitivity analyses, filtering out the frequently recurring episodes, the difference for episode length did become statistically significant. Children randomized to the MT group reported a higher Global Perceived Effect that was statistically significant. Thus, no increased effectiveness was evident and no harm was detected.

To our knowledge, this is the first RCT evaluating the added benefit of manipulative therapy in children with spinal pain (i.e. back and/or neck pain). Michaleff et al\textsuperscript{43} found only four RCTs dealing with conservative interventions for low back pain in children and all had a high risk of bias. Only one of these included manual therapy combined with exercise, but it had only 45 participants.

Because this study was a two-armed parallel trial with manipulative therapy as an addition to other conservative care, it is probably not surprising that we did not find a large difference between the two groups. This RCT was nested in a large cohort study, and hence we could not prolong the study period to increase the sample size; however, given the small absolute differences found on both primary and secondary outcomes, this is unlikely
to have changed our conclusions. We originally intended to analyse the three spinal regions separately, however the pain site could change within the same individual during follow up, and many individuals reported pain from several regions. Therefore, such an analysis would have been difficult to interpret.

The Numerical Rating Scale has been shown to be a valid tool for assessing pain in children\textsuperscript{53,69,93}, and in this study, the children also appeared to be able to rate their pain on the scale quite easily. However, when analyzing the data, we found that Numerical Rating Scale ratings were not always in accordance with Global Perceived Effect ratings, i.e. some children would say they felt better, although reporting a higher score on the Numerical Rating Scale at follow up than at baseline. This noise may be caused by variation in cognitive abilities and maturity between the children, and is probably equally distributed between groups. Regardless, we did not find statistically significant differences between the groups on change in Numerical Rating Scale scores, and both achieved a mean change of 2.3, which can be regarded as a clinically meaningful change, as studies have shown a minimal clinically important change to be +/- 1\textsuperscript{71,72}.

We could not find any literature supporting the validity of measures of Global Perceived Effect in children, but validity of this measure has been shown to be good in adults\textsuperscript{73,74} and we therefore included it as a measure of the child’s own perception of improvement. We would have expected that statistically significant differences between the groups would follow the same pattern for the Numerical Rating Scale and the Global Perceived Effect, but this was not the case. Therefore, the validity of both of these as outcome measures in clinical trials involving children should be further explored.

\textit{Strengths and weaknesses}

The principal strength of this study was the school-based design, which had a number of advantages: the logistical burden for the parents was reduced because the treatment took place during school time, social bias was likely to be minimal or absent because everybody was invited to participate in the study, and there was equal access because all treatment in the trial was free. Also, this design allowed for a long follow-up period for most children. By nesting this RCT in a school-based cohort, we may however have included children who
would not normally have sought care, i.e. likely to have had sub-clinical pain. The inclusion criterion of a Numerical Rating Scale score of 3 or more is probably also below the normal pain intensity threshold for seeking treatment and many parents would probably have waited until the pain had become worse or lasted longer before seeking care. On the other hand, the number and duration of spinal pain episodes were higher in the study sample than in the full cohort (mean number 3.5 versus 2, mean duration 4.6 versus 2.8)⁴, suggesting that the children enrolled in this study were more affected by pain than their non-participating peers.

SMS is a very efficient way of collecting frequent data over a long time⁵¹,⁵². In this study, the SMS responses were a reflection of how often the parents reported on their child's pain and might not have been a true reflection of how the child actually felt. We know that there is a discrepancy between parental and child reporting of spinal pain¹²,⁶²,⁹⁴. Parents appear to under-report compared to their child when pain is at a low level, whereas concordance is higher when the pain is more severe. Thus, it is possible that the parents stopped reporting pain because they assumed the complaint to be minor, even though the child might still have had pain. This could explain some of the difference between outcomes reported by the children (Global Perceived Effect) and outcome reported by the parents (SMS).

Using different practitioners prevents a potential patient-practitioner relationship and is considered a strength; however, the more people involved, the more irregularities and mistakes are likely to occur. One example of this is the poor response rate to the measures collected by the clinicians, e.g. Numerical Rating Scale and Global Perceived Effect scores.

Missing data
The amount of missing data was substantial for some of the secondary outcomes, and therefore we analysed only those for the first spinal pain episode. However, there was no difference in response rates between groups, and it was assumed that data were missing completely at random and not due to any underlying confounding factors or bias. Possible reasons for missing data could be practitioners’ forgetfulness or an electronic system defect resulting in missing data. Because of missing data, we cannot say anything valid
about the course of pain, e.g. whether there is a learning effect over time or whether expectations of treatment differ over time between the two groups.

Future research
Since the inclusion criteria in this study were very broad, subgroup analyses would be valuable to inform future studies, i.e. if there are subgroups of children who respond better or worse to manipulative therapy than to other treatments. Future RCTs should include care-seeking children who self-report their response to treatment in order to evaluate effectiveness in that population. In addition, inclusion of an untreated group would elucidate the effect of treating these children, whether manipulative therapy is included or not.

Conclusion
We found no significant difference in the number of recurrences of episodes of spinal pain in a school-based cohort of children when adding manipulative therapy to advice, exercises, and soft tissue therapy. The study population may not be comparable to a normal care-seeking population and therefore the results may not be directly transferrable.

Authors’ contributions
All authors participated in the design and interpretation of analyses of this study. Kristina Boe Dissing was project manager for the trial and drafted the manuscript. All authors contributed with revisions and approved the final version of the manuscript.

Acknowledgement
The authors gratefully acknowledge the Nordic Institute of Chiropractic and Clinical Biomechanics for providing office space and support. Furthermore we would like to thank Suzanne Capell for proof reading the manuscript. Finally we would like to thank the participants and their parents and the participating schools, and Professor Werner Vach and Associate Professor Eleanor Boyle for advice in matters relating to sample size calculations and description of the analysis. In addition, we acknowledge all the members of the CHAMPS Study-DK and the clinicians taking part in this study for making it possible.


23. Dissing KB, Hartvigsen J, Wedderkopp N, Hestbaek L. Conservative care with or without manipulative therapy in the management of back and neck pain in Danish


31. Castarlenas E, Miro J, Sanchez-Rodriguez E. Is the verbal numerical rating scale a valid tool for assessing pain intensity in children below 8 years of age? The journal


Paper IV

Identifying potential treatment effect modifiers associated with the outcome of manipulative therapy for spinal pain in Danish children aged 9-15. Secondary analysis of a randomized controlled trial.

Dissing KB, Vach W, Hartvigsen J, Wedderkopp N, Hestbaek L
Title
Identifying potential treatment effect modifiers associated with the outcome of manipulative therapy for spinal pain in Danish children aged 9-15.
Secondary analysis of a randomised controlled trial.

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Background

Although spinal pain, i.e. back and/or neck pain, is transitory for most children, a considerable subgroup has recurrent and bothersome complaints\(^3, 4\). Considering that spinal pain in adolescence is a strong predictor for similar problems in adulthood\(^2, 5, 8\), and spinal pain ranks third among individuals living with disability within the range of 15-19 years\(^6\), it is important to explore the effectiveness of treatments for spinal pain in these most severely affected children. Manipulative therapy is increasingly being used, despite lack of evidence of its effectiveness in children\(^44, 84, 85\). Current guidelines on treatment of spinal pain rely on studies of adults\(^45-47\) and few randomised controlled trials (RCTs) have been conducted on children, and most are of low quality\(^42, 43\). Because of the dire lack of evidence about treatment of spinal pain in this age group, data from existing studies should be exploited to the fullest.

In the area of spinal pain, it is generally acknowledged that a particular intervention may be more effective for a subgroup of people\(^95, 96\), and that it is possible to identify such subgroups. Studies of adult populations have found some variables with weak to strong evidence of a modifying effect on the treatment of spinal pain\(^79, 97\), e.g. age, expectations of treatment, educational level and quality of life. To our knowledge, no studies have investigated potential effect modifiers of treatment for spinal pain in children.

RCTs are conducted to estimate potential differences in the effect of two interventions (or intervention versus no intervention) on a given outcome. They are typically designed to estimate effects at the group level and are usually not sufficiently powered to explore modifying effects on particular subgroups. Nevertheless, data from such trials may be used for explorative analyses to give indications of which treatments work for whom, and whether a particular intervention is more effective in a subgroup of people with identifiable characteristics (i.e. effect modifiers)\(^78, 98\).

This study is a secondary analysis of data from an RCT (submitted for publication) comparing advice, exercises and soft tissue treatment with or without the addition of manipulative therapy in Danish school children aged 9-15 years with spinal pain. The
primary outcome was number of recurrent spinal pain episodes during the follow-up period. Secondary outcomes were average spinal pain episode length, total number of weeks with spinal pain during the follow-up period, change in pain intensity, and Global Perceived Effect. In the primary analysis, we found no significant differences between the two groups, which could be explained by a number of factors including no benefit of adding manipulative therapy to the treatment, very broad inclusion criteria resulting in a heterogeneous cohort, or outcomes that were not responsive. In this paper, we wanted to explore if we could identify treatment effect modifiers, i.e. certain baseline participant characteristics that may be associated with difference in outcomes between the groups. Identification of such characteristics could potentially enhance clinical reasoning when selecting whether or not to include manipulative therapy in the treatment of spinal pain in older children. Because this was a small cohort, these analyses were explorative and could at best be hypothesis-generating for finding potential characteristics to be incorporated in future bigger trials.

The aim of this study was therefore to explore whether potential treatment effect modifiers influenced outcomes in groups with those characteristics. Potential effect modifiers being explored were:

- Number of weeks with spinal pain 6 months prior to inclusion,
- Number of weeks with co-occurring musculoskeletal pain 6 months prior to inclusion,
- Expectations of the clinical course,
- Pain intensity, and
- Quality of life.

**Method**

**Setting and participants**
We used data from a randomised controlled trial nested in a longitudinal school-based open cohort study (CHAMPS Study-DK)^50,92^. The trial was a pragmatic parallel observer-blinded RCT including 238 children aged 9 to 15 years from 13 Danish public schools reporting spinal pain, and randomised individually from February 2012 to April 2014. The
children were followed weekly with text messages (SMS) to one of their parents inquiring about any musculoskeletal pain the child might have had during the previous week. The response options were ‘1’ for spinal pain, ‘2’ for upper extremity pain, ‘3’ for lower extremity pain, ‘4’ for no pain, or a response containing any combination of the three first options. If a parent answered positively for spinal pain, they received a standardised telephone interview regarding the complaint. This interview formed the basis for eligibility for the RCT and within the subsequent 2 weeks, the child was evaluated for inclusion into the trial (Table 1). Thus, there was continuous inclusion and, to include as many participants as possible, we continued to recruit participants until 3 months prior to the end of data collection in summer 2014, resulting in 3 to 27 months of follow up.

### Table 1

<table>
<thead>
<tr>
<th>Eligibility criteria</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain was spinal and still present at the time of the interview</td>
<td>Spinal pain equal to or greater than 3 on an 11-box Numerical Rating Scale for more than 3 days</td>
<td>Serious pathology (cancer, inflammatory diseases, vertebral fractures, cauda equina syndrome)</td>
</tr>
<tr>
<td>Parent had agreed, on behalf of the child, to inclusion in the RCT</td>
<td></td>
<td>Fever and/or weight loss, Nightly pain, Unexplainable bruises</td>
</tr>
<tr>
<td>No manual treatment of the spine during the previous 2 months</td>
<td></td>
<td>Handicaps preventing normal physical activity</td>
</tr>
</tbody>
</table>

The primary aim of the RCT was to determine the effectiveness of adding manipulative therapy to other conservative care of spinal pain, i.e. back and/or neck pain, on both primary and secondary outcomes. Interventions included either 1) advice, exercises, and soft tissue treatment, or 2) advice, exercises, and soft tissue treatment plus manipulative therapy, and both groups were treated by licensed chiropractors. Details of the protocol have been described elsewhere and results of the primary analysis are in the publication process.
Outcomes

Weekly positive answers to questions about spinal pain constituted the basis for the following outcomes:

1. Number of recurrences. A recurrence was defined as a positive answer of spinal pain following an answer of no spinal pain.
2. Total number of pain weeks. This was measured by the total number of weeks with positive answers of spinal pain in the follow-up period. Because of the continuous inclusion, children could have different follow-up times.
3. Length of episodes. This was measured by the number of consecutive weeks with positive answers of spinal pain.

Potential treatment effect modifiers

The choice of a few potential effect modifiers was based on their relationship with spinal pain as indicated by the existing literature, as recommended by Hancock et al.\textsuperscript{99}. In addition to variables measured at inclusion, we included the number of weeks of spinal pain and co-occurring musculoskeletal pain during the 6 months prior to inclusion. In general, we hypothesised that the most affected children would improve more with manipulative treatment when compared to the least affected. To make this comparison, we chose to dichotomise the variables by using the upper 10% as the cut point, thereby assessing the most affected children. All potential effect modifiers were dichotomised to make this comparison.

1. Spinal pain. Previous studies have shown that the duration of symptoms and the number of previous episodes are predictive of recovery and how beneficial the treatment will be\textsuperscript{79, 100, 101}. We therefore hypothesised, that the most affected children with a high number of spinal pain reports prior to inclusion would gain the most benefit from being in the manipulative therapy group. This was defined by the number of weeks with spinal pain during the 6 months prior to inclusion. Six months was chosen because we considered this to be an adequate time span for experiencing persistent or recurring pain. Spinal pain for more than 20% of the time was considered a considerable amount of pain, and the variable was dichotomised into ‘less than 20%’ and ‘20% or more’. 
2. **Co-occurring musculoskeletal pain.** Co-occurrence of musculoskeletal symptoms seems to be predictive of more persistent pain\(^{102, 103}\), and therefore we considered this as a potential effect modifier. We hypothesised that children with a high number of co-occurring musculoskeletal pain episodes prior to inclusion would gain the most benefit from being in the manipulative therapy group. As for spinal pain, considerable co-occurring musculoskeletal pain was defined as having pain in more than one region (spine, upper and/or lower extremity) more than 20% of the time during the 6 months prior to inclusion and dichotomised accordingly.

3. **Expectations of the clinical course.** Expectations of the clinical course has been identified as a potential effect modifier for response to treatment for low back pain in adults\(^{79}\), and an association has been suggested between expectations and outcome for musculoskeletal pain conditions\(^{81, 104}\). Furthermore, these associations seem to be independent of type of treatment\(^{82}\). We hypothesised that children with low expectations would have a better outcome in the manipulative therapy group. The child was asked prior to treatment: “What do you expect the outcome of your low back pain will be compared with how it is now?” This was rated on a 5-point scale with ‘1’ being ‘much worse’ and ‘5’ being ‘much better’. This was dichotomised into two groups: ‘Much better’ (value=5) and ‘The same or worse’ (value<5). This was chosen due to a very small number of children in the most extreme category and because we were more certain that the children stating ‘Much better’ were most likely to be certain about their prognosis, whereas the middle categories could be more imprecise.

4. **Pain intensity.** Pain intensity is known to be predictive of future pain and has been shown to have moderate effect on recovery and treatment effect in adults\(^{79, 80, 101}\). We hypothesised that children with a high level of baseline pain would have a better outcome in the manipulative therapy group. This was rated on an 11-point Numerical Rating Scale with ‘0’ being ‘no pain’ and ‘10’ being ‘worst pain’. To assess the most affected children, we chose the upper 10% of children as the cut point - children who had a score >7. Therefore, we dichotomised them into the following two groups (≤7 vs. >7), indicating low or high level of pain.
5. **Quality of life.** A low level of quality of life is predictive of a higher level of spinal pain\(^{25,105}\), and it has been shown to be a potential effect modifier in adults\(^{79}\). We hypothesised, that children with a low level of quality of life would have a better outcome in the manipulative therapy group, as presumably they are the most affected. Quality of life was measured using a KIDScreen 27-item questionnaire covering five domains: Physical wellbeing, Psychological wellbeing, Autonomy and relation, Social support and peers, and School. Raw scores were transformed into T-values based on Rasch person parameter estimates with a higher score indicating higher quality of life\(^{106}\). Each domain was dichotomised into high versus low quality of life, using the 10% threshold from our own population as cut points, thereby assessing the most affected children.

**Ethics**
All parents gave written informed consent to participation on behalf of their child and the children gave oral consent. A child could be withdrawn from the study at any time during the study period and the study was conducted according to the Declaration of Helsinki. The project was approved by the Regional Committee on Health Research Ethics (#S-20110042) and data were handled according to the regulations set by the Danish Data Protection Agency (#2013-41-1738).

**Analysis**
The analysis included the entire cohort and followed intention-to-treat principles. The size of a potential effect modification was explored by comparing the outcome between the two intervention groups in each of the two strata, e.g. high versus low level of pain at baseline. Interaction tests were conducted for each of the potential modifiers using the same type of regression models as in the primary analysis (Table 2) including intervention group, the potential modifier and the interaction between intervention group and modifier.
Table 2 Outcomes and statistical methods

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Definition</th>
<th>Statistical method</th>
</tr>
</thead>
</table>
| Number of recurrences of spinal pain (3-27 months follow up) in relation to individual follow-up time | i) A positive answer on the weekly SMS for spinal pain  
ii) Minimum of 1 week without report of spinal pain prior to the recurrence | To estimate level of statistical significance, a hierarchical negative binomial regression model with follow-up time included as exposure time was used. Intervention effects were expressed as incidence rate ratio |
| Duration of spinal pain episodes                                         | The number of consecutive weeks the child was affected by spinal pain (response option ‘1’)                                          | To estimate level of statistical significance, a mixed effects linear regression model with subject as random effect, outcome log transformed was used. Intervention effects were expressed as β-coefficient |
| Total duration of complaint time in relation to individual follow-up time | Total number of weeks a child was affected by spinal pain (response option ‘1’) in the entire follow-up period | To estimate level of statistical significance, a hierarchical negative binomial regression model with follow-up time included as exposure time was used. Intervention effects were expressed as incidence rate ratio |

An incidence rate ratio of less than 1 or a β-coefficient of less than 0 indicated a better outcome in the manipulative therapy group compared with the non-manipulative therapy group (low number of recurrences, short episodes and low number of total pain weeks). The interaction term isolates the impact of the modifier on the effect of the intervention treatment (manipulative therapy) versus the control treatment (non-manipulative therapy). Forest plots were made for graphical interpretation and confidence intervals and p-values were inspected for significance. STATA 14.2 (StataCorp, College Station, Texas, USA) was used for data analyses. Significance level was set to 5%.
Results

Data from 238 children were available from the original RCT and used in the analysis of the number of recurrences. For the variables spinal pain and co-occurring musculoskeletal pain prior to inclusion, 211 children fulfilled the criterion of half a year of text message answers before inclusion. There were more girls (63%) than boys, mean age at inclusion was 12.6 years, and the distribution between the intervention groups was 116 in the non-manipulative therapy group (49%) and 122 in the manipulative therapy group (51%). Distribution of the potential effect modifiers in the two intervention groups can be seen in Table 3. Figures 1-3 display the distribution of potential effect modifiers in the manipulative therapy group versus the non-manipulative therapy group for the three outcomes, including results for interaction.
Table 3 Baseline variables between intervention groups

<table>
<thead>
<tr>
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<th>MT (N=122)</th>
<th></th>
<th>Non-MT (N=116)</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td><strong>SP six months before inclusion</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤20% of time</td>
<td>103</td>
<td>95%</td>
<td>86</td>
<td>84%</td>
</tr>
<tr>
<td>&gt;20% of time</td>
<td>6</td>
<td>5%</td>
<td>16</td>
<td>16%</td>
</tr>
<tr>
<td><strong>CMP six months before inclusion</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤20% of time</td>
<td>98</td>
<td>90%</td>
<td>88</td>
<td>86%</td>
</tr>
<tr>
<td>&gt;20% of time</td>
<td>11</td>
<td>10%</td>
<td>14</td>
<td>14%</td>
</tr>
<tr>
<td><strong>EoCC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Better</td>
<td>24</td>
<td>20%</td>
<td>22</td>
<td>19%</td>
</tr>
<tr>
<td>Worse/same</td>
<td>55</td>
<td>45%</td>
<td>57</td>
<td>49%</td>
</tr>
<tr>
<td>Missing</td>
<td>43</td>
<td>35%</td>
<td>37</td>
<td>32%</td>
</tr>
<tr>
<td><strong>NRS baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤7</td>
<td>111</td>
<td>97%</td>
<td>108</td>
<td>93%</td>
</tr>
<tr>
<td>&gt;7</td>
<td>11</td>
<td>9%</td>
<td>8</td>
<td>7%</td>
</tr>
<tr>
<td><strong>KID Physical</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High QoL</td>
<td>108</td>
<td>88%</td>
<td>104</td>
<td>90%</td>
</tr>
<tr>
<td>Low QoL</td>
<td>13</td>
<td>11%</td>
<td>7</td>
<td>6%</td>
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<td>1</td>
<td>1%</td>
<td>5</td>
<td>4%</td>
</tr>
<tr>
<td><strong>KID Psychological</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High QoL</td>
<td>112</td>
<td>92%</td>
<td>95</td>
<td>82%</td>
</tr>
<tr>
<td>Low QoL</td>
<td>7</td>
<td>6%</td>
<td>15</td>
<td>12%</td>
</tr>
<tr>
<td>Missing</td>
<td>3</td>
<td>2%</td>
<td>6</td>
<td>6%</td>
</tr>
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<td><strong>KID Autonomy</strong></td>
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<td></td>
</tr>
<tr>
<td>High QoL</td>
<td>105</td>
<td>86%</td>
<td>95</td>
<td>82%</td>
</tr>
<tr>
<td>Low QoL</td>
<td>14</td>
<td>12%</td>
<td>16</td>
<td>14%</td>
</tr>
<tr>
<td>Missing</td>
<td>3</td>
<td>2%</td>
<td>5</td>
<td>4%</td>
</tr>
<tr>
<td><strong>KID Social</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High QoL</td>
<td>109</td>
<td>89%</td>
<td>91</td>
<td>79%</td>
</tr>
<tr>
<td>Low QoL</td>
<td>12</td>
<td>10%</td>
<td>20</td>
<td>17%</td>
</tr>
<tr>
<td>Missing</td>
<td>1</td>
<td>1%</td>
<td>5</td>
<td>4%</td>
</tr>
<tr>
<td><strong>KID School</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High QoL</td>
<td>98</td>
<td>80%</td>
<td>91</td>
<td>78%</td>
</tr>
<tr>
<td>Low QoL</td>
<td>23</td>
<td>19%</td>
<td>20</td>
<td>18%</td>
</tr>
<tr>
<td>Missing</td>
<td>1</td>
<td>1%</td>
<td>5</td>
<td>4%</td>
</tr>
</tbody>
</table>


**Number of recurrences (Figure 1)**

For spinal pain, co-occurring musculoskeletal pain and quality of life, there was a tendency for the most affected children, i.e. high spinal pain, high co-occurring musculoskeletal pain.
and low quality of life, to have a better outcome in the manipulative therapy group, except for the school domain, where no trend was seen. Similarly, although the non-manipulative therapy group as a whole had better outcomes than the manipulative therapy group, there was a tendency for the most affected children in the non-manipulative therapy group to not do as well as the rest of that group on the outcomes of expectations of the clinical course and pain intensity. The regression analyses showed a statistically significant result for the psychological domain, but not for the remaining variables.

Figure 1

<table>
<thead>
<tr>
<th>Predictor</th>
<th>IRR (95% CI)</th>
<th>n</th>
<th>Interaction</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>SP before inclusion (≤20%)</td>
<td>1.32 (0.99, 1.75)</td>
<td>189</td>
<td>0.57 (0.24, 1.34)</td>
<td>0.20</td>
</tr>
<tr>
<td>SP before inclusion (&gt;20%)</td>
<td>0.75 (0.34, 1.68)</td>
<td>22</td>
<td>0.72 (0.34, 1.50)</td>
<td>0.38</td>
</tr>
<tr>
<td>CMP before inclusion (≤20%)</td>
<td>1.24 (0.93, 1.65)</td>
<td>186</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMP before inclusion (&gt;20%)</td>
<td>0.89 (0.45, 1.76)</td>
<td>25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EoCC (Better)</td>
<td>1.48 (0.73, 2.99)</td>
<td>46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EoCC (Worse or same)</td>
<td>1.04 (0.70, 1.53)</td>
<td>112</td>
<td>0.70 (0.31, 1.57)</td>
<td>0.39</td>
</tr>
<tr>
<td>NRS (≤7%)</td>
<td>1.27 (0.98, 1.65)</td>
<td>219</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NRS (&gt;7%)</td>
<td>1.09 (0.45, 2.63)</td>
<td>19</td>
<td>0.85 (0.34, 2.15)</td>
<td>0.74</td>
</tr>
<tr>
<td>KID physical (High)</td>
<td>1.25 (0.97, 1.62)</td>
<td>212</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KID physical (Low)</td>
<td>0.96 (0.36, 2.57)</td>
<td>20</td>
<td>0.77 (0.28, 2.12)</td>
<td>0.61</td>
</tr>
<tr>
<td>KID psychological (High)</td>
<td>1.34 (1.03, 1.73)</td>
<td>207</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KID psychological (Low)</td>
<td>0.46 (0.19, 1.12)</td>
<td>22</td>
<td>0.34 (0.14, 0.87)</td>
<td>0.02</td>
</tr>
<tr>
<td>KID autonomy (High)</td>
<td>1.29 (0.99, 1.68)</td>
<td>200</td>
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</tr>
<tr>
<td>KID autonomy (Low)</td>
<td>0.89 (0.44, 1.79)</td>
<td>30</td>
<td>0.69 (0.32, 1.45)</td>
<td>0.32</td>
</tr>
<tr>
<td>KID social (High)</td>
<td>1.31 (1.00, 1.72)</td>
<td>200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KID social (Low)</td>
<td>0.87 (0.45, 1.69)</td>
<td>32</td>
<td>0.66 (0.33, 1.36)</td>
<td>0.26</td>
</tr>
<tr>
<td>KID school (High)</td>
<td>1.22 (0.93, 1.61)</td>
<td>189</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KID school (Low)</td>
<td>1.15 (0.64, 2.07)</td>
<td>43</td>
<td>0.94 (0.49, 1.79)</td>
<td>0.86</td>
</tr>
</tbody>
</table>


Length of spinal pain episode (Figure 2)

For expectations of the clinical course and the physical domain, there was a tendency for the most affected children to have a better outcome in the manipulative therapy group.
Similarly, although the non-manipulative therapy group as a whole had better outcomes than the manipulative therapy group, there was a tendency for the most affected children in the non-manipulative therapy group to not do as well as the rest of that group on the outcomes of spinal pain and co-occurring musculoskeletal pain. For the remaining quality of life domain, the directions varied, but primarily favouring the non-manipulative therapy group. Regarding pain intensity, the most affected children had a better outcome in the non-manipulative therapy group. The regression analyses showed statistical significance for experience of the clinical course and pain intensity.

**Figure 2**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>ES (95% CI)</th>
<th>n</th>
<th>Interaction</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>SP before inclusion (≤20%)</td>
<td>1.20 (0.99, 1.46)</td>
<td>570</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SP before inclusion (&gt;20%)</td>
<td>1.06 (0.59, 1.89)</td>
<td>116</td>
<td>0.88 (0.48, 1.62)</td>
<td>0.68</td>
</tr>
<tr>
<td>CMP before inclusion (≤20%)</td>
<td>1.17 (0.96, 1.42)</td>
<td>568</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMP before inclusion (&gt;20%)</td>
<td>1.10 (0.68, 1.79)</td>
<td>120</td>
<td>0.94 (0.56, 1.59)</td>
<td>0.83</td>
</tr>
<tr>
<td>EoCC (Better)</td>
<td>1.48 (0.99, 2.22)</td>
<td>105</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EoCC (Worse or same)</td>
<td>0.94 (0.74, 1.19)</td>
<td>338</td>
<td>0.63 (0.40, 1.00)</td>
<td>0.05</td>
</tr>
<tr>
<td>NRS (≤7%)</td>
<td>1.06 (0.88, 1.27)</td>
<td>764</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NRS (&gt;7%)</td>
<td>2.27 (1.21, 4.24)</td>
<td>66</td>
<td>2.15 (1.12, 4.13)</td>
<td>0.02</td>
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<tr>
<td>KID physical (High)</td>
<td>1.11 (0.92, 1.34)</td>
<td>762</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KID physical (Low)</td>
<td>0.94 (0.48, 1.84)</td>
<td>54</td>
<td>0.85 (0.42, 1.70)</td>
<td>0.64</td>
</tr>
<tr>
<td>KID psychological (High)</td>
<td>1.16 (0.96, 1.41)</td>
<td>723</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KID psychological (Low)</td>
<td>1.08 (0.56, 2.06)</td>
<td>77</td>
<td>0.92 (0.47, 1.61)</td>
<td>0.82</td>
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<tr>
<td>KID autonomy (High)</td>
<td>1.10 (0.90, 1.33)</td>
<td>713</td>
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<td></td>
</tr>
<tr>
<td>KID autonomy (Low)</td>
<td>1.24 (0.75, 2.05)</td>
<td>99</td>
<td>1.14 (0.66, 1.95)</td>
<td>0.64</td>
</tr>
<tr>
<td>KID social (High)</td>
<td>1.08 (0.89, 1.31)</td>
<td>695</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KID social (Low)</td>
<td>1.61 (1.00, 2.58)</td>
<td>121</td>
<td>1.48 (0.89, 2.48)</td>
<td>0.13</td>
</tr>
<tr>
<td>KID school (High)</td>
<td>1.06 (0.87, 1.30)</td>
<td>658</td>
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<td></td>
</tr>
<tr>
<td>KID school (Low)</td>
<td>1.27 (0.84, 1.92)</td>
<td>158</td>
<td>1.19 (0.75, 1.89)</td>
<td>0.46</td>
</tr>
</tbody>
</table>

**Total number of pain weeks (Figure 3)**

For the variables spinal pain, expectations of the clinical course and quality of life, there was a tendency for the most affected children to have a better outcome in the manipulative therapy group. For co-occurring musculoskeletal pain and the school domain, there was no trend found. Regarding pain intensity, the most affected children had a better outcome in the non-manipulative therapy group. The regression analyses showed statistical significance for experience of the clinical course, pain intensity and the psychological domain.

**Figure 3**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>IRR (95% CI)</th>
<th>n</th>
<th>Interaction</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>SP before inclusion (≤20%)</td>
<td>1.31 (1.01, 1.70)</td>
<td>189</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SP before inclusion (&gt;20%)</td>
<td>0.78 (0.54, 1.76)</td>
<td>22</td>
<td>0.59 (0.25, 1.40)</td>
<td>0.23</td>
</tr>
<tr>
<td>CMP before inclusion (≤20%)</td>
<td>1.18 (0.91, 1.54)</td>
<td>186</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMP before inclusion (&gt;20%)</td>
<td>1.16 (0.57, 2.37)</td>
<td>25</td>
<td>0.98 (0.46, 2.10)</td>
<td>0.97</td>
</tr>
<tr>
<td>EoCC (Better)</td>
<td>1.67 (0.97, 2.87)</td>
<td>46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EoCC (Worse or same)</td>
<td>0.86 (0.61, 1.21)</td>
<td>112</td>
<td>0.52 (0.27, 0.98)</td>
<td>0.04</td>
</tr>
<tr>
<td>NRS (≤7%)</td>
<td>1.06 (0.83, 1.36)</td>
<td>219</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NRS (&gt;7%)</td>
<td>3.38 (1.41, 8.10)</td>
<td>19</td>
<td>3.18 (1.28, 7.88)</td>
<td>0.01</td>
</tr>
<tr>
<td>KID physical (High)</td>
<td>1.16 (0.90, 1.49)</td>
<td>212</td>
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<tr>
<td>KID physical (Low)</td>
<td>0.80 (0.34, 1.88)</td>
<td>20</td>
<td>0.69 (0.29, 1.69)</td>
<td>0.42</td>
</tr>
<tr>
<td>KID psychological (High)</td>
<td>1.36 (1.06, 1.75)</td>
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<td>0.32 (0.14, 0.75)</td>
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<td>1.22 (0.94, 1.59)</td>
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</tr>
<tr>
<td>KID autonomy (Low)</td>
<td>0.80 (0.41, 1.56)</td>
<td>30</td>
<td>0.66 (0.32, 1.34)</td>
<td>0.25</td>
</tr>
<tr>
<td>KID social (High)</td>
<td>1.23 (0.95, 1.59)</td>
<td>200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KID social (Low)</td>
<td>0.96 (0.50, 1.83)</td>
<td>32</td>
<td>0.78 (0.39, 1.57)</td>
<td>0.49</td>
</tr>
<tr>
<td>KID school (High)</td>
<td>1.13 (0.87, 1.48)</td>
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<td></td>
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</tr>
<tr>
<td>KID school (Low)</td>
<td>1.08 (0.83, 1.37)</td>
<td>43</td>
<td>0.96 (0.52, 1.75)</td>
<td>0.89</td>
</tr>
</tbody>
</table>


**Discussion**

To our knowledge, this is the first study that has tried to identify treatment effect modifiers when comparing two different conservative interventions for spinal pain in school.
children. Overall, we found weak tendencies supporting our hypotheses about improvement in response to manipulative therapy in the most affected children, whereas the least affected children showed no, or even negative, response if they were randomised to the manipulative therapy group. We originally intended to include more children in the RCT, but because the CHAMPS Study data collection period ended, we were unable to extend the inclusion.

The CHAMPS cohort is different from a normal clinical population and therefore results of this trial cannot be extrapolated to a normal care-seeking population. For example the proportion of children being examined and diagnosed with ‘any musculoskeletal complaint’, i.e. spinal and/or extremity complaints, following an SMS report of pain, were 65% of the total cohort (1465 children) between 2011 and 2014. In contrast, only 5.4% of Danish children in the same age group consulted a chiropractor or a physiotherapist during the same time period61. This huge difference reflects a lower threshold in the screening team for examining a child in this project because of the overall research setting in which the RCT was nested. Furthermore, 3 or more on an 11-point Numerical Rating Scale rated by the child for inclusion into the trial might also be low compared with when a parent would normally have sought care on behalf of their child. Therefore we cannot rule out that complaints in some of the included children would have resolved without treatment or that maybe some complaints worsened after treatment. But it is also true that looking at the children with pain higher than 7 on the Numerical Rating Scale, the results were better when looking at duration of back pain for the non-manipulative therapy group.

*Directions of effect modification*

Our overall hypothesis was that children being worse off at baseline (high level of spinal pain and co-occurring musculoskeletal pain prior to inclusion, high pain intensity and low expectations of the clinical course and quality of life) would have a better outcome if randomised to the manipulative therapy group. This tendency was confirmed and seen primarily for spinal pain prior to inclusion, expectations of the clinical course and quality of life, and to a lesser extent for co-occurring musculoskeletal pain prior to inclusion.
Gurung et al.\textsuperscript{79} reviewed four studies including 5514 participants and found that previous back pain in adults was likewise identified as a potential modifier with strong evidence that those who had longer duration of pain prior to inclusion in clinical trials gained greater benefit from therapist-delivered interventions. Similarly, Sherman et al.\textsuperscript{80} found that people with more severe pre-treatment back dysfunction demonstrated greater benefits from acupuncture measured by the Roland Morris Disability Questionnaire.

The fact that both a high level of spinal pain and co-occurring musculoskeletal pain seemed to have a modifying effect in favour of a better outcome in the manipulative therapy group could indicate that some children were more prone to pain and that pain problems may cluster. This is in line with previous studies, showing clustering of pain syndromes in adults\textsuperscript{107} and also in adolescents\textsuperscript{27}. Thus, these children might benefit more from treatment and should be paid more attention than those with single episodes or single site pain.

Other studies have demonstrated the importance of taking expectations into account when looking at treatment effect, and higher expectations usually predict a better outcome\textsuperscript{81-83}. Myers et al. found an association between higher general expectations for improvement in back pain and worse pain or function at baseline\textsuperscript{82}. However, a fundamental difference from our study, apart from their patients being adults, was that they were not randomly assigned to an intervention, but could choose between three CAM therapies. We hypothesised that the most affected children would have low expectations of outcome, whereas the least affected children would probably be more positive. Other questions that could be relevant to include in future trials are expectations of the specific treatment and the clinicians’ expectations of the treatment for a particular child. It could be of great benefit if a clinician, through a few questions, could predict the potential treatment effect, and thereby have a better foundation for deciding when and on whom to intervene.

Thus, we believe that all three variables (spinal pain, co-occurring musculoskeletal pain and expectations of the clinical course) may be considered candidates for effect modification and, therefore, deserve exploration.
A low level of spinal pain has been regarded as predictive of a better outcome\textsuperscript{101}, whereas high levels of pain provide greater potential for improvement. Therefore, we would have expected to find a modifying effect in the same direction as the other variables, but the tendency was in the opposite direction with statistical significance for length of episodes and total number of pain weeks. This is, of course, most likely to reflect that the level of pain is unrelated to treatment response or that children with a high level of pain simply do not benefit from manipulative treatment, but it could also relate to the psychometric properties of the Numerical Rating Scale instrument. In the main study, there was no significant difference in change in pain intensity between the two intervention groups, even though children in the manipulative therapy group indicated statistically significant better Global Perceived Effect; some children would say they felt better, although reporting a higher score on the Numerical Rating Scale at follow up than at baseline. Hence one could question the validity of the Numerical Rating Scale or Global Perceived Effect in this age group, despite studies having validated the Numerical Rating Scale in paediatric samples\textsuperscript{53, 69}.

We found some confirmation of interactions between quality of life (KID questionnaire) and type of treatment, favouring manipulative treatment. This was primarily seen for the psychological domain, being statistically significant for the number of recurrences and total number of pain weeks. We would have expected especially the physical domain to have a modifying effect, as all the children in our study were somehow physically affected, and this was also the case for all three outcomes; however, they were not statistically significant. We know from other studies that quality of life is associated with spinal pain in children, and Dolphens et al.\textsuperscript{25} found that the comorbid pain domain followed by the physical domain were particularly important. Balague et al.\textsuperscript{108} reported that low back pain marginally affects quality of life, but a subgroup of children with both low back pain and whole body pain had significantly impaired quality of life. We believe, that quality of life should be considered for further exploration as an effect modifier in future trials, with particular focus on the psychological aspect.

\textit{Strengths and limitations}
The primary strength of this study is that it is based on data from an RCT, which is considered to be the definitive type of data to explore effect modification, and we limited the number of predictors included to minimise the risk of spurious findings. Secondly, we have weekly data, which gives a very complete picture of the outcomes. We did have missing data (Table 1), but they were equally distributed between intervention groups and hence should not pose a problem.

Our trial was clearly underpowered for this type of analysis and therefore our results can at best be regarded as hypothesis-generating. However according to Pincus, most datasets are under-analysed in back pain trials and therefore post-hoc analysis should be cautiously supported. We therefore followed the methodological criteria for exploring modification effect by Pincus: modifiers should be measured prior to randomisation, measurement of baseline factors should be of adequate quality, and the analysis should include an explicit interaction test.

We are aware that multiple testing can lead to spurious findings. Furthermore, we recognise that by dichotomising variables, we also reduce the potential information available from these variables. We have noticed a great variety in how studies on effect modification have been analysed, and we chose this approach so as to be able to compare the most affected with the least affected children and to facilitate interpretation of the results.

**Conclusion**

We investigated potential treatment effect modifiers for manipulative therapy in school children reporting spinal pain and found weak tendencies supporting our hypotheses about a greater chance of improvement in response to manipulative therapy in the most affected children. The least affected children showed no, or even negative, response if they were randomised to the manipulative therapy group. In future clinical trials on effectiveness of spinal manipulation in children, we recommend including only children with longer lasting and more intense spinal pain and not children with mild pain.

**Acknowledgements**
We acknowledge all the members of the CHAMPS Study DK and the clinicians taking part in this study and making it possible. We would like to thank Suzanne Capell for proof-reading the manuscript.

Finally we would like to express our gratitude to the participants and their parents and the participating schools.

References


Appendix 2: Additional files

SMS questions

1. Has <FIRSTNAME> had pain for the last week?

1. Neck, back or lumbar spine
2. Shoulder, arm or hand
3. Hip, leg or foot
4. No, my child has not had any pain

2. How many times has <FIRSTNAME> been to organized sports in his/her leisure time in the past week?

0 = 0 times
1 = 1
2 = 2
3 = 3
4 = 4
5 = 5
6 = 6
7 = 7
8 = more than 7 times

3. <FIRSTNAME> which kinds of sports?
1. Soccer
2. Handball
3. Basketball
4. Volleyball
5. Gymnastics
6. Tumbling
7. Swimming
8. Horse back riding
9. Dancing
10. Other

Numerical Rating Scale
I would like you to rate your pain on a scale from 0 to 10, where 0 is ‘no pain’ and 10 is ‘the worst pain possible’.

Jeg vil bede dig om at fortælle hvor ondt du har på en skala fra 0 til 10, hvor 0 er ’ingen smerte’ og 10 er ’værste smerte du kan forestille dig’.
**Expectations of the Clinical Course**

Spørg barnet INDEN 1. behandling:

Hvordan tror du det kommer til at gå med din ryg/nakke/arm...?

1. meget værre
2. lidt værre
3. det samme
4. lidt bedre
5. meget bedre

Hvis det går væk, tror du så det kommer tilbage?

1. ja
2. nej

Skrives under behandlingsnote som forkortelse ETT og angivet tal for svar, fx ETT 4.1

**Global Perceived Effect**

Hvordan vil du beskrive hvordan du har det nu i læng/nakke/ryg (og evt. ben/arm) nu, hvis du sammenligner med hvordan du havde det for 2 uger siden (inden eventuel behandling)?

(Afkryds kun ét felt)

- Meget bedre
- Bedre
- Lidt bedre
- Næsten det samme
- Lidt værre
- Værre
- Meget værre

Værdisættes med 1-7 i journalen, med 1 som meget bedre og 7 som meget værre
KID Screen questionnaire

KIDSCREEN-27
Health Questionnaire for Children and Young People
Child and Adolescent Version
8 to 18 Years
Danish (DK)
Hej,


Først skal du læse hvert spørgsmål grundigt. Hvad er det første du tænker på? Sæt et kryds i den cirkel, som passer bedst til dit svar.

Husk: Det er ikke en prøve, så der findes ingen forkerte svar. Men det er vigtigt, at du besvarer alle spørgsmål og at vi kan se dit svar tydeligt. Når du skal tænke over dit svar, så prøv at huske sidste uge.

Du behøver ikke at vise dine svar til nogen. Ingen som kender dig, vil få skemaet at se, når du er færdig med det.
1. Fysiske aktiviteter og sundhed

Hvordan er dit helbred generelt?

- Fremragende
- Meget godt
- Godt
- Nogenlunde
- Dårligt

Tænk på sidste uge ...

<table>
<thead>
<tr>
<th></th>
<th>Slit ikke</th>
<th>Lidt</th>
<th>Moderat</th>
<th>Meget</th>
<th>Rigtig meget</th>
</tr>
</thead>
<tbody>
<tr>
<td>Har du følt dig rask og godt tilpas?</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Har du været fysisk aktiv (f.eks. kunne løbe, klare og cykle)?</td>
<td>○</td>
<td>○</td>
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<tr>
<td>Har du kunne løbe derud af?</td>
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</tr>
</tbody>
</table>

Tænk på sidste uge...

5. Har du følt dig fuld af energi?

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<thead>
<tr>
<th></th>
<th>Aldrig</th>
<th>Sædvanligt</th>
<th>Ret til</th>
<th>Meget til</th>
<th>Aldtid</th>
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</table>

2. Generelt humør og dine følelser

Tænk på sidste uge...

1. Har dit liv været sjovt?

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<thead>
<tr>
<th></th>
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<th>Rigtig meget</th>
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</table>

Tænk på sidste uge...

2. Har du været i godt humør?

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3. Har du haft det sjovt?

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<th>Meget til</th>
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<tbody>
<tr>
<td>Tænk på sidste uge...</td>
<td>Aldrig</td>
<td>Sjældent</td>
<td>Ret tilt</td>
<td>Meget tilt</td>
<td>Alltid</td>
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<tr>
<td>5. Har du haft det så dårligt, at du ikke havde lyst til at lave noget som helst?</td>
<td>Aldrig</td>
<td>Sjældent</td>
<td>Ret tilt</td>
<td>Meget tilt</td>
<td>Alltid</td>
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</tbody>
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</table>

### 3. Familie og Fritid

<table>
<thead>
<tr>
<th>Tænk på sidste uge...</th>
<th>Aldrig</th>
<th>Sjældent</th>
<th>Ret tilt</th>
<th>Meget tilt</th>
<th>Alltid</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Har du haft tid nok til dig selv?</td>
<td>Aldrig</td>
<td>Sjældent</td>
<td>Ret tilt</td>
<td>Meget tilt</td>
<td>Alltid</td>
</tr>
<tr>
<td>2. Har du kunnet gøre de ting, som du gerne ville i din fritid?</td>
<td>Aldrig</td>
<td>Sjældent</td>
<td>Ret tilt</td>
<td>Meget tilt</td>
<td>Alltid</td>
</tr>
<tr>
<td>3. Har dine forældre haft tid nok til dig?</td>
<td>Aldrig</td>
<td>Sjældent</td>
<td>Ret tilt</td>
<td>Meget tilt</td>
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<tbody>
<tr>
<td>6. Har du haft penge nok til at gøre de samme ting som dine venner?</td>
<td>Aldrig</td>
<td>Sjældent</td>
<td>Ret tilt</td>
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<td>Alltid</td>
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</table>
4. Dine venner

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<thead>
<tr>
<th>Tænk på sidste uge...</th>
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</thead>
<tbody>
<tr>
<td>1. Har du været sammen med dine venner?</td>
<td>○</td>
<td>○</td>
<td>○</td>
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<tr>
<td>2. Har du haft det sjovt med dine venner?</td>
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</thead>
<tbody>
<tr>
<td>3. Har du og dine venner hjulpet hinanden?</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
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<tr>
<td>4. Har du kunnet regne med dine venner?</td>
<td>○</td>
<td>○</td>
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</table>

5. Skole og læring

<table>
<thead>
<tr>
<th>Tænk på sidste uge...</th>
<th>Slekt ikke</th>
<th>Lidt</th>
<th>Moderat</th>
<th>Meget</th>
<th>Rigtig meget</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Har du været glad i skolen?</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>2. Har du klaret dig godt i skolen?</td>
<td>○</td>
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<tbody>
<tr>
<td>3. Har du været i stand til at være opmærksom?</td>
<td>○</td>
<td>○</td>
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<td>○</td>
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<tr>
<td>4. Har du været på god fod med dine lærere?</td>
<td>○</td>
<td>○</td>
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<td>○</td>
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