Eveline Bunge

Idiopathic scoliosis

Evaluation of screening and treatment

Eveline Bunge

Idiopathic scoliosis

Evaluation of screening and treatment

ISBN 978-90-8559-486-4

Cover illustration © iStockphoto.com / BlaneyPhoto
Layout and cover design: Anna Bosselaar (anna@zoiets.com)
Printed by Optima Grafische Communicatie BV (www.ogc.nl)

This thesis was printed with financial support of the J.E. Jurriaanse Stichting, the GGD Netherlands, Het Anna Fonds, the Department of Public Health, Erasmus MC Rotterdam and Pallas, health research and consultancy.

Idiopathic Scoliosis: Evaluation of Screening and Treatment

Idiopatische scoliose: evaluatie van screening en behandeling

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus
Prof.dr. S.W.J. Lamberts
en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
vrijdag 6 maart 2009 om 13:30 uur

door

Eveline Margaretha Bunge

geboren te Rotterdam

Promotiecommissie

Promotoren:	Prof.dr. H.J. de Koning
	Prof.dr. J.D.F. Habbema
Overige leden:	Prof.dr. J.A.N. Verhaar
	Prof.dr. R.A. Hira Sing
	Prof.dr. B.W. Koes

Contents

Publications

The chapters in this thesis are based on the following publications:

Chapter 2: Bunge EM, Juttmann RE, de Koning HJ, and the steering committee of the NESCIO group. Screening for scoliosis: do we have indications for effectiveness? *J Med Screen* 2006;13:29-33*

Chapter 3: Bunge EM, Juttmann RE, van Biezen FC, Creemers H, Hazebroek-Kampschreur AAJM, Luttmer LCF, et al. Estimating the effectiveness of screening for scoliosis; a case control study. *Pediatrics* 2008;121:9-14**

Chapter 4: Bunge EM, de Koning HJ, and the brace trial group. Bracing patients with idiopathic scoliosis: design of the Dutch randomized controlled treatment trial. *BMC Musculoskelet Disord* 2008;9:57*

Chapter 5: Bunge EM, Habbema JDF, de Koning HJ. A randomised controlled trial on the effectiveness of bracing patients with idiopathic scoliosis; failure to include patients and lessons to be learnt. *submitted*

Chapter 6: Bunge EM, Juttmann RE, de Kleuver M, van Biezen FC, de Koning HJ, and the NESCIO group. Health-related quality of life in patients with adolescent idiopathic scoliosis after treatment: short-term effects after brace or surgical treatment. *Eur Spine J.* 2007;16:83-9*

Chapter 7: Bunge EM, de Bekker-Grob EW, van Biezen FC, Essink-Bot ML, de Koning HJ. Patients' preferences for scoliosis brace treatment: a discrete choice experiment. *submitted*

General introduction

1

Background

Scoliosis is a rather common condition of the back. Scoliosis is a deformation of the spine consisting of a lateral curvature combined with a fixed rotation of one or more vertebrae and a rotational deformation of those vertebrae[1] (Figure 1.1). The severity of scoliosis can be assessed by X-ray and is expressed in the size of the Cobb angle, which is the angle between the upper most inclined vertebra and the lower most inclined vertebra. Someone is being diagnosed to have scoliosis when the Cobb angle is larger than 10 degrees[1]. The most common type of scoliosis is idiopathic scoliosis (IS). As the name indicates, the cause of that type is unknown. There is, however, a known relationship with gender, age, maturity and familial predisposition. Progressive scoliosis occurs 5-10 times more often in girls than in boys[2]. Genetic research showed a significantly higher prevalence of scoliosis in first-degree family members[3-5]. Today, it is not fully known which genes are involved, but research on this topic is ongoing. Other types of scoliosis include neuromuscular scoliosis and congenital scoliosis. Neuromuscular scoliosis can occur in patients with neuropathic or myopathic conditions, such as cerebral palsy, poliomyelitis and Duchenne Muscular disease[1]. Congenital scoliosis is caused by the presence of vertebral anomalies, which develop during pregnancy[1]. This thesis will deal with idiopathic scoliosis.

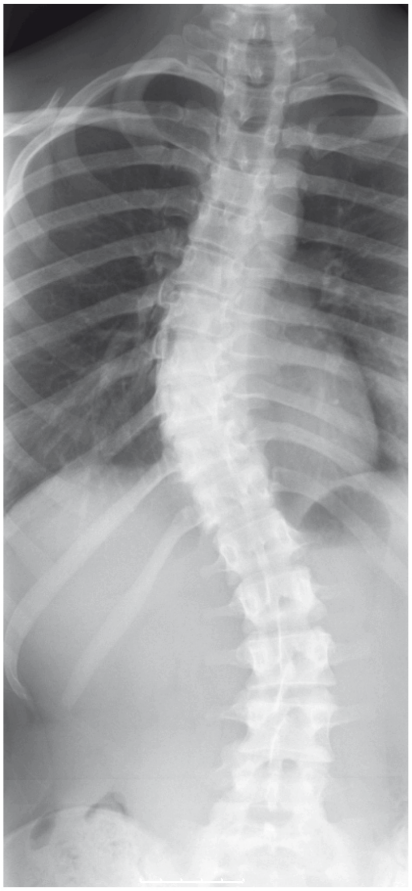


Figure 1.1 X-ray of a female patient with idiopathic scoliosis

Idiopathic scoliosis is usually divided into three types: infantile, juvenile and adolescent idiopathic scoliosis. The difference between these types is largely based on age at presentation. The infantile type presents between birth and 3 years; the juvenile type presents between 4 and 9 years of age, and the adolescent type presents between 10 and 16 years of age[1]. The adolescent type is the most common type and accounts in the US for 85% and in the UK for 55% of all idiopathic scoliosis patients[1]. Besides a difference in age at presentation, some clinical differences exist. In daily practise the distinction is not always as clear as suggested in these age definitions. For instance, in a child who is detected at the age of 10 and who has a curvature of 30º, the diagnosis according to the definition would be adolescent idiopathic scoliosis. However, chances are high that if for some other reason an X-ray had been taken before the age of 10, a curvature of more than 10 degrees would have been discovered. In

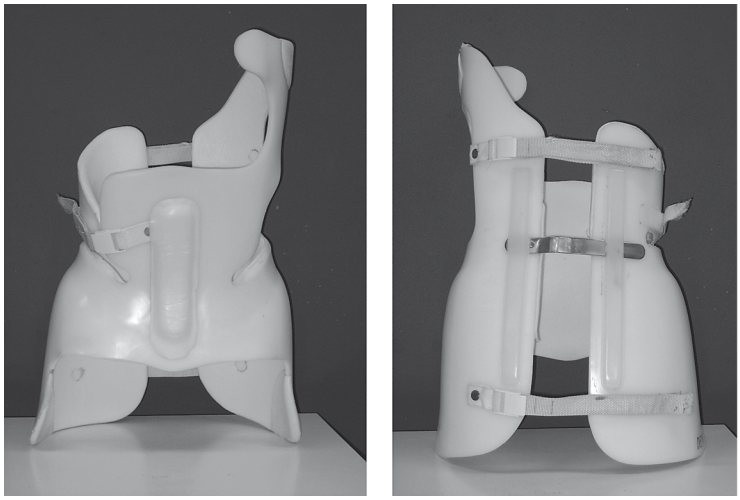
that last scenario the same patient would have been diagnosed with juvenile idiopathic scoliosis. This thesis deals with adolescent idiopathic scoliosis and the upper end of the age spectrum of juvenile idiopathic scoliosis. Since adolescent idiopathic scoliosis is commonly used for the patient group we are referring to in this thesis, we used this term at first. However, acknowledging the above mentioned, after some time we replaced this term for idiopathic scoliosis (IS). In this thesis, both terms refer to patients with adolescent idiopathic scoliosis and the upper end of the age spectrum of juvenile idiopathic scoliosis.

For IS, only prevalence data are described. In 2-3% of children between 10 and 16 years, IS is manifest. In about 85% of these children, the curvature does not progress, whereas in approximately 15% the curvature progresses to over 20 degrees over course of time. About half of the curvatures that progresses to over 20 degrees will further progress to over 30 degrees[1,2,6]. For the Netherlands, exact data on the number of new cases per year are lacking.

Progression and treatment

Progression of the curvature in IS usually occurs just before or during adolescent growth spurt, in girls before the menarche. Patients who are skeletally immature, with Cobb angles over 20-25 degrees which have shown progression of at least 5 degrees are usually treated with a (Boston) brace[1] (Figure 1.2). A brace is a close-fitting device applied to the trunk to correct (in brace), as much as possible, the lateral curvature of the spine. A brace should be worn for 18-23 hours a day and for about three to six years during adolescence. A brace is supposed to prevent further progression and thereby to prevent the need for surgical treatment[7]. Generally, the best result that one may expect from a brace is stabilization of the curvature. Permanent improvement of the curvature by bracing is rarely seen[1].

Figure 1.2
Boston brace



In case a skeletally immature patient has a Cobb angle of more than about 45-50 degrees, surgery can become necessary to correct as much as possible the curvature and to prohibit further progression[1]. With surgery, the spine is perpetually stabilized by rods. The most serious risk of surgery is damage to the spinal cord (about 0.5-1%)[1,8]. Close monitoring of the spine during surgery using evoked potentials is supposed to decrease the risk of damage to the spinal cord as much as possible. Severe cases of scoliosis with Cobb angles of more than 100-120 degrees may, besides cosmetic concerns and pain, lead to intrathoracal problems, which impede the well functioning of the heart and lungs[2].

Besides medical problems, patients with IS could also suffer from psychosocial problems[9,10]. IS can be a stigmatizing disorder, because a prominent rib 'hump' (hunchback), is visible in more severe cases. Being treated with a brace is often visible for family, friends and peers. Furthermore, for the majority of the patients, the brace is uncomfortable to wear. These problems deserve our attention, especially since we are dealing with patients in puberty.

Screening

To prevent patients with scoliosis from needing surgery, screening for scoliosis was introduced in the USA and many other countries in the 1970s[11]. The screening test for scoliosis is the Adam's forward bending test. A school physician examines the child's uncovered back while the child is bending forward; in case of scoliosis, a rib 'hump' is present[12,13]. This rib hump is not always visible in a standing position. The size of the trunk rotation angle can be measured by a scoliometer (i.e., an inclinometer used for measuring trunk rotation, see Figure 1.3)[13]. In the recently developed Dutch protocol on screening for scoliosis it is agreed that, if an immature child has a rib hump of 7 degrees or more, measured with a scoliometer, the child should be referred to his or her general practitioner. The general practitioner has the ability to refer the child to an orthopaedic surgeon for further examinations.

The screening aims at detecting patients in an early stage of the clinical course, in order to apply brace treatment to try and prevent further progression and ultimately the need for surgical treatment[7,14,15]. In 2000, a pilot study was performed to establish what kind of research was necessary in this field of screening and treatment for

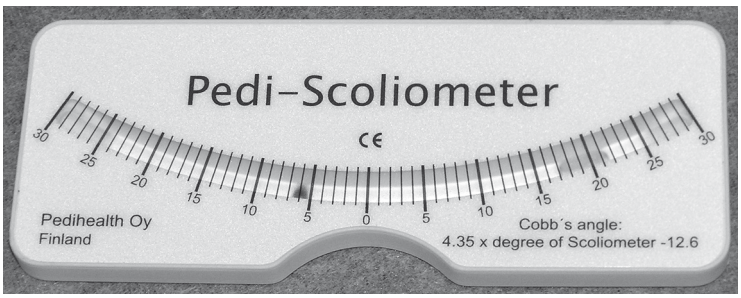


Figure 1.3
Scoliometer

scoliosis. The main conclusion was that the effectiveness of both screening and early treatment with a brace has not been sufficiently established[16]. Some authors conclude that screening is effective[7,11,17-20], while others doubt the effectiveness or even consider such screening as unethical[21-25]. Also, some authors conclude that bracing is effective[26-28], while others conclude that the effectiveness is doubtful or recommend a RCT[16,21,29,30]. The designs of these studies were however not convincing; no randomized controlled trials have been done.

Because of this lack of evidence, and literature is ambiguous, there is at present no nationally covered screening program for scoliosis in the Netherlands[16]. Furthermore, there is debate on bracing patients with IS. The main recommendations of the pilot study of Korfage et al. were (1) to perform a case control study to estimate the effectiveness of screening on reducing the need for surgery, (2) to perform a RCT to establish the effectiveness of early treatment by bracing and (3) to come to consensus for a national protocol on screening for scoliosis[16]. The first issue was also addressed in the "Programmeringsstudie Effectonderzoek Jeugdgezondheidszorg"[31]. This thesis will concern three issues, among which the first two recommendations of that pilot study. The third issue will concern the patients' perception of treatment.

The research questions of this study

1. Does screening for scoliosis lead to earlier detection and to a reduction in the need for surgery? (Chapters 2 and 3)
2. What is the effectiveness of bracing patients with idiopathic scoliosis? (Chapters 4 and 5)
3. Do patients treated with a brace differ in health-related quality of life after treatment in comparison with patients who needed surgery? (Chapter 6)
4. What are patients' preferences on treatment for scoliosis? (Chapter 7)

Outline

Part I deals with the estimation of the effectiveness of screening for scoliosis in reducing the need for surgery. To explore whether screening for scoliosis could be effective, a retrospective follow-up study of patients with IS was performed (chapter 2). This study gives information on whether two essential prerequisites for a screening program for scoliosis to be potentially effective, namely earlier detection and less surgery, were met. Using this design, however, no definitive answer on the effectiveness of screening in reducing the need for surgery could be given, because of biases. Therefore, a case control study was performed to evaluate the effectiveness of screening for scoliosis in reducing the need for surgery (chapter 3).

Part II concerns the treatment of scoliosis. In chapter 4, the protocol for the Dutch randomized controlled treatment trial on bracing patients with IS is described. Despite cooperation of 10 hospitals who agreed with this protocol, the inclusion of patients in this trial did not succeed. In chapter 5 we evaluated how this could have happened.

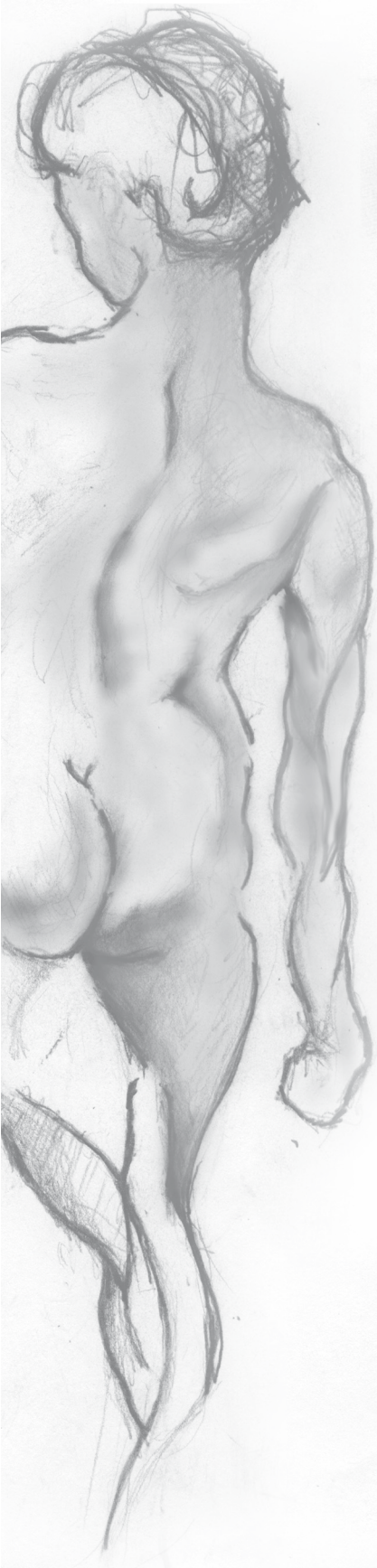
Part III evaluates quality of life and patients' preferences. Chapter 6 describes whether there are short-term differences in quality of life after treatment between patients who were treated with a brace and patients treated surgically. Chapter 7 describes patients' preferences on treatment for scoliosis. We evaluated how effective treatment with a brace in reducing the need for surgery must be, so that patients consider this as an acceptable treatment.

Chapter 8, finally, is a discussion in which the results of these studies are integrated and interpreted. Furthermore, recommendations for further research will be given.

References

1. Campbell W, Canale S, Daugherty K, et al. Scoliosis and Kyphosis. In: Canale ST, editor. Campbell's Operative Orthopaedics. St. Louis, MO: Mosby; 2003. p. 1751-1984.
2. Weinstein SL. Natural history. *Spine* 1999;24(24):2592-600.
3. Miller NH, Justice CM, Marosy B, et al. Identification of candidate regions for familial idiopathic scoliosis. *Spine* 2005;30:1181-7.
4. Aulisa L, Papaleo P, Pola E, et al. Association between IL-6 and MMP-3 gene polymorphisms and adolescent idiopathic scoliosis: a case-control study. *Spine* 2007;32:2700-2.
5. Miller NH. Genetics of familial idiopathic scoliosis. *Clin Orthop Relat Res* 2007;462:6-10.
6. Schaapveld K, Hirasing RA. Preventiegids. Assen: Van Gorcum & Comp. B.V. 1997.
7. Bunnell WP. Selective screening for scoliosis. *Clin Orthop Relat Res* 2005(434):40-5.
8. Scoliosis Research Society. Morbidity and Mortality Committee report. Vancouver: Scoliosis Research Society; 1987.
9. Matsunaga S, Hayashi K, Naruo T, et al. Psychologic management of brace therapy for patients with idiopathic scoliosis. *Spine* 2005;30:547-550.
10. Tones M, Moss N, Polly DW, Jr. A review of quality of life and psychosocial issues in scoliosis. *Spine* 2006;31:3027-38.
11. Lonstein JE, Bjorklund S, Wanninger MH, et al. Voluntary school screening for scoliosis in Minnesota. *J Bone Joint Surg [Am]* 1982;64:481-8.
12. Behrman R, Kliegman R, Arvin A. Nelson's Textbook of Pediatrics. 15th ed. Philadelphia: W.B. Saunders Company; 1996.
13. Bunnell WP. An objective criterion for scoliosis screening. *J Bone Joint Surg Am* 1984;66: 1381-7.
14. Goldbloom RB. Screening for idiopathic adolescent scoliosis. In: Canadian Task Force on the Periodic Health Examination. Ottawa: Health Canada; 1994. p. 346-354.
15. Scoliosis Research Society. Scoliosis and Kyphosis: a Handbook for Patients, Read Brochure Spinal Deformity Technical Paper. Scoliosis Research Society; 1993.
16. Korfage IJ, Juttmann RE, Das BV, et al. [Idiopathic scoliosis in adolescents; an inventory into the possibilities of studying the efficacy of screening and treatment] Idiopathische scoliose bij adolescenten; inventarisatie van mogelijkheden van onderzoek naar de effectiviteit van screening en behandeling. *Ned Tijdschr Geneeskd* 2002;146:1228-33.
17. Montgomery F, Willner S. Screening for idiopathic scoliosis. Comparison of 90 cases shows less surgery by early diagnosis. *Acta Orthop Scand* 1993;64:456-8.
18. Soucacos PN, Soucacos PK, Zacharis KC, et al. School-screening for scoliosis. A prospective epidemiological study in northwestern and central Greece. *J Bone Joint Surg Am* 1997;79: 1498-503.
19. Torell G, Nordwall A, Nachemson A. The changing pattern of scoliosis treatment due to effective screening. *J Bone Joint Surg [Am]* 1981;63:337-41.
20. Winter RB, Lonstein JE. To brace or not to brace: the true value of school screening [editorial]. *Spine* 1997;22:1283-4.

21. Dickson RA, Weinstein SL. Bracing (and screening)--yes or no? *J Bone Joint Surg Br* 1999;81: 193-8.
22. Goldberg CJ, Dowling FE, Fogarty EE, et al. School scoliosis screening and the United States Preventive Services Task Force. An examination of long-term results. *Spine* 1995;20:1368-74.
23. Karachalios T, Sofianos J, Roidis N, et al. Ten-year follow-up evaluation of a school screening program for scoliosis. Is the forward-bending test an accurate diagnostic criterion for the screening of scoliosis? *Spine* 1999;24:2318-24.
24. Morais T, Bernier M, Turcotte F. Age- and sex-specific prevalence of scoliosis and the value of school screening programs. *Am J Public Health* 1985;75:1377-80.
25. Wiegersma PA, Hofman A, Zielhuis GA. The effect of school screening on surgery for adolescent idiopathic scoliosis. *Eur J Public Health* 1998;8:237-240.
26. Nachemson AL, Peterson LE. Effectiveness of treatment with a brace in girls who have adolescent idiopathic scoliosis. A prospective, controlled study based on data from the Brace Study of the Scoliosis Research Society. *J Bone Joint Surg Am* 1995;77:815-22.
27. Rowe DE, Bernstein SM, Riddick MF, et al. A meta-analysis of the efficacy of non-operative treatments for idiopathic scoliosis. *J Bone Joint Surg Am* 1997;79:664-74.
28. Wiley JW, Thomson JD, Mitchell TM, et al. Effectiveness of the Boston brace in treatment of large curves in adolescent idiopathic scoliosis. *Spine* 2000;25:2326-32.
29. Focarile FA, Bonaldi A, Giarolo MA, et al. Effectiveness of nonsurgical treatment for idiopathic scoliosis. Overview of available evidence. *Spine* 1991;16:395-401.
30. Goldberg CJ, Dowling FE, Hall JE, et al. A statistical comparison between natural history of idiopathic scoliosis and brace treatment in skeletally immature adolescent girls. *Spine* 1993;18:902-8.
31. TNO Preventie en gezondheid. Programmeringsstudie Effectonderzoek Jeugdgezondheidszorg. Leiden: TNO; 2000.



Part I

Screening for idiopathic scoliosis

Screening for scoliosis: do we have indications for effectiveness?

2

Eveline M Bunge, Rikard E Juttmann, Harry J de Koning and the steering committee of the NESCIO group

J Med Screen. 2006;13:29-33

Abstract

Objective: The effectiveness of screening for scoliosis has not been established. This study investigated whether patients with adolescent idiopathic scoliosis detected by screening are detected in an earlier stage of the clinical course, and whether these patients have better outcome than otherwise detected patients.

Setting: The study is a retrospective follow-up study of patients with adolescent idiopathic scoliosis who had completed treatment with a brace, by surgery, or with a brace followed by surgery. Of the 143 patients, (born on or after 1 January 1984) consecutively recruited from 12 hospitals in the Netherlands, 125 (87%) agreed to participate. Of these, 51 patients were treated with a brace only and 74 patients were operated on. Screening for scoliosis is carried out in 80% of Dutch children.

Methods: Data on being screen detected or otherwise detected and Cobb angle at diagnosis were collected using youth health-care files, medical files and interviews by telephone with the patients.

Results: About 55% of the patients were detected by screening (programme sensitivity). Screen-detected patients had a significantly smaller Cobb angle at diagnosis (28° versus 40°; $p < 0.01$) and had a 73% lower chance of having had surgery (45% versus 75%; $p < 0.01$) than otherwise-detected patients.

Conclusion: In the present study, two essential prerequisites necessary for a screening programme for scoliosis to be effective have been met. However, definite proof of the effectiveness of screening still needs to be established because length bias and over-treatment bias cannot be ruled out using this design.

Introduction

In the Netherlands an estimated 80% of the children are screened for adolescent idiopathic scoliosis (AIS) at least once[1]. AIS is defined as a lateral curvature of the spine of unknown origin in teenagers; there is also a fixed rotation of one or more vertebrae and a rotational deformation of that vertebra. The severity of this condition can be assessed by X-ray, and is usually expressed in the size of the 'Cobb angle', which is the angle between the axes of the upper and the lower of the most inclined vertebra. The screening test for scoliosis is the Adam's forward bending test. A school physician examines the child's uncovered back while the child is bending forward; in case of scoliosis a rib 'hump' is present because of trunk rotation, which can be measured by a scoliometer[2,3]. This rib hump is not always obvious in a standing position.

Screening for AIS was introduced in the USA and many other countries in the 1970s[4]. Screening aims at detecting patients in an early stage of the clinical course, in order to apply brace treatment to try and prevent further progression and the need for surgical treatment[5,6]. At a young age, surgical treatment can have considerable implications and complications[7]. So far, however, the effectiveness of this screening has not been sufficiently established[1,6]. Some studies conclude that screening for scoliosis is effective,[4,8-12] while others doubt the effectiveness or even consider such screening to be unethical[13-16]. In 2004, the US Preventive Services Task Force recommended against screening for scoliosis, because of a lack of evidence[17]. They concluded that there is lack of evidence that earlier detection of scoliosis is accomplished by screening, that most cases detected through screening will not progress to a clinically significant form of scoliosis; that screening for scoliosis can lead to unnecessary brace wear and/or specialty care and that these harms exceed the potential benefits. However, for researchers and practitioners, to continue screening for scoliosis or not is still under discussion.

In an ecological case-control study Wiegersma et al. found no support for the hypothesis that an active screening programme for scoliosis prevents surgical interventions (odds ratio 1.00; 95% C.I. 0.74–1.35)[18]. However, in their study, exposure to screening was established on an ecological instead of a personal level, i.e. as the formal screening policy in the municipality, where the children lived at the time of the study. Whether cases and controls actually were exposed to that policy, or whether they actually lived in the municipality involved at the time they should have been screened, was not established[19]. Moreover, no insight could be given as to the causes of the reported absence of effectiveness of the screening.

From a methodological point of view, a randomised controlled trial (RCT) is the best design to establish the effectiveness of screening for scoliosis. However, because AIS is not very common, an RCT would demand a very large study population to gain sufficient power, which makes an RCT unfeasible[20]. The next best design is a case-control study[21]. In such a design, screening exposure of patients with the adverse outcome (in this case scoliosis patients needing surgery) must be compared with screening exposure of a (random) population control group. Although this design is less laborious than an RCT, it still requires considerable effort and costs.

However, before executing such a study, it is both worthwhile and simple to test

whether or not screening for scoliosis could be effective at all. If screening for scoliosis is effective, it is expected that (1) screen-detected patients are detected at an earlier stage of the clinical course than otherwise-detected patients, and (2) screen-detected patients have a better outcome than otherwise-detected patients. It is noteworthy that, to our knowledge, such a simple study has not been done before. If one or both hypotheses could be falsified, a laborious evaluation study (such as a case-control study) would no longer be necessary. However, if these hypotheses could not be falsified, this study would not provide enough evidence to state that screening for scoliosis is effective.

The purpose of the present study is to evaluate whether patients detected by screening were detected at an earlier stage of the clinical course, and whether patients detected by screening had better outcome than otherwise-detected patients. Also evaluated are the programme sensitivity and whether differences exist in the age at detection and at diagnosis between screen-detected and otherwise-detected patients.

Materials and methods

According to Dutch law, observational health surveys are exempted from requesting approval from a medical ethical committee. The study was conducted according to the principles of the Declaration of Helsinki.

Design

The study was a retrospective follow-up study of AIS patients who had completed treatment with a brace, by surgery, or with a brace followed by surgery. The patients treated with a brace only were not expected to be eligible for surgical treatment in the future, as far as could be judged at the time of inclusion based on curve characteristics and cessation of growth.

Study population

Orthopaedic surgeons from 12 hospitals in the Netherlands where patients with AIS are treated were requested to report all consecutive patients who had completed treatment for idiopathic scoliosis between June 2002 and October 2004 and who were born on or after 1 January 1984. Of the 143 eligible patients who were invited to participate, 125 (87%) gave their informed consent. One large hospital in the northern part of the Netherlands did not participate; we have no reasons to believe that the results of this study would be different if that hospital had participated.

Scoliosis screening programme in the Netherlands

In the Netherlands, there are 40 Municipal Health Services, each with their own youth health-care department. School physicians and nurses of about 80% of these youth health-care departments screen children for scoliosis. Screening is generally offered at a mean age of 11 and/or at a mean age of 14 years, often as part of a periodical medical examination. There is also a periodical medical examination at about the

age six, during which the back is often inspected for deformities. When the school physician detects a scoliosis, patients generally have to visit their general practitioner before being referred to an orthopaedic surgeon. The general practitioner or the orthopaedic surgeon orders an X-ray to establish the severity of the scoliosis.

The programme sensitivity of screening for scoliosis represents the proportion of the patients who were detected by this programme in relation to the total study group.

Variables and measurements

We collected the following data: being detected by screening or otherwise; Cobb angle at diagnosis; outcome; age at detection of AIS and age at diagnosis. Screen-detected patients were defined as being detected by the school physician and/or referred to the general practitioner or the orthopaedic surgeon by the school physician. For these patients the school physician clearly exerted the most influence in the detection and/or referral process. Patients who did not meet this latter criterion were defined as otherwise detected. The orthopaedic surgeon established the diagnosis of idiopathic scoliosis. Cobb angle at diagnosis was used as a measure for the stage of the scoliosis at detection. Outcome was defined as being operated (whether or not being braced before surgery), or being treated with a brace only.

The youth health-care files were used to collect data on age at detection by screening; medical files were used to collect data on age and Cobb angle at diagnosis, and telephone interviews with the patients and the youth health-care files were used to collect data on the first person to detect the scoliosis. If the school physician did not detect the scoliosis, the patients were asked when the scoliosis was detected. If the patient did not remember the exact month of detection but did remember the season, we set the date of detection at 15 January in case of 'winter', 15 April, in case of 'spring', 15 July, in case of 'summer' and 15 October in case of 'autumn'; this was done for eight patients. In the case of 'otherwise detected', because we asked the patients only for the month and year, the date of this detection was set at the 15th of the month.

Statistical analysis

The independent variable is being screen detected or being otherwise detected. The dependent variables are the Cobb angle at diagnosis and the outcome.

The programme sensitivity is determined by the proportion of patients detected by screening in relation to the total study group.

Because some data were skewed and many subgroups contained less than 30 cases, the Mann-Whitney U test was used to reveal significant differences between screen-detected patients and otherwise-detected patients in the Cobb angle, age at detection, and age at diagnosis. Binary logistic regression analysis was used to calculate the odds ratio and 95% CI for having surgery depending on whether or not being screen detected. Separate analyses were carried out for the patients detected before the age of 11 years and those detected at or after the age of 11 years to evaluate whether or not the contribution of screening for scoliosis depended on age. The age of 11 years was chosen because if school physicians decide to provide screening for

AIS, they are advised to do this between the ages of 11 and 13 years.

Separate analyses were done to evaluate whether the missing data on scoliosis detection could influence the study results.

The SPSS 11.0.1 package was used for all analyses.

Results

Of the 125 patients in the total study group, 66 were detected by screening and 53 were detected otherwise. Of the remaining six patients, for two patients, data on detection were missing; for four patients it was not possible to judge whether they were detected by the school physician or otherwise. The programme sensitivity was 66/119 (i.e. 55%).

Table 2.1 shows that 82% of the patients were girls. The distribution of curve types was similar in screen-detected and otherwise-detected patients. Patients detected by screening were significantly younger at detection and at diagnosis than patients detected otherwise. Patients detected by screening were operated on at a significantly younger age.

Table 2.2 shows that screen-detected patients had a significantly smaller Cobb angle at diagnosis than otherwise-detected patients. Patients older than 11 years at detection had a larger Cobb angle than patients younger than 11 years, and in patients older than 11 years at detection, the Cobb angle was significantly larger than in patients detected otherwise.

Table 2.1 Characteristics of the study population

	n	Screen-detected (n=66)		Otherwise-detected (n=53)	
Gender		**n (%)**		**n (%)**	
Boys	22 (18%)	10 (15%)		12 (23%)	
Girls	97 (82%)	56 (85%)		41 (77%)	
Curve type[a]		**n (%)**		**n (%)**	
Thoracic	31 (28%)	19 (32%)		12 (24%)	
Thoracolumbar	29 (26%)	16 (27%)		13 (26%)	
Lumbar	5 (5%)	2 (3%)		3 (6%)	
Double thoracic	1 (1%)	1 (1%)		0 (0%)	
Thoracic lumbar	44 (40%)	22 (37%)		22 (44%)	
Age (in years)		**Mean (SD)**	**Median**	**Mean (SD)**	**Median**
Detection	83[b]	9.9 (2.6)	10.4**	12.6 (2.4)	13.0**
Diagnosis	83[b]	10.9 (2.5)	11.4**	13.1 (2.5)	13.6**
Stop brace treatment	49	16.0 (1.3)	16.0	15.9 (1.6)	16.1
Surgery	70	14.9 (1.5)	14.9*	15.7 (1.7)	15.9*

[a] The curve type of nine patients was unknown

[b] Only patients with available data on both age at detection and age at diagnosis were included in this analysis. Date of diagnosis was sometimes missing when the patient was sent to another orthopaedic surgeon for treatment; not all patients were able to recall the date of detection in case of 'otherwise detected', and for a few patients the date of screen detection was missing.

** $p < 0.01$; * $p < 0.05$

Table 2.2 Cobb angle at diagnosis

	n	Screen-detected		Otherwise-detected	
		Mean (SD)	Median	Mean (SD)	Median
Total group[a]	100	28 (12.6)	24**	40 (15.7)	38**
< 11 years at detection[b]	41	25 (12.3)	22	29 (12.5)	32
≥ 11 years at detection[b]	40	32 (11.9)	32*	44 (15.6)	47*

[a] The Cobb angle of 19 patients was not available in the medical files
[b] Data on the exact age at detection of 19 patients (with known Cobb angles) were missing
** $p < 0.01$
* $p < 0.05$

Table 2.3a shows that 45% of the screen-detected patients needed surgery, compared with 75% of the otherwise detected patients. The odds ratio for surgery for screen-detected patients was 0.27 (95% CI 0.12-0.60). This means that patients who were detected by screening had a 73% lower chance of an adverse outcome (i.e. needing surgery) than patients who were detected otherwise. Patients younger than 11 years at detection and who were screen detected had a slightly lower chance (but not significantly) of needing surgery than patients who were over 11 years at detection and who were screen detected (Tables 2.3b and 2.3c).

Separate analyses were done to evaluate whether the six patients for whom it was not possible to judge whether they were detected by screening or otherwise could influence the results. Considering these patients as screen detected, and also as otherwise detected, had no significant effect on the study results.

Table 2.3a Odds ratio for outcome if screen-detected (total group)

Detected by	Surgery (n)	Brace (n)
Screening	30	36
Otherwise	40	13

Odds ratio: 30:40 / 36:13 = 0.27 (95% CI 0.12- 0.60)

Table 2.3b Odds ratio for outcome if screen-detected (<11 years old at detection)[a]

Detected by	Surgery (n)	Brace (n)
Screening	21	21
Otherwise	7	1

[a] Data on the age of detection of 22 patients were missing
Odds ratio: 21:7 / 21:1 = 0.14 (95% CI 0.02 – 1.27)

Table 2.3c Odds ratio for outcome if screen-detected (≥11 years old at detection)[a]

Detected by	Surgery (n)	Brace (n)
Screening	9	13
Otherwise	19	6

[a] Data on the age of detection of 22 patients were missing
Odds ratio: 9:19 / 13:6 = 0.22 (95% CI 0.06 – 0.76)

Discussion

In the present study, patients detected by screening had a smaller Cobb angle at diagnosis and had a better outcome (i.e. less surgery) than patients detected otherwise. In addition, the screening programme detected 55% of the patients, and patients detected by screening were younger at both detection and diagnosis.

Montgomery et al. also tested whether outcome improved (i.e. less surgery) after the introduction of screening for scoliosis and they concluded that screening for scoliosis is effective because of the observed reduction in surgery after screening was introduced[11]. However, Montgomery et al. did not measure on a patient level whether these patients were actually detected by screening or not, and they did not take into account the following possible biases.

In cohort studies such as ours and that of Montgomery et al., the four types of bias, which can overestimate the effectiveness of screening are lead-time bias, selection bias, length bias, and over-treatment bias[22].

Lead-time bias occurs when patients do not reach the definite outcome during the study period. The screening population may contain a large proportion of patients with disorders in a very early stage who will not have reached the (adverse) outcome during the study period; this will lead to an overestimation of the positive effect of screening. In the present study, the outcome (i.e. surgery, or treatment with a brace only) of all patients could be determined. Patients either had surgery (whether or not being braced before surgery) or were treated with a brace only. The latter group was not expected to be eligible for surgical treatment in the future, as far as could be judged at time of inclusion, because of their curve characteristics and cessation of growth. Therefore, it is not likely that lead-time bias occurred in our study.

Selection bias can occur when those who are vigilant about their health and seek medical help in time anyway have a greater chance of being screened than others; this will lead to an overestimation of the effect of screening. In the Netherlands, screening for scoliosis is performed in about 80% of all youth health-care departments. Because most children will visit the school physician when they are invited for an examination, being exposed to screening for scoliosis will depend more on whether or not the youth health-care department offers the screening for scoliosis than on the child's or parents' characteristics. This is not likely to lead to selection bias at the individual level and therefore selection bias is not considered an important problem in screening for scoliosis in the Netherlands.

Length bias occurs when patients with a rapidly progressive form of a disease will have less chance of being detected by screening and have a higher risk of reaching the adverse outcome. This will lead to an over-representation of these patients in the otherwise-detected group and thus to an overestimation of the effect of screening. Scoliosis is not a uniform disorder. Scoliosis patients with a large curvature at younger age or with a rapidly progressive curvature (more severe cases) have a higher risk of needing surgery than less severe cases[23]. More severe cases of scoliosis have less chance of being detected by screening, because of the short pre-clinical detectable phase. Thus, length bias could be a serious problem when evaluating screening for scoliosis in a follow-up study.

Over-treatment bias occurs when patients are unnecessarily treated. Over-treatment with surgery in case of scoliosis is rare, because most patients will only be surgically treated when they have a Cobb angle of 40-45° or over and have reasonable physical growth remaining. Over-treatment with a brace, however, cannot be ruled out. Patients with a relatively small Cobb angle are more likely to be detected by screening than otherwise. Some of these patients will be treated with a brace, whereas they would not have visited an orthopaedic surgeon and received or needed treatment at all if they had not been detected by screening[24]. This will lead to an overestimation of the effect of screening in the evaluation of differences in outcome between screen-detected and otherwise-detected patients. Therefore over-treatment could be a serious issue when evaluating screening for scoliosis in a follow-up study.

Finally, it remains unclear whether or not early intervention with a brace is an effective strategy in preventing surgery in AIS patients[13,25,26]. This is probably one of the most important questions, but no answer is likely to emerge in the near future.

In conclusion, in the present study, two basic prerequisites for an effective screening programme for scoliosis have been met, (i.e. earlier detection and less surgery in screen-detected patients). If these prerequisites had not been met, further evaluation would not be necessary; however, definite proof of the effectiveness of this programme now needs to be established because length bias and over-treatment bias cannot be ruled out. Therefore, it is worthwhile to conduct a case-control study to establish the effectiveness of this screening programme. The case group should consist of AIS patients treated surgically (i.e. the outcome that screening is supposed to prevent) and the control group should consist of a random sample of the source population. Instead of evaluating detection by screening, which was evaluated in the study in this paper, differences in exposure to screening between the case group and the control group should be evaluated. Such a study is planned for the near future.

Acknowledgements

This study was funded by the Netherlands Organisation for Health Research and Development (ZonMw) Grant # 2200.0127. The authors would like to thank all the school physicians and nurses of the Municipal Health Services who participated in this study by providing us the data on the screening history of the patients. We are also very grateful to the patients and parents who participated in this study.

References

1 Korfage IJ, Juttmann RE, Das BV, et al. [Idiopathic scoliosis in adolescents; an inventory into the possibilities of studying the efficacy of screening and treatment]
Idiopathische scoliose bij adolescenten; inventarisatie van mogelijkheden van onderzoek naar de effectiviteit van screening en behandeling. *Ned Tijdschr Geneeskd* 2002;146:1228-33.

2 Behrman R, Kliegman R, Arvin A. Nelson's Textbook of Pediatrics. 15th ed. Philadelphia: W.B. Saunders Company; 1996.

3 Bunnell WP. An objective criterion for scoliosis screening. *J Bone Joint Surg Am* 1984;66:1381-7.

4 Lonstein JE, Bjorklund S, Wanninger MH, et al. Voluntary school screening for scoliosis in

Minnesota. *J Bone Joint Surg [Am]* 1982;64:481-8.
5 Scoliosis Research Society. Scoliosis: A Handbook for Patients: Park Ridge, Ill, Scoliosis Research Society; 1986.
6 The Canadian Task Force on the Periodical Health Examination. Screening for idiopathic adolescent scoliosis. In: The Canadian guide to clinical preventive health care; 1994. p. 346-54.
7 Campbell W, Canale S, Daugherty K, et al. Scoliosis and Kyphosis. In: Canale ST, editor. Campbell's Operative Orthopaedics. St. Louis, MO: Mosby; 2003. p. 1751-984.
8 Bunnell WP. Selective screening for scoliosis. *Clin Orthop Relat Res* 2005:40-5.
9 Soucacos PN, Soucacos PK, Zacharis KC, et al. School-screening for scoliosis. A prospective epidemiological study in northwestern and central Greece. *J Bone Joint Surg Am* 1997;79:1498-503.
10 Torell G, Nordwall A, Nachemson A. The changing pattern of scoliosis treatment due to effective screening. *J Bone Joint Surg [Am]* 1981;63:337-41.
11 Montgomery F, Willner S. Screening for idiopathic scoliosis. Comparison of 90 cases shows less surgery by early diagnosis. *Acta Orthop Scand* 1993;64:456-8.
12 Winter RB, Lonstein JE. To brace or not to brace: the true value of school screening [editorial]. *Spine* 1997;22:1283-4.
13 Dickson RA, Weinstein SL. Bracing (and screening)--yes or no? *J Bone Joint Surg Br* 1999;81:193-8.
14 Goldberg CJ, Dowling FE, Fogarty EE, et al. School scoliosis screening and the United States Preventive Services Task Force. An examination of long-term results. *Spine* 1995;20:1368-74.
15 Karachalios T, Sofianos J, Roidis N, et al. Ten-year follow-up evaluation of a school screening program for scoliosis. Is the forward-bending test an accurate diagnostic criterion for the screening of scoliosis? *Spine* 1999;24:2318-24.
16 Morais T, Bernier M, Turcotte F. Age- and sex-specific prevalence of scoliosis and the value of school screening programs. *Am J Public Health* 1985;75:1377-80.
17 US Preventive Services Task Force. Screening for Idiopathic Scoliosis in Adolescents: *Recommendation Statement*. Rockville. MD: Agency for Healthcare Research and Quality; June 2004.
18 Wiegersma PA, Hofman A, Zielhuis GA. The effect of school screening on surgery for adolescent idiopathic scoliosis. *Eur J Public Health* 1998;8:237-40.
19 Hazebroek-Kampschreur AAJM, Creemers H. The effect of school screening on surgery for adolescent idiopathic scoliosis: a comment. *Eur J Public Health* 1999;9:152.
20 Black N. Why we need observational studies to evaluate the effectiveness of health care. *BMJ* 1996;312:1215-8.
21 Weiss NS. Application of the case-control method in the evaluation of screening. *Epidemiol Rev* 1994;16:102-8.
22 Juttmann RE, Hess J, van Oortmarssen GJ, et al. Patient follow up screening evaluations. Examples with regard to congenital hip dislocation and congenital heart disease. *J Epidemiol Community Health* 2001;55:126-31.
23 Lonstein JE. Adolescent idiopathic scoliosis. *Lancet* 1994;344:1407-12.
24 US Preventive Services Task Force. Screening for adolescent idiopathic scoliosis. Review article. *JAMA* 1993;269:2667-72.
25 Donnelly MJ, Dolan LA, Weinstein SL. How effective is bracing for treatment of scoliosis? *Am Fam Physician* 2003;67:32.
26 Goldberg CJ, Moore DP, Fogarty EE, et al. Adolescent idiopathic scoliosis: the effect of brace treatment on the incidence of surgery. *Spine* 2001;26:42-7.

Estimating the effectiveness of screening for scoliosis; a case control study

3

Eveline M Bunge, Rikard E Juttmann, Frans C van Biezen, Huub Creemers, Alice AJM Hazebroek-Kampschreur, Bert (L) CF Luttmer, P Auke Wiegersma, Harry J de Koning for the NESCIO group
Pediatrics. 2008;121:9-14

Abstract

Objectives: The aim of this study was to test the hypothesis that screening for scoliosis is effective in reducing the need for surgical treatment.

Methods: The study was a case-control study. A total of 125 consecutive patients who were treated surgically for idiopathic scoliosis between January 2001 and October 2004 and who were born on or after January 1, 1984, were invited; 108 agreed to participate. A total of 216 control subjects were selected randomly and anonymously, matched with respect to age and gender. For 279 adolescents, exact screening exposure and outcomes could be analyzed. Case subjects were recruited from four university and six nonuniversity Dutch hospitals; control subjects were recruited from all 37 municipal health services in the Netherlands.

Results: Screen-detected patients received diagnosis at a significantly younger age than did otherwise-detected patients (10.8±2.6 vs. 13.4±1.7 years). In total, 32.8% of the surgically treated patients had been screened between 11 and 14 years of age compared with 43.4% of the control subjects. The odds ratio for being exposed to screening was 0.64. In total, 28% of the patients were diagnosed as having scoliosis before 11 years of age.

Conclusions: Our results showed no evidence that screening for scoliosis reduced the need for surgery. Abolishing screening seems justified, especially because the effectiveness of early treatment with bracing is still strongly debated. A randomized controlled trial on the effectiveness of treating patients with idiopathic scoliosis with bracing is urgently needed.

Introduction

Idiopathic scoliosis (IS) is defined as lateral curvature of the spine (minimum Cobb angle of 10°), of unknown origin, with concomitant vertebral rotation[1]. Screening for IS was introduced in the United States and many other countries in the 1970s[2]. Screening aims at detecting patients in an early stage of the clinical course to allow brace treatment with the aim of preventing further progression and the need for surgical treatment[3]. In the Netherlands an estimated 80% of children are screened for IS at least once.

To date, however, the effectiveness of such screening (and early treatment) has not been established sufficiently, because of a lack of randomized, controlled trials (RCTs)[4]. Some studies concluded that screening for scoliosis is effective[2,5-7], while others doubted the effectiveness or even considered such screening to be unethical[8-10]. The US Preventive Services Task Force recommends against the routine screening of asymptomatic adolescents for IS, because evidence has shown that the balance of benefits (few) and harms (more than a few) is negative[11]. Another important issue is that, because the cause of this form of scoliosis is unknown, the current screening test and the early treatment may not be the most appropriate ones.

Earlier, we found that screen-detected patients were detected at an earlier stage of the clinical course and that screen-identified patients had a 73% lower chance of needing surgery[12]. However, overtreatment bias and length-biased sampling, leading to overestimation of the effect of screening, could be serious problems in such a study[12-13].

The present study investigated the effect of screening for scoliosis on reduction of the need for surgery. From a methodological viewpoint, a RCT is the best design to establish the effectiveness of screening for scoliosis. Because IS is not a common condition, however, such a design would require a very large study population to gain sufficient power, which makes a RCT less feasible[14]. The second-best design is a case-control study[15], which we performed with individual data on exposure to screening.

Methods

Design

This was a case-control study, in which the case group consisted of patients with IS who were treated surgically and the control group consisted of a random sample of Dutch youths. Control subjects were matched to case subjects with respect to age and gender. Matching with respect to age was performed to provide equal opportunities for case subjects and control subjects to be exposed to screening in the past. Because IS occurs more often in girls than in boys, matching with respect to gender was applied.

Study population

Case subjects

In the Netherlands, ~50 patients with IS each year need surgical treatment; >90% of these operations take place in 11 hospitals. Orthopedic surgeons in 10 hospitals (4 university and 6 nonuniversity hospitals) in the Netherlands where patients with IS are treated conservatively and surgically were willing to cooperate in this study. They were requested to report all patients who were treated surgically for IS between January 2001 and October 2004 and who were born on or after January 1, 1984. These patients (n=125) were invited to participate in this study; 108 patients (86%) and their parents (if the patient was <16 years of age) gave informed consent for participation.

Control subjects

The control subjects were matched to the case subjects with respect to age and gender; all control subjects were selected randomly from the source population. For each case subject, 2 control subjects were sampled. Data on the control subjects were collected from the databases of all municipal health services (MHSs) in the Netherlands (n=37), which include almost all youths. Each time a case subject was included in the study, we selected randomly 2 MHSs, weighted with respect to the number of youths registered in each MHS. We requested the MHS to select a control subject whose date of birth and gender matched those of the case subject. Because it was possible that a MHS would have >1 match in its database, we requested that the MHS start searching family names from a certain letter of the alphabet until the first match was found; these letters were distributed randomly among the control subjects. If there was no match in the database, then the MHS was requested to search for a control subject who was born 1 day after the case subject. If that still did not lead to a match, then the MHS had to search for a control born 1 day before the case subject and then, if necessary, 2 days after the case subject was born, and so forth, until a match was found. Such adjustments needed to be made for only 9 control subjects (the maximal difference that was needed was 5 days). We emphasized that the gender of the control subject had to be the same as that of the case subject. Because the control subjects were kept anonymous for the researchers, informed consent from the control subjects was not necessary.

The study was conducted according to the principles of the Declaration of Helsinki. Under Dutch law, observational health surveys are exempted from needing approval from a medical ethics committee.

Variables and measurements

Case subjects and control subjects

School physicians received a questionnaire that they were requested to complete. Data on being exposed to screening, ages at screenings, and whether Adam's forward bending test was performed were collected from youth health care files. Being

exposed to screening was defined as being examined for scoliosis during a periodic medical examination or a 'single scoliosis screening' with at least Adam's forward bending test[3]. All examinations that were performed at a specific request of someone (for example, a gym teacher or parent) and that were not incorporated in the usual screening program were not considered exposure to screening.

Case subjects
Data on the Cobb angle, curve type, brace treatment, age at detection otherwise (i.e. not through screening), and age at diagnosis were collected by using medical files and telephone interviews with participating patients treated for scoliosis. If the school physician had detected the scoliosis, then the date of detection was retrieved from the youth health care file. The orthopedic surgeon established the diagnosis of IS.

Statistical analysis

Power calculations
In total, 102 case subjects and 204 control subjects were needed to obtain a probability of 80% for establishing a 50% reduction in surgery for patients with IS, with $\alpha = 0.05$.

Statistics
Because some data were skewed and some subgroups were smaller than n=30, we used the Mann-Whitney *U* test to evaluate significant differences between screen-detected and otherwise-detected patients with respect to median Cobb angles, age at detection, age at diagnosis, time period between detection and diagnosis, and age at surgery.

Only screenings that were performed before IS was diagnosed by an orthopedic surgeon counted as exposure to screening. For the control subjects, only screenings that were performed before IS was diagnosed for the matched case subjects were valid[16]. The odds ratios (ORs) and their 95% confidence intervals (CIs) for being exposed to screening were calculated using binary logistic regression analysis. To account for matching with respect to gender, gender was added as a categorical covariate. We did not use matched analysis (e.g. conditional logistic regression) because the matching factors did not influence the exposure measure such that they would lead to bias.

First, the OR for being ever/never screened before diagnosis was calculated. We then calculated the OR for being screened or not between 11 and 14 years of age (i.e. the ages at which screening is recommended in the Netherlands). The latter was performed only for the case subjects and matched control subjects who were still eligible for screening (i.e. scoliosis had not yet been diagnosed).

Estimation of costs
Costs for screening for scoliosis were estimated on the basis of the cost of activities model for a MHS[4]. This model considers that 42% of the screenings are part of a

school physician's consult, 20% a single screening performed by school physicians, 31% part of a school nurse's consult and 7% a single screening performed by school nurses. Estimation of the costs of IS surgery were based on Dutch health care fees.

Results

For 7 selected case subjects and one control subject the youth health care files were not retrievable. For 1 selected case subject and 2 control subjects we did not receive a completed questionnaire; for another 5 case subjects the age of diagnosis was missing. One case was diagnosed before the age of 5 years. Because this case might have represented some sort of very early-onset scoliosis, we deleted this case subject and the matched control subjects from all analyses.

Table 3.1 shows the characteristics of the patients with IS that were treated surgically. The ratio of girls to boys was 4:1. Screen-detected patients had significantly smaller Cobb angles at diagnosis compared with otherwise-detected patients (p <

Table 3.1 Characteristics of the scoliosis patients treated surgically

	Total group (n=107)		Screen-detected (n=43)[a]		Otherwise-detected (n=57)[a]	
Gender	**n**	**%**	**n**	**%**	**n**	**%**
Girls	86	80	35	81	45	79
Boys	21	20	8	19	12	21
Curve type[b]						
Thoracic	29	31	14	36	14	29
Thoracolumbar	21	23	11	29	10	20
Lumbar	1	1	1	3	0	0
Double thoracic	3	3	1	3	1	2
Double thoracic lumbar	39	42	11*	29	24*	49
Cobb angle (°)	**Mean (SD)**	**Median**	**Mean (SD)**	**Median**	**Mean (SD)**	**Median**
At diagnosis[c]	42 (15.8)	43	34 (16.1)	35**	46 (13.3)	46**
Pre surgery[d]	56 (10.4)	55	54 (8.2)	53	57 (11.7)	56
Post surgery[e]	32 (11.3)	30	30 (12.9)	28	33 (10.2)	34
Duration brace treatment before surgery (n=46)[f]	**Mean (SD) (n=46)**	**Median**	**Mean (SD) (n=25)[g]**	**Median**	**Mean (SD) (n=18)[g]**	**Median**
Years[f]	2.5 (2.1)	2	2.9 (2.4)	2	1.9 (1.6)	1.4

[a] For 7 patients data on being screen detected or otherwise detected were missing. For the screen detected patients, the school physician clearly exerted the most influence in the screening and/or referral process.
[b] For 14 patients the exact curve type could not be clearly extracted from the medical files.
[c] missing n = 17; [d] missing n = 44; [e] missing n = 44
[f] 49 patients were treated with a brace for more than 6 months before surgery; for 3 patients the total brace period is unknown (patients who were not treated with a brace were excluded from calculation of the average brace time).
[g] For 3 patients data on being screen detected or otherwise detected are missing
* $p < 0.05$; ** $p < 0.01$

Table 3.2 Age at detection, diagnosis and surgery, and time period between detection and diagnosis

Age (years)[a]	Mean (SD)	Median
Age at detection	11.1 (2.7)	11.4
Screen-detected	9.7 (2.6)	10.4*
Otherwise-detected	12.9 (1.6)	13.2*
Age at diagnosis	12.0 (2.6)	12.4
Screen-detected	10.8 (2.6)	11.2*
Otherwise-detected	13.4 (1.7)	13.8*
Age at surgery	14.9 (1.6)	14.9
Screen-detected	14.7 (1.4)	14.8
Otherwise-detected	15.1 (1.8)	15.1
Time period (years)		
Between detection and diagnosis	0.9 (1.2)	0.3
Screen-detected	1.1 (1.4)	0.3
Otherwise-detected	0.5 (0.7)	0.2

[a] only patients with available data on both age at detection and diagnosis were included in this analysis. Of this group (n=66), 37 patients were screen detected and 29 patients were otherwise detected. Of all these 66 patients, data on age at surgery was available.
* $p < 0.01$

0.01). After surgery, Cobb angles did not differ significantly between screen-detected and otherwise-detected patients. Approximately one half of the patients were treated with a brace before surgery. Although there was no significant difference in duration of brace treatment between screen-detected and otherwise-detected patients, screen-detected patients had an almost threefold greater chance of being treated with a brace before surgery (OR 3.1 (95% CI: 1.3-7.0) compared with otherwise-detected patients. On average, brace treatment lasted for 2.5 years.

Table 3.2 shows mean and median ages at detection, diagnosis and surgery and the time period between detection and diagnosis. Screen-detected patients were ~2.5 years younger at detection (Figure 3.1) and at diagnosis. On average, there

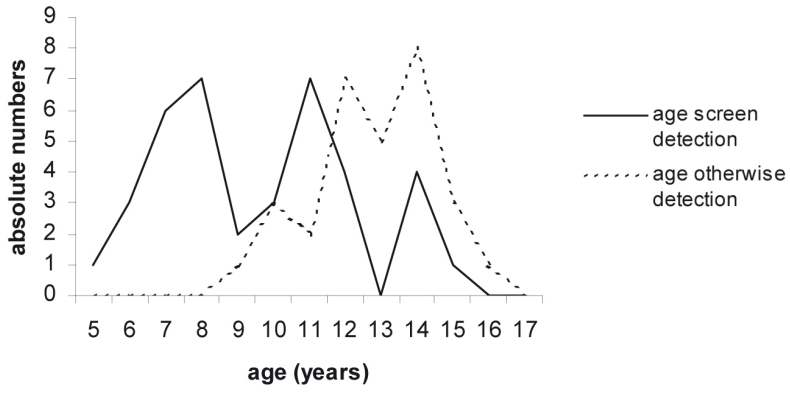


Fig. 3.1 Age at screen detection vs. age at otherwise detection
(Missing data of 39 patients)

were >12 months between detection and diagnosis for screen-detected patients and 6 months for otherwise-detected patients. In total, 55% of the screen-detected patients and 66% of the otherwise- detected patients were diagnosed by an orthopedic surgeon within 4 months after detection. In figure 3.1, the 3 peaks in the screen-detected curve correspond to the ages at which school physicians perform periodical medical examinations in the Netherlands.

The majority (74%) of children had been exposed to screening at least once (Table 3.3). The proportion of case subjects exposed to screening was slightly greater (80.5%) than the proportion of control subjects exposed to screening (74.0%). The OR for being exposed to screening was 1.44 (95% CI 0.77-2.68; p = 0.25).

The OR for being screened at the age of 11, 12, 13 or 14 years was 0.64 (95% CI 0.34-1.19; p = 0.16) (Table 3.4). The proportion of case subjects exposed to screening was smaller than the proportion of control subjects exposed to screening, but screening did not reduce the chance of surgery significantly. It should be noted that 30 case subjects (28%) were diagnosed as having IS before they were 11 years of age.

Costs to screen 80% of 1 Dutch birth cohort (~200,000) were estimated at 3 million euros. Costs for 1 scoliosis operation were estimated at 11,000 euros. Total surgical costs were estimated at 550,000 euros, given 50 operations in 1 year.

Table 3.3 Number of cases and controls and their exposure earlier to screening

	Cases		Controls		Total[a]	
	n	%	n	%	n	%
Exposed to screening	70	80.5	142	74.0	212	76.0
Not exposed to screening	17	19.5	50	26.0	67	24.0

Odds ratio and 95% C.I. 1.44 (0.77-2.68) (p = 0.25)

[a] Because some data were missing on whether or not the bending test was performed and whether or not the test could be defined as screening, the numbers do not add up to 107 cases and 214 controls.

Table 3.4 Number of cases and controls and their exposure to screening when they were 11-14 years old

	Cases		Controls		Total[a]	
	n	%	n	%	n	%
Exposed to screening	21	32.8	59	43.4	80	40.0
Not exposed to screening	43	67.2	77	56.6	120	60.0

Odds ratio and 95% C.I. 0.64 (0.34-1.19) (p = 0.16)

[a] 30 cases were diagnosed with IS before the age of 11.

Discussion

The results of this study did not show a significant reduction in the need for scoliosis surgery attributable to screening. Patients detected trough screening were significantly younger at diagnosis than patients who were detected otherwise. This means that the screen-detected patients had additional years of concern about the disease and they had a greater chance of brace treatment but without better final outcomes. With detailed data for 200 case subjects and control subjects, we had 80% power to show a 59% reduction in scoliosis operations. Our results confirm the conclusion of Wiegersma et al. who also reported that screening for scoliosis did not reduce the need for surgery[10].

Case-control studies are susceptible to different kinds of bias. In this study, all patients already suffer from the serious outcome that screening is supposed to prevent, therefore ascertainment bias is not a serious problem. Because the control subjects were kept anonymous to the researchers, there was no nonresponse in the control group that could lead to nonresponse bias. The response rate for participation among the patients was high (86%). If we had considered the nonresponders as not being exposed to screening, then we would have found a positive effect of screening. However, this is a highly unlikely scenario, because we have no indications that the nonresponders would be different from the responders. Furthermore, being exposed to screening for scoliosis depends more on whether the youth health care department offers the screening for scoliosis in general than on the characteristics of the child or the parents; therefore, we do not expect selection bias to influence the results substantially. Recall bias could be a problem for otherwise-detected case subjects in relation to data on the detection date; patients might have underestimated the time between detection and diagnosis. This could also apply to the age at diagnosis if the medical chart was incomplete.

Our results do not show a significant reduction in the need for surgery attributable to screening for scoliosis among children 11 to 14 years of age (the ages that screening is usually recommended). If we assume that the OR of 0.64 is the true size of the effect, then the costs of keeping 1 patient from the need for surgery are estimated at (at least) 130,000 euros, and ~5800 children would need to be screened. These are relatively high costs and involve considerable effort, given that severe scoliosis is neither common nor fatal. Furthermore, screening identifies some children who ultimately receive treatment but involves referral of many more who do not[18]. Therefore, these costs are an underestimation of the real costs, because they exclude the costs of visits to general practitioners and orthopedic surgeons and radiographs attributable to false-positive results. Yawn et al. calculated that case finding costs for screening were 10,836 dollars per child treated (conservatively or surgically) for scoliosis[17].

In our previous study, we found that 2 prerequisites for an effective screening program were met, that is, earlier detection and less surgery in the screen-detected group[12]. However, overtreatment bias and length-biased sampling could not be ruled out. In the present study, we also found that screen detected patients were diagnosed in an earlier stage and had a greater chance on being treated with a brace.

However, we could not prove that exposure to screening led to less surgery. One explanation for this could be that screening for scoliosis may lead to overtreatment with a brace[11]. Patients with a relatively small Cobb angle are more likely to be detected through screening than otherwise (e.g. by themselves or by their parents). Some of these patients are treated with a brace, whereas they would not have visited an orthopedic surgeon and received or needed treatment at all, if they had not been identified trough screening.

The relatively low sensitivity (55%) of the screening program[12], could perhaps explain why we did not find a beneficial effect. Furthermore, low levels of compliance with brace treatment could lead to ineffective treatment with a brace, which could result in more operations. More importantly, it is still unclear whether early intervention with a brace is an effective strategy in preventing surgery for patients with IS. Some authors consider a brace effective[19,20], whereas others conclude that the effectiveness of bracing is doubtful or they recommend a RCT on brace treatment[4,8,21-22]. If we had found convincing evidence for the beneficial effects of screening for scoliosis, then this would have implied that early treatment with a brace is effective. Because we did not find convincing evidence that screening is effective, we need to determine whether early bracing is effective by means of a RCT; such a trial started in the Netherlands in 2006.

In conclusion, we think that abolishing screening for scoliosis seems justified, because of the lack of evidence that screening and/or early treatment with bracing is beneficial. For now, instead of screening large numbers of asymptomatic children, the appropriate approach would be to look at a child's back when there are indications that something is wrong. Such children should be examined and if necessary, referred to a specialist. If a RCT on brace treatment establishes that bracing is effective, then it will be worthwhile to determine which children could benefit from a screening program.

Acknowledgements

This study was funded by the Netherlands Organisation for Health Research and Development (ZonMw) Grant # 2200.0127. The funding source had no involvement in our work.

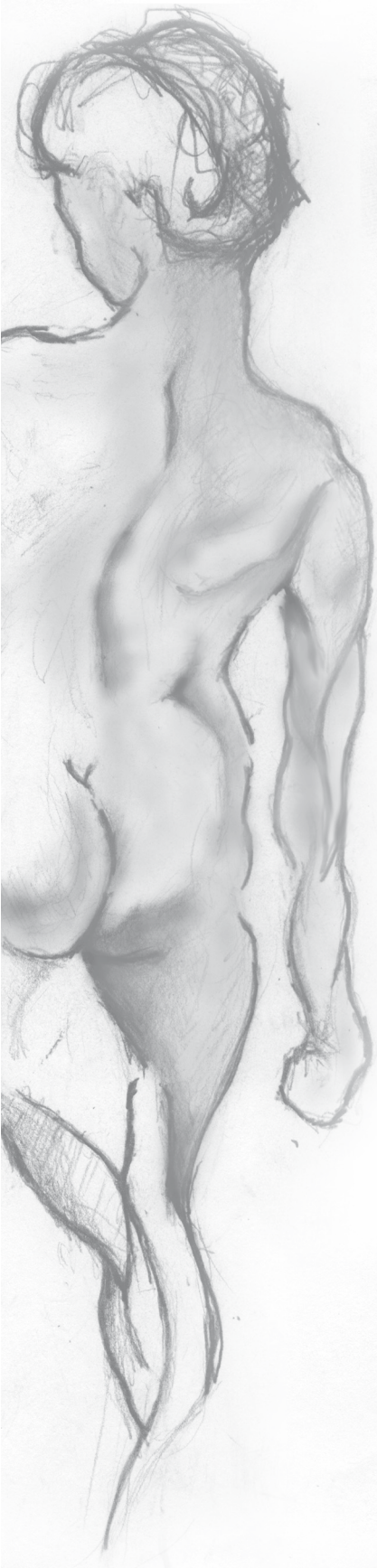
The authors thank Gerrit Draisma, MSc, Caspar Looman MSc and Rob Boer, PhD (Dept. of Public Health, Erasmus MC) for their statistical advice. We also thank all school physicians and nurses of the Municipal Health Services who participated in this study by providing us with the necessary data on screening history (Gemeente Den Haag, Dienst OCW, GG&GD Utrecht, GGD Amstelland – de Meerlanden, GGD Amsterdam, GGD Drenthe, GGD Eemland, GGD Eindhoven, GGD Fryslân, GGD Gelre-Ijssel, GGD Gooi & Vechtstreek, GGD Hart voor Brabant, GGD Hollands Midden vest. Gouda, GGD Hollands Midden vest. Leiden, GGD Kop van Noord-Holland, GGD Midden-Nederland, GGD Nieuwe Waterweg Noord, GGD Noord- en Midden Limburg, GGD Noord Kennemerland, GGD Regio IJssel-Vecht, GGD Regio Nijmegen, GGD Noord Veluwe, GGD Regio Twente, GGD Rivierenland, GGD Rotterdam e.o., GGD West-Brabant,

GGD Westfriesland, GGD Zaanstreek-Waterland, GGD Zeeland, GGD Zuid-Holland West, GGD Zuid-Holland Zuid, GGD Zuid Limburg, GGD Zuidhollandse Eilanden, GGD Zuidoost Brabant, Hulpverlening Gelderland Midden, Hulpverleningsdienst Flevoland, Hulpverleningsdienst Groningen, Hulpverleningsdienst Kennemerland). Last but not least, we are very grateful to the patients and their parents who participated in this study.

References

1 Campbell W, Canale S, Daugherty K, et al. Scoliosis and Kyphosis. In: Canale ST, editor. *Campbell's Operative Orthopaedics*. St. Louis, MO: Mosby; 2003. p. 1751-1984.
2 Lonstein JE, Bjorklund S, Wanninger MH, et al. Voluntary school screening for scoliosis in Minnesota. *J Bone Joint Surg Am* 1982;64:481-488.
3 US Preventive Services Task Force. Screening for adolescent idiopathic scoliosis. Review article. *JAMA* 1993;269:2667-2672.
4 Korfage IJ, Juttmann RE, Das BV, et al. [Idiopathic scoliosis in adolescents; an inventory into the possibilities of studying the efficacy of screening and treatment] Idiopathische scoliose bij adolescenten; inventarisatie van mogelijkheden van onderzoek naar de effectiviteit van screening en behandeling. *Ned Tijdschr Geneeskd* 2002;146:1228-1233.
5 Bunnell WP. Selective screening for scoliosis. *Clin Orthop Relat Res* 2005;434:40-45.
6 Soucacos PN, Soucacos PK, Zacharis KC, et al. School-screening for scoliosis. A prospective epidemiological study in northwestern and central Greece. *J Bone Joint Surg Am* 1997;79:1498-1503.
7 Montgomery F, Willner S. Screening for idiopathic scoliosis. Comparison of 90 cases shows less surgery by early diagnosis. *Acta Orthop Scand* 1993;64:456-458.
8 Dickson RA, Weinstein SL. Bracing (and screening)--yes or no? *J Bone Joint Surg B.* 1999;81:193-198.
9 Goldberg CJ, Dowling FE, Fogarty EE, et al. School scoliosis screening and the United States Preventive Services Task Force. An examination of long-term results. *Spine* 1995;20:1368-1374.
10 Wiegersma PA, Hofman A, Zielhuis GA. The effect of school screening on surgery for adolescent idiopathic scoliosis. *Eur J Public Health* 1998;8:237-240.
11 US Preventive Services Task Force. *Screening for Idiopathic Scoliosis in Adolescents: Recommendation Statement*. Rockville. MD: Agency for Healthcare Research and Quality; June 2004.
12 Bunge EM, Juttmann RE, Koning HJ de, et al. Screening for scoliosis: do we have indications for effectiveness? *J Med Screen* 2006;13:29-33.
13 Juttmann RE, Hess J, van Oortmarssen GJ, et al. Patient follow up screening evaluations. Examples with regard to congenital hip dislocation and congenital heart disease. *J Epidemiol Community Health* 2001;55:126-131.
14 Black N. Why we need observational studies to evaluate the effectiveness of health care. *BMJ* 1996;312:1215-1218.
15 Weiss NS. Application of the case-control method in the evaluation of screening. *Epidemiol Rev* 1994;16:102-108.
16 Connor RJ, Boer R, Prorok PC, et al. Investigation of design and bias issues in case-control studies of cancer screening using microsimulation. *Am J Epidemiol* 2000;151:991-998.
17 Yawn BP, Yawn RA. The estimated cost of school scoliosis screening. *Spine* 2000;25:2387-2391.
18 Yawn BP, Yawn RA, Hodge D, et al. A population-based study of school scoliosis screening. *JAMA* 1999;282:1427-1432.
19 Rowe DE, Bernstein SM, Riddick MF, et al. A meta-analysis of the efficacy of non-operative treatments for idiopathic scoliosis. *J Bone Joint Surg Am* 1997;79:664-674.

20 Nachemson AL, Peterson LE. Effectiveness of treatment with a brace in girls who have adolescent idiopathic scoliosis. A prospective, controlled study based on data from the Brace Study of the Scoliosis Research Society. *J Bone Joint Surg Am* 1995;77:815-822.
21 Focarile FA, Bonaldi A, Giarolo MA, et al. Effectiveness of nonsurgical treatment for idiopathic scoliosis. Overview of available evidence. *Spine* 1991;16:395-401.
22 Goldberg CJ, Dowling FE, Hall JE, et al. A statistical comparison between natural history of idiopathic scoliosis and brace treatment in skeletally immature adolescent girls. *Spine* 1993;18:902-908.



Part II

Treatment for idiopathic scoliosis

Bracing patients with idiopathic scoliosis: design of the Dutch randomized controlled treatment trial

4

Eveline M Bunge, Harry J de Koning and the brace trial group
BMC Musculoskelet Disord. 2008;9:57

Abstract

Background: The effectiveness of bracing patients with IS has not yet been convincingly established due to a lack of RCTs. Some authors suggest that their results confirm that bracing is effective; others conclude that the effectiveness of bracing is doubtful or recommend a RCT. The aim of this study was to establish whether bracing patients with idiopathic scoliosis (IS) in an early stage will result in at least 5 degrees less mean progression of the curvature compared to the control group after two years of follow-up.

Methods: A randomized controlled trial was designed. Eligible patients are girls and boys in the age group 8-15 years whose diagnosis of IS has been established by an orthopedic surgeon, who have not yet been treated by bracing or surgery, and for whom further growth of physical height is still expected based on medical examination and maturation characteristics (Risser ≤ 2). The Cobb angle of the eligible patient should either be minimally 22 and maximally 29 degrees with established progression of more than 5 degrees, or should be minimally 30 and maximally 35 degrees; established progression for the latter is not necessary. A total of 100 patients will be included in this trial. The intervention group will be treated with full-time Boston brace wear; the control group will not be braced. Every four months, each patient will have a physical and an X-ray examination. The main outcomes will be the Cobb angle two years after inclusion and health-related quality of life.

Discussion: The results of this trial will be of great importance for the discussion on early treatment for scoliosis. Furthermore, the result will also be important for screening for scoliosis policies.

Trial registration: Nederlands Trialregister ISRCTN36964733

Background

Idiopathic scoliosis (IS) is defined as a lateral curvature of the spine of unknown origin with a minimal Cobb angle of 10 degrees. The Cobb angle is the angle between the upper most inclined vertebra and the lower most inclined vertebra. Besides a lateral curvature of the spine, there is a fixed rotation of one or more vertebrae and a rotational deformation of that vertebra. Once the curvature shows progression and exceeds a Cobb angle of about 20 to 25 degrees, the curvature is not likely to disappear spontaneously. Progression of the curvature usually occurs just before or during the growth spurt[1].

IS patients who are not fully grown and who have Cobb angles over 20-25 degrees with established progression of at least 5 degrees are usually treated with a brace[1]. A brace is a close fitting device applied to the trunk to try and prevent further progression of the curvature and thereby ultimately the need for surgical treatment. Surgical treatment may become necessary when not fully grown patients reach Cobb angles over 45-50 degrees[1].

Although many orthopedic surgeons feel that bracing might slow down progression of IS and some believe that reduction of the lateral curvature is also feasible, the effectiveness of early treatment of IS with a brace has not yet been established. No randomized controlled trial (RCT) on bracing for IS can be found in the Cochrane library or in PubMed. The majority of the studies are retrospective cohort studies. Some authors suggest that their results confirm that the brace is effective[2-4]; others conclude that the effectiveness of bracing is doubtful or recommend a RCT[5-8]. Some studies were performed without a control group; these study results are compared with results on the natural history from other studies. Another problem in the interpretation of the results of these studies is that they lack consistency regarding both inclusion criteria and the definitions of brace effectiveness[9]. In practice, there is currently no trial evidence that bracing IS patients is better than observation and watchful waiting[10-12]. Several Dutch orthopedic surgeons have reached consensus that a RCT is justified under the condition that the patients included are in an early stage of the clinical course of scoliosis[5]. In collaboration with these orthopedic surgeons, we formulated the current study design.

At first, serious doubts about this RCT were expressed, particularly regarding the willingness of IS patients to go through the process of randomization. In a preliminary study on the feasibility of a RCT on brace treatment for IS, we investigated the willingness of IS patients to accept the process of randomization. We tested the hypothesis that over 50% of IS patients with an early stage of IS visiting an orthopedic outpatient clinic, but not yet treated with a brace for this disorder, would be willing to participate in a RCT. The opinion of their parents was also explored. Parents of 30 patients were invited to participate in this pilot study, of which 21 (70%) agreed to do so. Patients and their parents were interviewed after receiving written information about the principle of randomization and the advantages and disadvantages of participating in a RCT on the effectiveness of brace treatment. This information was also verbally clarified at the beginning of the interview. In total, 87% of the patients (95%CI: 57% - 91%) and 70% of the parents (95%CI: 48% - 85%) agreed to par-

Table 4.1 Odds ratios (OR) and 95% Confidence Intervals (C.I.) for willingness of parents to let their child participate in a RCT for treatment with bracing

Variables	Willingness of parents to agree with participation		OR (95% C.I.)
	Yes	No	
Age – per 1 year rise in age, in the range 9 to 15 years			1.28 (0.76-2.16)
Gender			
boy	6	2	1.88 (0.27-13.12)
girl	8	5	
Native country father			
Netherlands	12	3	8.00 (0.96-66.44)
Other countries	2	4	
Native country mother			
Netherlands	13	4	9.75 (0.78-121.96)
Other countries	1	3	
Educational level father			
≥ higher secondary education	9	1	10.75 (0.99-116.6)
< higher secondary education	5	6	
Educational level mother			
≥ higher secondary education	7	1	5.99 (0.56-63.53)
< higher secondary education	7	6	

ticipate in a RCT on bracing[13]. Table 4.1 shows the odds ratio for willingness to participate for some patient and parent characteristics. Fathers with a higher secondary education were borderline significantly more willing to participate in a RCT.

Methods

Setting

Orthopedic surgeons of 10 Dutch hospitals (3 teaching and 7 non-teaching hospitals) are willing to participate in this trial. Orthopedic surgeons will verbally inform all new patients who meet the inclusion criteria about the trial and give them written information (see table 4.2). Patients and their parents are asked for an informed consent. Together these orthopedic surgeons are expected to recruit 100 patients in a one-year period. All participating orthopedic surgeons have extensive experience with brace treatment in patients with IS.

Participants

Eligible patients are girls and boys in the age group 8-15 years whose diagnosis of IS has been established by an orthopedic surgeon, who have not yet been treated by bracing or surgery, and for whom further growth of physical height is still expected based on medical examination and maturation characteristics (Risser sign) established by X-ray. To expect further growth of physical height, only patients with

Table 4.2 Schematic overview of written information for (parents of) patients with idiopathic scoliosis

Subject	Short explanation
Background	• explanation what idiopathic scoliosis is • treatment options in early stages: brace or observation • effectiveness of brace treatment not established yet
Purpose	• establish whether early treatment with a brace prevents curve progression • evaluate the influence of treatment (brace vs. observation) on health-related quality of life
Design	• randomly assigned to brace or observation group by computer, no influence of patient, parent, orthopedic surgeon or researcher. 50-50% chance • all patients examined every four months, both groups same protocol • 4 times asked to fill in some questionnaires
Advantages and disadvantages	• not known yet who will have most advantages. brace group: maybe treated with effective brace; control group: delayed / no uncomfortable treatment of which effect has not been established
Risks	• both patients treated with a brace as patients being observed have risk on surgery; not yet known whether the risk is different between the groups • regular check-up; in case of progression > 10 degrees in patient in control group, the patient is available for brace
Closure	• end results after two years • depending on the results, again asked to give permission for follow-up until maturity
Voluntary participation	• participation is voluntarily, in case of refusal, the usual treatment in that hospital will be provided • can withdraw permission at any time of the study
Costs and incentive	• no extra costs for patients • no extra incentive for orthopedic surgeons for participation of a certain patient
Confidentiality	• all data will be treated confidentially • no names or data that can lead to identification will be used in reports etc. • protocol was approved by medical ethical review board
Insurance	• since no other treatment than currently used in the Netherlands is applied, an extra insurance for patients' safety was not necessary
Further information	• contact information of the researcher and an independent physician was supplied
Complaints	• contact information of a committee that handles complaints about the study

a Risser sign ≤ 2 will be included. All participating orthopedic surgeons agreed that the Cobb angle of the eligible patient should either be minimally 22 and maximally 29 degrees with established progression of more than 5 degrees, or should be minimally

30 and maximally 35 degrees; established progression for the latter is not necessary. At inclusion of the study, data on calendar age, gender, height, maturation characteristics (Risser sign, menarche), size and location of the curvature will be recorded for all patients.

Ethical Committee Approval

The Medical Ethical Review Board of the coordinating hospital approved this trial in December 2005 (MEC-2005-319). All other participating centers (n=10) obtained approval from their local Medical Ethical Committee between March 2006 and June 2007.

Intervention group

Early treatment of IS consists of wearing a brace that is intended to prevent the curvature from worsening. Patients in the intervention group will initially be braced for two years. The orthopedic surgeon will refer the patients to a qualified certified prosthetist orthotist who will measure, make and fit the brace. Each brace will be measured and modified individually for each patient to fit and correct her/his curvature. She/he will be advised to wear the brace every day for 18-23 hours. Boston braces will be used for all patients; this brace is used the most in the Netherlands. Patients are usually advised to attend physical therapy for muscle training and to correct body posture. Physical therapy alone is not expected to prevent further progression of the curvature[11]. Therefore, patients are free to choose whether or not they will attend physical therapy.

Although some orthopedic surgeons prefer to keep the patients in the hospital for a few days to allow them to become used to wearing the brace, others do not. The orthopedic surgeons are allowed to apply their own protocol concerning this hospital admission.

In case patients of the intervention group reach Cobb angles that require surgery, they can be operated.

Control group

Patients in the control group will initially not be braced during the two study years, unless their curvature shows more than 10 degrees progression compared to the Cobb angle at inclusion. In this case, the orthopedic surgeon, patients and their parents could decide to start brace treatment. The patients in the control group are allowed to attend physical therapy if they want to, because physical therapy alone will not prevent further progression of the curvature.

In case patients of the control group reach Cobb angles that require surgery, they can be operated.

Follow-up

Both the intervention and control group will follow the same protocol for monitoring the curvature during the two years of the study. Every four months the orthopedic surgeons will repeat the measurements of size and location of the abnormal curvature, physical height, maturation characteristics (menarche and Risser sign), brace

compliance, and whether or not surgery is indicated. These examinations will be conducted following a specific protocol: every four months a physical examination and an X-ray of the spine will take place. Patients will take off the brace the night before an X-ray is taken. Standard technique is a standing position of the patient and a posteroanterior projection. In patients with discrepancy in leg length, boards will be put under the shortest leg to correct for this.

Objectives

The purpose of this RCT is to establish whether brace treatment in IS patients with Cobb angles between 22 and 35 degrees significantly reduces further bending of the spine, thereby preventing surgery for some patients. The specific research questions are:

1. Will bracing patients with IS in an early stage result in at least 5 degrees less mean progression of the curvature compared to the control group after two years of follow-up?
2. Do differences in health-related quality of life exist between patients with IS who are treated with a brace and patients who are under watchful waiting?
3. If bracing proves to be effective, what is the cost-effectiveness of brace treatment, compared to regular surveillance only in terms of cost per avoided surgery and cost per QALY, accounting for the (increased) burden of bracing and the (reduced) burden of surgery? If bracing does not appear to be effective, what are the possible savings if treatment guidelines would be changed?
4. If bracing proves to be effective, what is the cost-effectiveness of the nationwide screening program for scoliosis?

Outcomes

The primary outcome of this RCT is that bracing will be considered potentially effective, if after two years the mean progression of the abnormal curvature in the intervention group is at least 5 degrees less than in the control group. Two years after date of randomization the primary outcome measure, progression in Cobb angle, will be established in each patient. Mean Cobb angles, as reported independently, in the intervention arm will be compared to mean Cobb angles in the control arm. To reduce inter-observer measurement errors, two orthopedic surgeons associated with the project team will judge all X-rays independently and without knowledge of the allocation arm. The mean value of the observed Cobb angles will serve as assessed value, whenever the difference between the two measurements is less than 3 degrees. If the difference is larger, a third orthopedic surgeon will be asked to measure the Cobb angle; the mean Cobb angle of all 3 measurements will serve as the assessed value.

The secondary outcomes of this study concern health-related quality of life (HR-QoL) and compliance to brace treatment. Because bracing is a burdensome procedure (including reduced activity in daily living, pain, and implications for self-esteem, satisfaction with appearance, and mood), HRQoL will be evaluated in the intervention and control group by a generic HRQoL questionnaire, i.e. Child Health Questionnaire-Child Form 87 items (CHQ-CF87) and the Child Health Questionnaire-Parent Form 50-items, (CHQ-PF50) EuroQol including a VAS for general health, and a disease-specific

questionnaire, i.e. the adjusted Scoliosis Research Society-22 Patient Questionnaire for Idiopathic Scoliosis (SRS-22r Patient Questionnaire). These questionnaires have been translated into Dutch; score distribution and internal consistency corresponded with the original versions[14-16]. Patients will be asked to fill out the CHQ-CF87, EuroQol and SRS-22 Patient Questionnaire just before every other visit to the orthopedic surgeon, thus 4 times in total. The EuroQol scores can be translated into utilities with values from the Dutch general population. The parents of the patients are requested to fill out the CHQ-PF50, EuroQol and SRS-22 at the same time that their child fills out her/his questionnaires. Patients and parents will receive the questionnaires and a return envelope about two weeks before every other visit to the orthopedic surgeon; thus they can fill out the questionnaires before they know the results of the X-ray (i.e., before knowing whether or not the curvature has progressed).

IS patients are usually advised to wear the brace for 18-23 hours every day as long as the patient is growing, which often implies wearing the brace during many years in adolescence. Hence, the risk of non-compliance is present. Lack of compliance in this group would lead to an underestimation of the treatment effect, if present, and would reduce the power of the trial. Compliance will be measured by three different means. The orthopedic surgeon will ask the patients and their parents how many hours a day the patients wear the brace. Because the patient has to return every 4 months for a check-up, the brace will be checked for signs of wear and tear typical for an intensively-used brace. Besides this, patients of the intervention group will receive a short questionnaire in which compliance, attitudes, social influences and barriers to wearing the brace will be measured at every other visit to the orthopedic surgeon.

Sample size

The Cobb angle at inclusion will on average be 29 degrees (range 22-35 degrees). Due to the standard error of radiographic production and intra and inter-observer measurement variation, a measurement error in Cobb angles of 5 degrees will appear[1]. To reduce the standard error of radiographic production, all patients will undergo X-ray following a strict protocol. Because inter-observer measurements errors are reduced (see *Outcomes*), measurement error will then be maximal 2 degrees, thus the 95% observation interval of Cobb angles at inclusion is 20-37 degrees. After two years, when the outcome will be determined, the range in change will be 0–15 ± 2 degrees. Assuming a uniform distribution of this change in Cobb angle between the patients after two years (most unfavorable scenario), the standard deviation of the difference in change between baseline and outcome measurement will be about 4.5 degrees.

Since bracing has to be better than observation to be justified as treatment for IS, a superiority design will be used. With a power of 95% and alpha =0.05, a mean difference of 5 degrees between the groups can be detected with 40 patients in both study arms. We will aim at a study population at start of 100 patients to take loss to follow-up into account.

Randomization

Patients and their parent(s) who decide to participate will be asked to return the informed consent form to the researchers. Upon receipt of this form, randomization will be performed centrally by the department of Public Health (Erasmus MC) using computer-generated lists. Lists will be constructed with randomly permuted blocks per stratum, where strata will be defined by the participating center. The orthopedic surgeon will notify the patients and their parents of the outcome of allocation to the intervention group or the control group.

Blinding

In this study, blinding of patients and orthopedic surgeons for treatment is not possible. However, a proper, blindly and independently conducted judgment of the X-rays in both trial groups is essential for the primary outcome. Two orthopedic surgeons will judge all X-rays of the patients of both groups and calculate the Cobb angles. To ensure blinding of the primary outcome, the randomization status of the participants will not be disclosed to these two orthopedic surgeons, who judge the patient's X-rays.

Statistical methods

The intervention and control group will be compared based on the 'intention to treat' principle. Differences in Cobb angle between the two groups and other continuous parameters will be measured using parametric or non-parametric tests (depending on skewness) for group comparisons. Categorical parameters will be compared by the Chi-square test. Logistic regression will be applied to measure the treatment effect (yes/no progression) adjusting for covariates. Since we have 4-month measurements on Cobb angles in both arms, progression in Cobb angle will be analyzed with a linear mixed effect model, where we will assume a simple compound symmetry structure. This may be particularly important for extrapolations to follow-up periods longer than 2 years after entry.

When a patient in the control group had to be braced before the end of the follow-up (because of a more than 10 degree progression of the curvature), her/his Cobb angle at the moment of commencing treatment will be considered as final outcome and will be included in the analysis.

In a second analysis, we will perform Kaplan-Meier analyses with these 'progression to more than 10 degrees' as events, in both arms (intention-to-treat).

Stratified analysis will be done to evaluate whether curve type, brace compliance, Cobb angle at inclusion and Risser sign at inclusion influence the effectiveness of brace treatment. Using logistic regression we will also evaluate whether brace compliance depends on gender and age.

Health-related quality of life and utilities will be compared between the intervention and control group. This will be done by basic descriptive statistics. Depending on the distribution of the data, parametric or non-parametric tests will be used.

Discussion

In collaboration with Dutch orthopedic surgeons we have designed the first randomized controlled treatment trial and started it in 2006. In 2007, dr. Weinstein et al. also started a randomized controlled treatment trial on bracing in the USA (BrAIST)[17]. The results of these trials will be of great importance to the discussion on bracing patients with IS. At the moment, patients and parents face a dilemma, because the only available treatment has not been proven effective, and is a rather burdensome one.

The results of this study will also be valuable for the screening program for scoliosis. Screening aims at detecting scoliosis in an early stage of the clinical course to allow brace treatment to try and prevent further progression of the curvature and reducing the need for surgery[11]. Recently, we performed a case control study on the effectiveness of screening for scoliosis. In that study, the case group consisted of surgically treated IS patients (the condition screening and early treatment should prevent) and the control group consisted of a random sample of Dutch youth. We found no evidence that cases were significantly less screened than controls[18]. If we had found a positive effect of screening, that would have implied that bracing is effective. A RCT on the effectiveness of bracing now seems even more justified. If bracing shows to be effective, the screening program needs to be revised. If bracing doesn't prove to be effective, a screening program is not applicable, since the availability of an effective early treatment is one condition for a screening program to be justified[19].

Acknowledgements

Members of the brace trial group are: Henk D Been, MD, PhD, Dept of Orthopedics, Academic Medical Centre, Amsterdam, the Netherlands; Frans C van Biezen, MD, Dept of Orthopedics, Erasmus MC Rotterdam, Rotterdam, the Netherlands; Bert (A) J de Gruijter, MD, PhD, Dept of Orthopedics, Medical Center Alkmaar, Alkmaar, the Netherlands; Hans Peter W van Jonbergen, MD, Dept of Orthopedics, Deventer Hospital, Deventer, the Netherlands; Luuk WL de Klerk, MD, PhD, Dept of Orthopedics, Erasmus MC Rotterdam, Rotterdam, the Netherlands; Marinus de Kleuver, MD, PhD, Dept of Orthopedics, Sint Maartenskliniek, Nijmegen, the Netherlands; Patrick HJ Klop, MD, Dept of Orthopedics, Ziekenhuis Walcheren, Vlissingen, the Netherlands; Frank de Nies, MD, Dept of Orthopedics, Onze Lieve Vrouwe Gasthuis, Amsterdam, the Netherlands; Hans EH Pruijs, MD, PhD, Dept of Orthopedics, University Medical Center Utrecht, Utrecht, the Netherlands; Marcel P Teeuwen, MD, Dept of Orthopedics, Oosterschelde Ziekenhuis, Goes, the Netherlands; Pieter BJ Tilman, MD, Dept of Orthopedics, Maasland Ziekenhuis, Sittard, the Netherlands.

This study is funded by the Netherlands Organisation for Health Research and Development (ZonMw) Grant # 945-06-354; Stichting Nuts Ohra Grant # SNO-T-06-27; Vereniging Trustfonds Erasmus Universiteit Rotterdam. The sources of funding had no involvement in our work.

References

1. Campbell W, Canale S, Daugherty K, et al. Scoliosis and Kyphosis. In: Canale ST, editor. Campbell's Operative Orthopaedics. St. Louis, MO: Mosby; 2003. p. 1751-1984.
2. Nachemson AL, Peterson LE. Effectiveness of treatment with a brace in girls who have adolescent idiopathic scoliosis. A prospective, controlled study based on data from the Brace Study of the Scoliosis Research Society. *J Bone Joint Surg Am* 1995;77:815-22.
3. Rowe DE, Bernstein SM, Riddick MF, et al. A meta-analysis of the efficacy of non-operative treatments for idiopathic scoliosis. *J Bone Joint Surg Am* 1997;79:664-74.
4. Wiley JW, Thomson JD, Mitchell TM, et al. Effectiveness of the boston brace in treatment of large curves in adolescent idiopathic scoliosis. *Spine* 2000;25:2326-32.
5. Korfage IJ, Juttmann RE, Das BV, et al. [Idiopathic scoliosis in adolescents; an inventory into the possibilities of studying the efficacy of screening and treatment] Idiopathische scoliose bij adolescenten; inventarisatie van mogelijkheden van onderzoek naar de effectiviteit van screening en behandeling. *Ned Tijdschr Geneeskd* 2002;146:1228-33.
6. Dickson RA, Weinstein SL. Bracing (and screening)--yes or no? *J Bone Joint Surg Br* 1999;81:193-8.
7. Focarile FA, Bonaldi A, Giarolo MA, et al. Effectiveness of nonsurgical treatment for idiopathic scoliosis. Overview of available evidence. *Spine* 1991;16:395-401.
8. Goldberg CJ, Dowling FE, Hall JE, et al. A statistical comparison between natural history of idiopathic scoliosis and brace treatment in skeletally immature adolescent girls. *Spine* 1993;18:902-8.
9. Richards BS, Bernstein RM, D'Amato CR, et al. Standardization of criteria for adolescent idiopathic scoliosis brace studies: SRS Committee on Bracing and Nonoperative Management. *Spine* 2005;30:2068-75.
10. Donnelly MJ, Dolan LA, Weinstein SL. How effective is bracing for treatment of scoliosis? *Am Fam Physician* 2003;67:32.
11. US Preventive Services Task Force. Screening for adolescent idiopathic scoliosis. Review article. *JAMA* 1993;269:2667-72.
12. Goldberg CJ, Moore DP, Fogarty EE, et al. Adolescent idiopathic scoliosis: the effect of brace treatment on the incidence of surgery. *Spine* 2001;26:42-7.
13. Benard M, Juttmann RE. Feasibility of an RCT on bracing patients with adolescent idiopathic scoliosis. Rotterdam: Erasmus MC, dept. of Public Health; 2001.
14. Raat H, Botterweck AM, Landgraf JM, et al. Reliability and validity of the short form of the child health questionnaire for parents (CHQ-PF28) in large random school based and general population samples. *J Epidemiol Community Health* 2005;59:75-82.
15. Raat H, Landgraf JM, Bonsel GJ, et al. Reliability and validity of the child health questionnaire-child form (CHQ-CF87) in a Dutch adolescent population. *Qual Life Res* 2002;11:575-81.
16. Bunge EM, Juttmann RE, Kleuver de M, et al. Health-related quality of life in patients with adolescent idiopathic scoliosis after treatment: short-term effects after brace or surgical treatment. *Eur Spine J* 2007;16:83-9.
17. http://clinicaltrials.gov. NCT00448448
18. Bunge EM, Juttmann RE, van Biezen FC, et al. Estimating the effectiveness of screening for scoliosis: a case-control study. *Pediatrics* 2008;121:9-14.
19. Wilson J, Junger C. Principles and practice of screening for disease: World Health Organization Public Health Paper 34; 1968.

A randomised controlled trial on the effectiveness of bracing patients with idiopathic scoliosis; failure to include patients and lessons to be learnt

5

Eveline M Bunge, J Dik F Habbema, Harry J de Koning
Submitted

Abstract

Trials often do not succeed in including as many patients as anticipated beforehand. The aim of this paper is to describe why we were not able to include more than a few patients in our randomized controlled treatment trial on the effectiveness of bracing patients with idiopathic scoliosis, and to describe which lessons can be learnt. A pilot study on the willingness to participate in such a trial was conducted among 21 patients and their parents. A description of how we prepared and designed this trial, the problems we faced and how we tried to improve the inclusion are given. A total of 4 patients were included, and 14 refused to participate in an 18 months period. There were a lot less eligible patients than anticipated (40 in stead of 100 per year) and the patients' participation rate was much lower than we had found in our pilot study (21% instead of 70%). The trial failed to include more than a few patients because of an overestimation of the number of eligible patients and because a lot less patients were willing to participate compared to our pilot study. One reason for a low participation rate could be that this trial evaluated a frequently used existing treatment in stead of a new treatment and patients and parents might be afraid of not being treated (despite an intensive secure system for the control arm).

Introduction

Idiopathic scoliosis (IS) is a lateral curvature with concomitant rotation of the spine of unknown origin with a minimal Cobb angle of 10 degrees. Progression of scoliosis usually occurs just before or during puberty. Early treatment by bracing is thought to prevent further progression of the curvature and thereby to prevent the need for surgery[1,2]. The effectiveness of bracing however, has not been sufficiently established due to a lack of randomized controlled trials[3,4]. The studies on bracing that have been done were mostly retrospective studies, or studies without a control group. Therefore, we designed a multicenter RCT on the effectiveness of bracing patients with IS in reducing further progression of the scoliosis. Exact data on incidence numbers are (inter)nationally lacking, but based on a questionnaire sent out to Dutch orthopaedic surgeons, and reported estimated international incidence rates if a screening program would exist, an estimated few hundred patients need brace treatment each year in the Netherlands[5,6]. These estimations range from at least 200 (based on data from 25 Dutch hospitals, excluding the data of at least three large scoliosis clinics) to 600 (based on estimations in the literature if a screening programme were performed).

To successfully implement a clinical guideline, or in this case a trial protocol, a number of factors should be considered during the developmental process[7]. To start with, the topic must be relevant for the clinicians who have to work with it. A balanced working group should be formed that describes the protocol, which should involve clinical experts. To promote support, the draft has to be presented to the users, so they can comment on it and give suggestions. Furthermore, there should be attention to the impact on resources, materials and facilities, and the protocol should be presented in an attractive design[7].

Of course, taking such factors in consideration does not guarantee that the implementation will succeed. Other factors, like barriers at the level of the patient, the individual professional, or the wider environment, can complicate the success of a trial[8]. Unfortunately, the above mentioned brace treatment trial had to be halted, because we were hardly able to include patients. The aim of this report is to describe how we prepared this trial, why we were not able to include the anticipated patients we had counted on beforehand in the trial, and to describe which lessons can be learnt.

Methods

In 2000, we held a national meeting on the need for research on screening and bracing for idiopathic scoliosis. This meeting was attended by orthopaedic surgeons, school doctors, school nurses, a representative of the Dutch Scoliosis Foundation, and researchers. It was agreed that a RCT on bracing for scoliosis, and a case control study on the effectiveness of screening for scoliosis were needed. A first step on designing the protocol for the RCT on bracing was then made, in collaboration with members from the Dutch Spine Society. The case control study was designed and performed between 2002 and 2006[9,10].

Since we were not sure whether patients with scoliosis would be willing to participate in such a trial, in 2002, we performed a pilot study to evaluate whether patients and their parents would be willing to participate in such a trial. These were IS patients who did not need brace treatment at that moment, but could need a brace in the near future. This was the most realistically possible method to estimate the percentage of patients and parents that would be willing to participate. In this pilot (n=21) we found that respectively 87% of the patients and 70% of the parents were willing to cooperate[11].

In 2004 and 2005, the study protocol for the treatment trial was further designed by the authors and several orthopaedic surgeons, and government funding was obtained in 2005. The semi-final protocol and logistics of the trial were discussed in the first telephone meeting with the participating orthopaedic surgeons in September 2005. Orthopaedic surgeons of 11 Dutch hospitals (3 university and 8 non-university) agreed to cooperate in this trial and after some adjustments were made, they approved the protocol. Furthermore, orthopaedic surgeons made an estimation on the number of eligible patients (i.e., patients that meet the inclusion criteria) during one year in their practice. Together, this would result in about 100 eligible patients per year.

The Medical Ethics Committee of the coordinating centre approved the trial in December 2005, after which all local Medical Ethics Committees approved the trial (between February 2006 and June 2007).

The design of the trial is extensively described in a protocol paper[12]. In short, the main aim of the trial was to establish whether bracing patients with IS in an early stage will result in at least 5 degrees less mean progression of the curvature compared to a control group in two years of follow-up. We aimed at including 100 patients with IS, 50 of which would be randomized to the intervention arm and 50 to the control arm. With about 100 eligible patients per year, and a participation rate of 70%, this would take about one year and a half. The intervention arm would be treated with a Boston brace for 18-23 hours a day. The control arm would initially not be braced. Eligible patients were girls and boys in the age group 8-15 years whose diagnosis of IS has been established by an orthopaedic surgeon, who had not yet been treated by bracing or surgery, and for whom further growth of physical height was still expected based on maturation characteristics (Risser ≤ 2). The Cobb angle of the eligible patient should have either been minimally 22 and maximally 29 degrees, with established progression of more than 5 degrees, or should have been minimally 30 and maximally 35 degrees; established progression for the latter was not necessary. Every four months, all patients would have had a physical examination and an X-ray of the spine. In case the curvature of a patient in the control arm would have progressed with 10 degrees or more compared to inclusion, it could be decided to start brace treatment.

The primary outcome was the Cobb angle two years after inclusion. The secondary outcomes were health-related quality of life and costs.

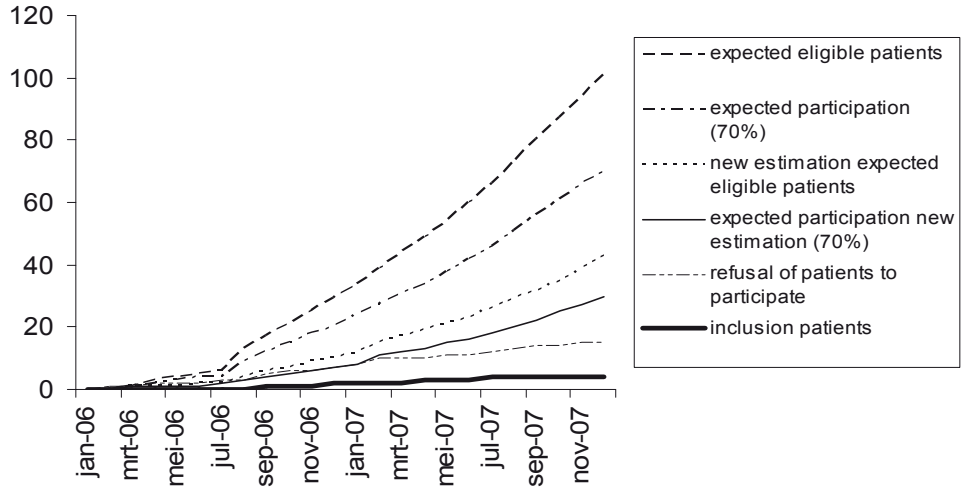


Figure 5.1 Progress of approval from local Medical Ethics Committees, the inclusion of patients and the refusal of patients to participate.
The patient that withdrew from the trial is included in the line 'refusal of patients to participate'.

Results

We were able to include 4 patients in about one and a half year. We faced (mostly administrative) delays in obtaining approval from local Medical Ethics Committees, and more importantly in including patients. Figure 5.1 gives an overview of these results during the two years of the study. An outline of the number of eligible participants, trial inclusion and refusal rates for the year 2006 is given in Figure 5.2.

Delay in getting the trial started

By the end of December 2005, we had obtained approval from the Medical Ethics Committee of the coordinating centre (Erasmus MC – University Medical Center Rotterdam). After that, we had to obtain approval from all other centres. After six months we had obtained approval to start the trial in seven of the ten participating hospitals, and after one and a half year, we obtained approval from all participating hospitals. The delay in obtaining approval was mostly attributable to logistics in the paperwork, and not because the local Committee disapproved the trial.

Two major problems

Eligible patients

Originally, there were 11 hospitals cooperating in this trial. Unfortunately, one hospital had to withdraw from the trial a few months after receiving approval from their local Medical Ethics Committee, because that hospital stopped treating scoliosis patients.

After the trial had started in the first few hospitals, we noticed that the number

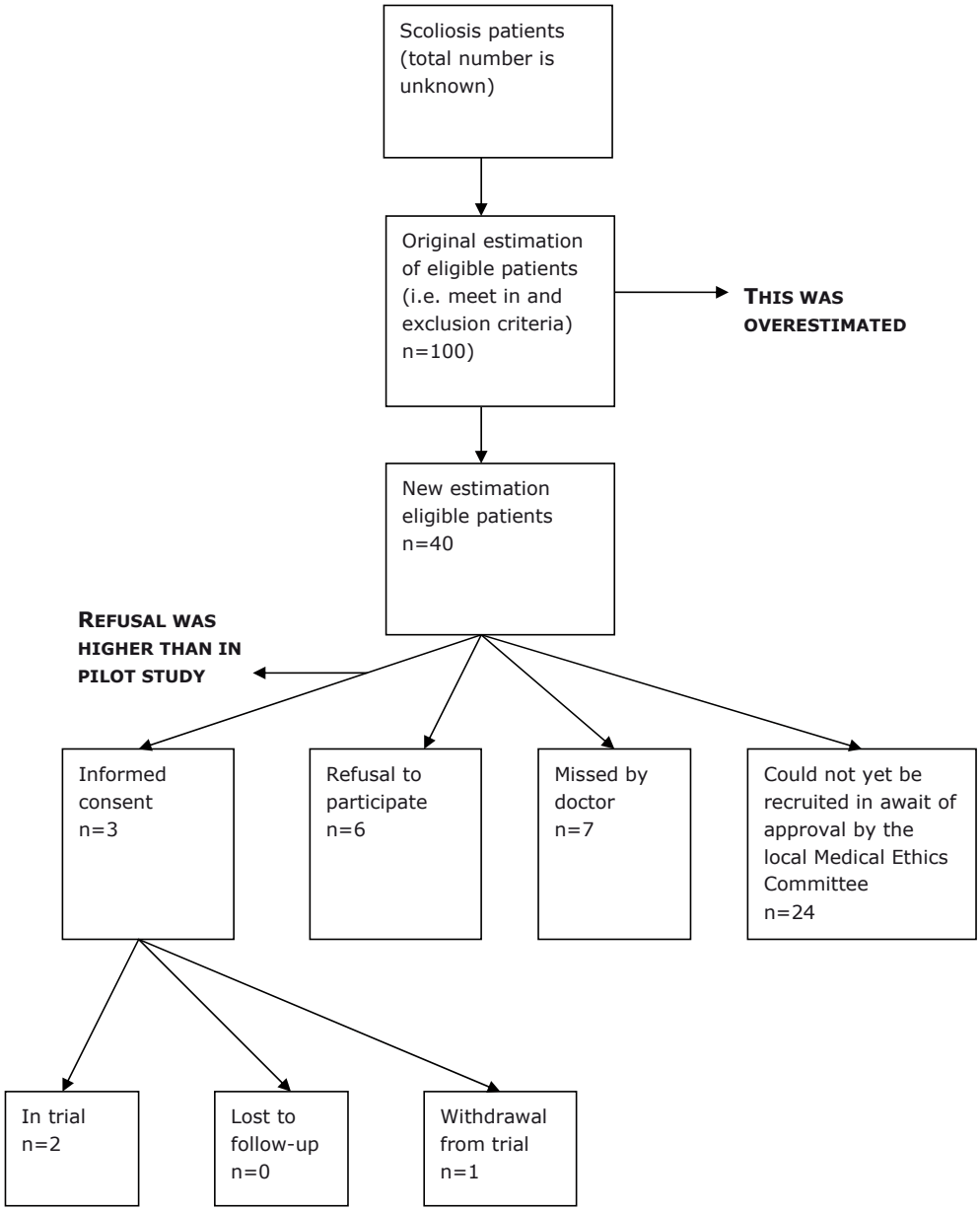


Figure 5.2 Number of eligible participants, trial inclusion and refusal rates in the scoliosis treatment trial for the year 2006

of eligible patients (i.e., fulfilling the inclusion criteria) was strikingly lower than the number we had anticipated on beforehand. Therefore, a new estimation of eligible patients was made, by reviewing the medical files of all scoliosis patients who visited the participating hospitals in 2006. In stead of 100 eligible patients we found about 40 eligible patients during that year. A note was made in the medical files of patients

who were not eligible for the trial yet, but who could be in the near future (e.g., the Cobb angle was too small to be included yet, but could progress to the inclusion criteria in the nearby future). An interesting finding was that in one hospital there were 8 eligible patients in 2006, while there was not one eligible patient in 2007.

By reviewing the medical files of all scoliosis patients who visited the participating hospitals in 2006, we noticed that in one hospital seven eligible patients (i.e., they met the inclusion criteria) had not been approached by their orthopaedic surgeon for participating in the trial in that year, and were therefore considered 'missed'; these patients all started brace treatment. This happened partly due to a combination of busy out-patient consultation hours and the fact that only one in so many scoliosis visits is made by a patient that is eligible for the trial. A large part of the visits is made by patients who are already being treated for scoliosis, and, in some hospitals relatively more than in others, not all patients have idiopathic scoliosis, but some other type of scoliosis. Besides this, a part of the new patients who visit the orthopaedic surgeon for the first time, is too young, or too old to participate, or their curvature does not fulfil the inclusion criteria. We therefore made a plastic card with the inclusion criteria and contact information of the coordinating researcher, which was supposed to help remind the orthopaedic surgeon whom to include. This card fitted in a breast pocket of a 'doctor's coat'.

Higher refusal rate than anticipated

In the trial, we found that only 4 in 19 patients (or in 2006 3 in 16 patients), i.e., about 21%, of the patients were willing to participate (see figure 1). We briefly asked for reasons not to participate in the trial. All patients and parents who refused to participate stated that they wanted to start brace treatment immediately. Some of them indicated that they considered the risk to be too high, i.e., they felt that postponing treatment would have a negative impact.

It is good to note here that in the trial for each patient every four months, X-rays were taken to examine whether the curvature had progressed. The patients in the control group were therefore also closely watched, and had a 'safety net'; in case their curvature would show more than 10 degrees progression compared to inclusion, the patient, parents and her/his orthopaedic surgeon could decide to start brace treatment.

Actions to improve inclusion

Every three to four months, we had a telephone conference with the orthopaedic surgeons to discuss the progress of the trial, and to ask what help we could offer to increase the inclusion of patients. We tried to include extra hospitals in the study between April 2007 and September 2007. The already participating orthopaedic surgeons recommended four hospitals. These were approached, but only one could be reached and was willing to cooperate.

To decrease the refusal to participate, we wrote an article about the trial in the patients magazine of the Dutch Scoliosis Foundation (summer 2007) in which we explained the trial. Possibly, this would have been more effective if we had published that in an earlier stage of the trial, although new patients are probably not yet a

member at the moment they are eligible for the trial, because, in most cases, that will be relatively shortly after diagnosis.

Discussion

The phenomenon that, during a trial, there appear to be less eligible patients than anticipated on beforehand is known as "Lasagna's Law"[13]. Grol et al., describes barriers to change in practice[8] (i.e., implication of clinical guidelines). These barriers can arise at different levels, amongst others at the level of the patient, the individual professional, or the wider environment, and we feel these can also arise in trials. We will describe these factors below.

Lasagna's Law

Literature shows that a lot of trials do not succeed in including as many patients as expected beforehand[14-16]. A review of 114 trials in the UK showed that approximately one third succeeded in including their targeted numbers. Half of the trials were awarded an extension. In 10% of the trials, enrolment was halted before the end of the recruitment period, because of poor recruitment. Reasons for slow enrolment were: less eligible patients than anticipated and a higher refusal rate. A total of 45% of the trials failed to recruit to within 80% of target[15]; our recruitment was far worse.

One of the difficulties in our trial could be that we focused mostly on incidence cases. Literature shows that trials were less successful in including patients if the study focused on incidence cases, rather than on prevalence cases[14,16]. We tried to keep attention for our trial by mailing the orthopaedic surgeons, having telephone meetings and giving them small plastic cards with the inclusion criteria and contact information of the coordinating researcher.

Level of the patient

The willingness to participate in the trial was much lower than found in the pilot study (25% vs. 70%). Apparently, even though the situation in our pilot study was a near-future situation, it did not reflect the choices that were made in the actual trial. The information for the patients and parents was almost the same for the pilot and the trial. The main difference was the type of person that approached the potential participants. In the pilot study, the patients and parents were approached by a medical student. The patients and parents received written information of what such a trial would concern. Then the medical student visited them and explained the trial verbally and asked them whether or not they would participate. In the trial, the study was explained by the orthopaedic surgeon or, in a few hospitals, by a research nurse. Although numbers are too small to draw conclusions, we do not have indications that the participation rate is higher in the hospitals that had a research nurse explaining the trial to the patient and her parent(s). Group seminars with potential participants may be a useful strategy for maximizing recruitment (at least from general practices)[17]. For our trial, however, this would have been too complicated to carry

out in practice, because there were only a couple of eligible patients per month, and they lived scattered over the whole country.

Level of the individual professional

It is possible that, even though all orthopaedic surgeons agreed to participate and agreed with the protocol, they perceived some conflict between their roles as scientific investigator and personal physician[18]. They braced many patients before the trial, and now they had to randomize their patients to treatment or watchful waiting. This brace is a regular treatment, and is preferred among most of the orthopaedic surgeons, and apparently also by patients and parents, even though evidence is not convincingly established. In this case, the only way for patients to be certain that they would be treated, was to not participate in the trial. Usually, in RCTs that test new medicines or devices, the only way to have access to that treatment for patients is to participate in that trial. This can make a big difference in inclusion rates. In the before mentioned review of 114 UK trials, it seemed that cancer or drug trials were associated with successful recruitment, even as trials in which one or more interventions were tested that were only available inside the trial, although these finding should be interpreted carefully[15]. We know of at least one published trial on a popular treatment, but based on weak evidence, that also failed to include patients[19]. Taking this and our trial recruitment into consideration, we also feel that it is harder to abolish or postpone a treatment in a RCT than to add a new treatment.

Level of the wider environment

Screening for scoliosis is necessary for detecting cases in an early stage of the clinical course[9]. In our recently published case control study on the effectiveness of screening for scoliosis, we did not find evidence that screening leads to a reduction in the need for surgery, which is the ultimate goal of screening[10]. One of the reasons why we did not find a beneficial effect of screening could be that brace treatment is not effective (enough) in (some of) these earlier detected patients. These results justified a RCT on bracing even more. In the Netherlands, the screening is performed by nearly 50% of the municipal health services (MHSs)[10]. Although we feel that abolishing screening for scoliosis is justified[10], we probably "need" screening to identify patients in an early stage to be eligible for this trial. We do not have indications that additional MHSs stopped screening between 2006 and the end of 2007. Otherwise, this could have (partly) explained the lower actual number of eligible patients for the trial than the expected number.

Another issue could be that some orthopaedic surgeons feel that the incidence of idiopathic scoliosis might be declining, but we do not have data to prove nor to disprove this. It is however not very likely that a decline in incidence can completely explain the lower number of eligible patients.

Internet is an important information source for people who want to learn more about their disease or condition. Supposing eligible patients would consult the Internet, before they visit an orthopaedic surgeon, they would now mostly find that bracing is a (effective) strategy to prevent them from worsening. Perhaps an Internet site with balanced information on the trial could have resulted in a higher participation

rate, although the value of audio-visual interventions for people considering participating in clinical trials is unclear[20].

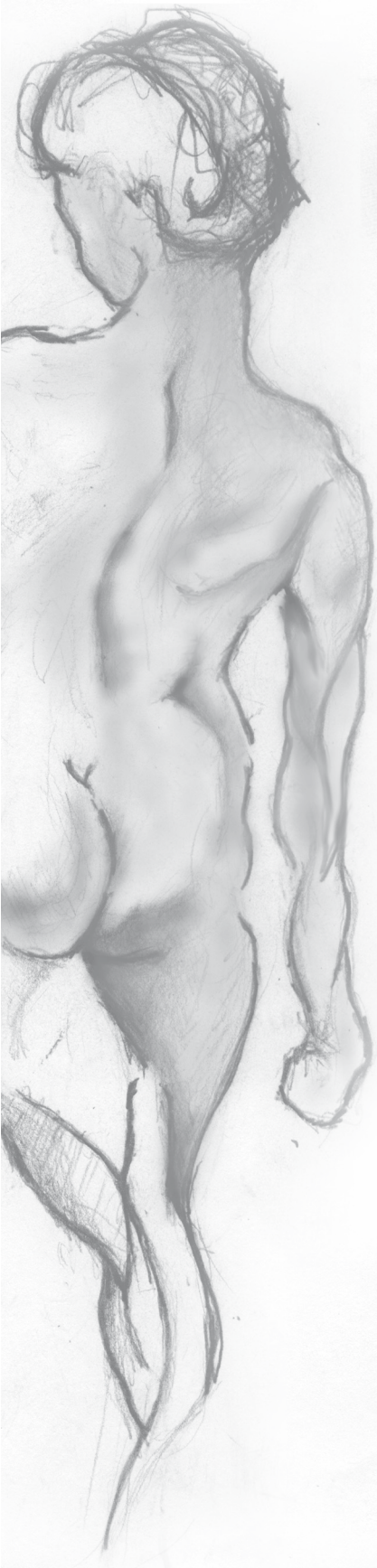
Conclusion

In conclusion, our RCT on the effectiveness of bracing patients with IS failed to include patients, despite a good preparation and a pilot study that showed good participation rates. This latter teaches us that making a choice in a near-future situation can be something else than making a choice in the actual situation. This has probably much to do with the fact that bracing is the regular treatment and once patients have progressive curvatures, they want to act and try their best to stop progression, even if evidence of effectiveness is not convincing. Another important lesson learnt is that beforehand as precise as possible estimations on the number of eligible patients need to be made. This seems obvious, but in about 10% of trials enrolment was halted, because of poor recruitment[15]. Finally, we feel that it is harder to perform a RCT that abolishes or postpones a treatment than a RCT that adds a new treatment, and this should probably lead to a standard adjustment in sample size calculations beforehand in such situations.

References

1. Bunnell WP. Selective screening for scoliosis. *Clin Orthop Relat Res* 2005(434):40-5.
2. Campbell W, Canale S, Daugherty K, et al. Scoliosis and Kyphosis. In: Canale ST, editor. Campbell's Operative Orthopaedics. St. Louis, MO: Mosby; 2003. p. 1751-1984.
3. Lenssinck ML, Frijlink AC, Berger MY, et al. Effect of bracing and other conservative interventions in the treatment of idiopathic scoliosis in adolescents: a systematic review of clinical trials. *Phys Ther* 2005;85:1329-39.
4. Weinstein SL, Dolan LA, Cheng JC, et al. Adolescent idiopathic scoliosis. *Lancet* 2008;371:1527-37.
5. Bunnell WP. Outcome of spinal screening. *Spine* 1993;18:1572-80.
6. Styblo K. Conservative treatment of juvenile and adolescent idiopathic scoliosis. A clinical, rontgenological and comparative retrospective study on the effects of conservative treatment by brace in 290 juvenile and adolescent consecutive patients. Thesis. 1991.
7. Wollersheim H, Burgers J, Grol R. Clinical guidelines to improve patient care. *Neth J Med* 2005;63:188-92.
8. Grol R, Grimshaw J. From best evidence to best practice: effective implementation of change in patients' care. *Lancet* 2003;362:1225-30.
9. Bunge EM, Juttmann RE, De Koning HJ, et al. Screening for scoliosis: do we have indications for effectiveness? *J Med Screen* 2006;13:29-33.
10. Bunge EM, Juttmann RE, van Biezen FC, et al. Estimating the effectiveness of screening for scoliosis: a case-control study. *Pediatrics* 2008;121:9-14.
11. Benard M, Juttmann RE. Feasibility of an RCT on bracing patients with adolescent idiopathic scoliosis. Rotterdam: Erasmus MC, dept. of Public Health; 2001.
12. Bunge EM, De Koning HJ, and the brace trial group. Bracing patients with idiopathic scoliosis: design of the Dutch randomized controlled treatment trial. *BMC Musculoskelet Disord* 2008;9:57.
13. Harris E, Fitzgerald J, eds. The principles and practices of clinical trials. Edinburgh: E&E Livingstone; 1970.
14. Haidich AB, Ioannidis JP. Patterns of patient enrolment in randomized controlled trials. *J Clin Epidemiol* 2001;54:877-83.
15. McDonald AM, Knight RC, Campbell MK, et al. What influences recruitment to randomised

controlled trials? A review of trials funded by two UK funding agencies. *Trials* 2006;7:9.
16. Van der Wouden JC, Blankenstein AH, Huibers MJ, et al. Survey among 78 studies showed that Lasagna's law holds in Dutch primary care research. *J Clin Epidemiol* 2007;60:819-24.
17. Paine BJ, Stocks NP, Maclennan AH. Seminars may increase recruitment to randomised controlled trials: lessons learned from WISDOM. *Trials* 2008;9:5.
18. Lumley J, Lester A, Renou P, et al. A failed RCT to determine the best method of delivery for very low birth weight infants. *Control Clin Trials* 1985;6:120-7.
19. Ruddell M, Spencer A, Hill K, et al. Fluoxetine vs placebo for depressive symptoms after stroke: failed randomised controlled trial. *Int J Geriatr Psychiatry* 2007;22:963-5.
20. Ryan R, Prictor M, McLaughlin K, et al. Audio-visual presentation of information for informed consent for participation in clinical trials. *Cochrane Database of Systematic Reviews* 2008(1): DOI: 10.1002/14651858.CD003717.pub2.



Part III

Quality of life and patients' preferences

Health-related quality of life in patients with adolescent idiopathic scoliosis after treatment: short-term effects after brace or surgical treatment

6

Eveline M Bunge, Rikard E Juttmann, Marinus de Kleuver, Frans C van Biezen, Harry J de Koning and the NESCIO group
Eur Spine J. 2007;16:83-89

Abstract

For treatment of teenagers with progressive adolescent idiopathic scoliosis in an early stage, two options are generally considered: treatment with a brace or observation followed by surgery if necessary. Many doctors and patients prefer conservative treatment (i.e. brace treatment) to surgical treatment, because surgery of the spine is generally considered a drastic intervention. Because potential differences in health-related quality of life (HRQoL) after treatment between braced and surgically treated patients are not well explored, this study aimed to determine whether short-term differences exist in HRQoL between adolescents treated with a brace or treated surgically. A cross-sectional analysis of HRQoL was made of 109 patients with adolescent idiopathic scoliosis who, after completing treatment, filled out the Dutch SRS-22 Patient Questionnaire. All patients had been treated either with a brace or surgery, or with a brace followed by surgery. Patients treated surgically had significantly higher mean scores in the satisfaction with management domain than those treated with a brace. No other consistent differences in HRQoL were found between patients treated with a brace and patients treated surgically. Gender, curve type and curve size had no relevant effect on HRQoL. We conclude that short-term differences in HRQoL after treatment in adolescent patients with idiopathic scoliosis are negligible and cannot support preference of one treatment above the other.

Introduction

For treatment of teenagers with progressive adolescent idiopathic scoliosis (AIS) in an early stage, two options are generally considered: treatment with a brace or observation followed by surgery if necessary. In practice, some patients treated with a brace will eventually also need surgical treatment[1]. Many doctors and patients prefer conservative treatment (i.e. brace treatment) to surgical treatment, because surgery of the spine is generally considered a drastic intervention. The risk of damage of the spinal cord during such operations is often emphasized although, at present, that risk may be considered relatively small (less than 0.5%)[2].

The debate about the best option remains undecided[3-6]. Besides clinical outcomes, health-related quality of life (HRQoL) is an important measure in evaluating treatment, especially in non-life-threatening conditions[7,8]. Therefore, potential differences in HRQoL after treatment between conservatively treated and surgically treated patients can also be considered. Some information is available on long-term follow-up in AIS, but study results are not unanimous. Weinstein et al concluded in a 50-year natural history study of untreated patients with late onset idiopathic scoliosis (LIS) that untreated LIS causes little physical impairment other than back pain and cosmetic concerns, and causes no increase in clinical depression compared to controls[9]. Ascani et al on the other hand, found no increased incidence of pain, but found real psychological disturbances in 19% of untreated AIS patients[10]. With respect to long-term follow-up on HRQoL in conservatively treated patients, Danielsson et al. concluded that minimal pain occurred compared with normal controls[11] and that psychosocial well-being is quite good 20 years after brace or surgical treatment and is equal to the general population[12]. However, at the start of the 21st century with changing adolescent culture and experience, it is important to keep evaluating HRQoL in new AIS patient groups.

Measuring HRQoL in idiopathic scoliosis patients is feasible. Haher et al. designed the Scoliosis Research Society (SRS) Outcome Instrument, which is a simple, disease-specific, patient-based assessment[13]. Modifications of this instrument resulted in the SRS-22 Patient Questionnaire that covers the domains of function/activity, pain, self-image/appearance, mental health and satisfaction with management. This instrument has proved to be reliable[14], reproducible[14], valid[14], discriminative[15] and responsive to change[16]. In Spain, the SRS-22 has been translated into Spanish, which resulted in an instrument apparently equivalent to the original version and suitable for clinical research[17,18].

We studied the SRS-22 Patient Questionnaire outcomes in adolescents who had completed brace treatment or surgical treatment. The aim of this study was to determine if there were short-term differences in HRQoL between adolescents treated with a brace and those treated surgically.

Materials and methods

The Regional Medical Ethical Review Board approved this study.

Study population

Orthopaedic surgeons from 12 hospitals in the Netherlands where patients with AIS are treated were requested to report all consecutive patients who had completed their treatment between June 2002 and September 2004 (n=143). Of these patients, 122 gave their informed consent and were invited, without incentives, to participate in this study; 109 agreed to do so.

The total research group (n=109) consisted of two separate subgroups; patients treated with a brace (B group, n=45) and patients treated surgically (S group, n=64). Brace treatment consisted of a Boston brace, and in five patients additionally a TriaC brace. In the Netherlands, orthopaedic surgeons usually recommend surgery when the Cobb angle reaches 40-45° and further growth of physical height is still expected. All patients had completed treatment; patients in the B group were not expected to be eligible for surgical treatment in the future, as far as could be judged at time of inclusion based on curve characteristics and cessation of growth. In the surgery group, 31 patients were treated with a brace before surgery (BS group) and 32 patients were treated only surgically (OS group); separate analyses were made for those two latter groups.

In the brace group, 12 patients had a single thoracic curve, 9 a single thoracolumbar curve, 5 a single lumbar curve, 1 a double thoracic curve, and 15 had a double thoracic lumbar curve (data on curve type of 3 patients were missing). In the surgery

Table 6.1 Characteristics of the study population

	Total (n=97) Mean (SD)	**Brace** (n=36) (B group) Mean (SD)	**Brace and surgery** (n=31) (BS group) Mean (SD)	**Only surgery** (n=30) (OS group) Mean (SD)	**Surgery total** (n=61) (S group) Mean (SD)
Age (in years) at filling out SRS-22	16.3 (1.6)	16.6 (1.3)	16.2 (1.9)	16.1 (1.6)	16.1 (1.8)
Girls[a]	78 (80%)	32 (89%)	23 (74%)	23 (77%)	46 (75%)
Boys	19 (20%)	4 (11%)	8 (26%)	7 (23%)	15 (25%)
Total bracing period (months)	24.3 (28.0)	38.7 (23.7)	32.6 (30.8)	NA	16.4 (27.1)
Cobb angle at first visit to orthopaedic surgeon (°)[b]	33 (14.3)	24 (8.5)†,‡,§	34 (12.6)†,#	43 (14.5)‡,#	39 (14.3)§
Cobb angle after treatment (°)[b]	32 (10.6)	33 (8.6)	34 (13.3)	30 (11.1)	32 (12.2)
Cobb angle pre-surgery (°)[b]	54 (9.5)	NA	56 (10.7)	52 (8.3)	54 (9.5)
Thoracal curve	29 (30%)	12 (33%)	6 (19%)	11 (37%)	17 (28%)
Thoracolumbar curve	25 (26%)	9 (25%)	7 (23%)	9 (30%)	16 (26%)
Double curvec	42 (44%)	15 (42%)	18 (58%)	10 (33%)	28 (46%)

[a] All groups have significantly more girls than boys,
[b] On average, 71% of the Cobb angles were available,
[c] Double curves were only thoracic lumbar curves, N
NA = not applicable,
†,‡,§ $p < 0.01$; # $p < 0.05$.

group, 17 patients had a single thoracic curve, 16 a single thoracolumbar curve, and 28 had a double thoracic lumbar curve (data on curve type of 3 patients were missing). To optimise similarity of the brace and surgery group, we only used data from patients with thoracic, thoracolumbar and double thoracic lumbar curves for the analysis, because these curves were almost equally distributed in the two study groups.

Table 6.1 shows the characteristics of the study population. Mean Cobb angles were calculated using the largest thoracic, thoracolumbar or lumbar component. At first visit the Cobb angle was 24° (±8.5) in the B group, 34° (±12.6) in the BS group, 43° (±14.5) in the OS group and 39° (±14.3) in the S group (differences are significant between B group and BS group ($p < 0.01$), B group and OS group ($p < 0.01$), B group and S group ($p < 0.01$) and BS group and OS group ($p < 0.05$)). The Cobb angle before surgery was 56° (±10.7) in the BS group, and 52° (±8.3) in the OS group (difference not significant). The Cobb angle after treatment was 33° (±8.6) in the B group, 34° (±13.3) in the BS group, 30° (±11.1) in the OS group, and 32° (±12.2) in the S group (differences between these groups are not significant).

Measurements

All participants received a Dutch version of the SRS-22 Patient Questionnaire by mail, and were requested to fill out the questionnaire themselves. Time span between completing treatment and filling out the questionnaire was completely random; on average, patients of the B group filled out the questionnaire 11 months after completing brace treatment (range 0 – 27 months), and patients of the S group 10 months after surgery (range 0 – 28 months).

Three members of the research team (native Dutch speakers) individually translated the original SRS-22 questionnaire into Dutch. On the basis of these three translations they formed consensus on one version that was back translated into English by a native English speaker. The back translation and the original version were compared and appeared to be similar; after some minor changes, the Dutch version was finalised.

We added one question about general health ("How is your health status now?" on a scale from 0-100 where 100 indicates the best possible health status and 0 indicates the worst possible health status) using the Visual Analogue Scale (VAS)[19].

The Dutch version of the SRS-22 Patient Questionnaire was pre-tested on 47 patients who were also either treated with a brace or surgically, or with a brace followed by surgery. These patients had completed treatment between January 2001 and June 2002, thus before the inclusion period of this study. There were no floor effects, and ceiling effects were in general smaller than in the original version and the Spanish version. Cronbach's alphas were adequate to excellent (function/activity 0.74; pain 0.75; self-image 0.85; mental health 0.90; satisfaction with management 0.71, and total score 0.93) and comparable with the original and Spanish version.

Additionally, the orthopaedic surgeons were given the opportunity to express their personal satisfaction with management for a patient, recorded on a 5-point scale (from very satisfied to very unsatisfied).

Statistical analyses

Mean domain scores and VAS score were calculated for the total group and for all subgroups. For the SRS-22 scores, we used non-parametric tests because SRS-scales are not continuous and show ceiling effects. Furthermore, some scales were skewed. The Mann-Whitney U test was used for the evaluation of significant differences in median domain scores of the SRS-22. Spearman's rank order correlation coefficients were applied to evaluate correlations between SRS-22 scores and time span between completing treatment and filling out the questionnaire. The patients and the surgeons' opinion about satisfaction with management were evaluated and were tested for significant differences by the Wilcoxon Signed Ranks test. Level of significance was defined as $\alpha < 0.05$.

SPSS 11.0.1 was used for the analyses.

Results

There were no significant correlations between the Cobb angles after treatment and SRS-22 scores within the total group, or within the B and S group. Boys and girls showed no significant differences in SRS-22 domain scores within the total group, or within the B and S group. In the total group, patients with thoracolumbar curves had worse function scores than patients with thoracic curves ($p < 0.05$), and patients with thoracic lumbar curves were less satisfied with management than patients with thoracolumbar curves ($p < 0.05$). In the surgery group, patients with thoracic lumbar curves were less satisfied with management than patients with thoracolumbar curves ($p < 0.01$). There were no differences in SRS-22 scores between curve types within the brace group.

In the total group, there is a weak but significant correlation between individual improvement in Cobb angle and satisfaction with management (spearman's rho -0.39, $p < 0.01$). This means that patients who improved most in Cobb angle were more satisfied with management. Although, neither in the B group nor in the S group this correlation was significant, Spearman's rho was much higher in the S group than in the B group (-0.30 vs. 0.01). No other correlation between improvement in Cobb angle and SRS-22 scores were found.

On four domains differences were found between the treatment groups. Table 6.2 shows that patients of the B group had a significantly better mean function score than the BS group, the OS group and the S group. The OS and S group had significantly more pain than the B group. The OS group had significantly better mean self-image/appearance scores than the B group and the BS group. The BS group, the OS group and the S group were significantly more satisfied with management than the B group.

Table 6.2 also shows that data are comparable to (more limited) data of two earlier international studies [14,18].

Table 6.2 Mean (SD) SRS-22 scores for the Dutch, original and Spanish version

Domain	n	Median	Dutch version Mean (SD)	Original version[14] (n=58) Mean (SD)	Spanish version[18] (n=175) Mean
Function/Activity					
Total	97	4.2	4.1 (0.54)		4.2
Brace	36	4.4	4.3 (0.51)†,‡,§		
Brace and surgery	31	4.0	3.9 (0.55)†		
Only surgery	30	4.0	4.0 (0.52)‡		
Surgery, total	61	4.0	3.9 (0.53)§	4.2 (0.64	
Pain					
Total	97	4.4	4.2 (0.75)		4.4
Brace	36	4.7	4.5 (0.57)¶,#		
Brace and surgery	31	4.4	4.1 (0.90)		
Only surgery	30	4.2	4.1 (0.71)¶		
Surgery, total	61	4.4	4.1 (0.81)#	4.2 (0.85)	
Self image/appearance					
Total	97	4.0	4.0 (0.50)		3.9
Brace	36	3.8	3.9 (0.49)¶		
Brace and surgery	31	4.0	3.9 (0.47)#		
Only surgery	30	4.2	4.1 (0.52)¶,#		
Surgery, total	61	4.0	4.0 (0.51)	4.2 (0.60)	
Mental health					
Total	96	4.0	4.0 (0.64)		4.0
Brace	36	4.2	4.1 (0.72)		
Brace and surgery	31	4.0	4.0 (0.60)		
Only surgery	29	4.0	4.0 (0.61)		
Surgery, total	60	4.0	4.0 (0.60)	4.1 (0.76)	
Subtotal score					
Total	97	4.1	4.1 (0.45)		
Brace	36	4.2	4.2 (0.41)		
Brace and surgery	31	4.0	4.0 (0.50)		
Only surgery	30	4.1	4.1 (0.43)		
Surgery, total	61	4.1	4.0 (0.46)		
Satisfaction with management					
Total	97	4.5	4.2 (0.79)		4.4
Brace	36	4.0	3.8 (0.70)†,‡,§		
Brace and surgery	31	4.5	4.3 (0.86)†		
Only surgery	30	5.0	4.7 (0.56)‡		
Surgery, total	61	5.0	4.5 (0.74)§	4.5 (0.80)	
Total score					
Total	97	4.1	4.1 (0.44)		
Brace	36	4.1	4.1 (0.41)		
Brace and surgery	31	4.1	4.0 (0.49)		
Only surgery	30	4.3	4.2 (0.43)		
Surgery, total	61	4.2	4.1 (0.46)		

†,‡,§ $p < 0.01$
¶,# $p < 0.05$

Table 6.3 Spearman's Correlations between SRS-22 scores and time span between completing treatment and filling out the questionnaire

	Time span between completing treatment and filling out SRS-22			
Domain	**Brace group** (n=36) (B group)	**Brace and surgery** (n=31) (BS group)	**Only surgery** (n= 30) (OS group)	**Surgery group** (n=61) (S group)
	Spearman's rho	Spearman's rho	Spearman's rho	Spearman's rho
Function/activity	-0.15	0.47**	0.54**	0.50**
Pain	-0.01	0.22	0.27	0.23
Self-image/appearance	-0.11	-0.09	-0.08	-0.03
Mental Health	-0.18	0.20	0.25	0.23
Subtotal score	-0.15	0.27	0.32	0.30*
Satisfaction with management	-0.12	-0.21	0.19	0.03
Total score	-0.13	0.19	0.35	0.27*

** $p < 0.01$
* $p < 0.05$

Significant correlations between time span between completing treatment and filling out the questionnaire and function, subtotal and total scores were found only in the surgery (sub)group(s) (Table 6.3). Patients with a longer time span had better scores. Within the brace group there were no significant correlations between time span and SRS-22 scores.

There is a significant interaction effect of time span and treatment group on function scores ($p < 0.01$). However, sub-analysis showed no significant differences in function scores between patients of the B group and the S group who filled out the questionnaire at least 12 months after completing treatment (data not shown). For pain, self-image/appearance, mental health and satisfaction with management, no interaction effects of time span and treatment group were found.

The single-item general health measure (VAS score) showed significant differences only between the BS group and the OS group (Table 6.4). The OS group had the highest mean score.

For 10 patients in the brace group and 32 patients in the surgery group, the orthopaedic surgeons' opinion about satisfaction with management results was recorded. Orthopaedic surgeons were more satisfied with management results in pa-

Table 6.4 Single-item general health, scale 0-100

Group	n	Median	Mean (SD)
Total	94	85	83.8 (11.4)
Brace (B group)	35	82	83.3 (12.4)
Brace and surgery (BS group)	30	80*	80.9 (11.8)
Only Surgery (OS group)	29	90*	87.6 (8.9)
Surgery total (S group)	59	85	84.1 (10.9)

* $p < 0.05$

Table 6.5 Patients' and surgeons' reports on a 5-point scale on satisfaction with management

Satisfaction with management	n	Median Patients	Mean (SD) Patients	Median Surgeons	Mean (SD) Surgeons	P-value
Brace (B group)	10	4.0	3.9 (0.99)	5.0	4.6 (0.70)	NS
Brace and surgery (BS group)	15	5.0	4.5 (0.74)	5.0	4.4 (0.74)	NS
Surgery only (OS group)	17	5.0	4.8 (0.39)	5.0	4.5 (1.18)	NS
Surgery total (S group)	32	5.0	4.7 (0.60)	5.0	4.4 (0.98)	NS

NS; not significant

tients treated with a brace than the patients themselves (although the difference was not significant). In patients treated surgically, the opinion of the orthopaedic surgeon about management results was in accordance with the opinion of the patients (Table 6.5).

Discussion

Patients treated surgically were much more satisfied with management than patients treated with a brace, despite Cobb angles after treatment being quite similar in both groups. This difference may partly be attributed to the fact that patients treated surgically had an improved Cobb angle (from 54° before surgery to 32° after surgery), while patients treated with a brace had a larger Cobb angle at the end (32°) than at the first visit to the orthopedic surgeon (24°). However, this difference in satisfaction cannot only be explained by improvement of Cobb angle, since we only found a weak correlation between improvement in Cobb angle and satisfaction in the S group. Climent et al.[17] also found that patients treated with a brace were less satisfied with management than patients treated surgically. A similar trend was seen in a study by Danielsson et al.[12] on HRQoL after follow-up of at least 20 years in patients treated with a brace and patients treated surgically; they reported a more negative effect of the treatment period on patients treated with a brace than on patients treated surgically, but in that study different measures were used than in our study.

Furthermore, in the present study, patients treated only surgically had highest scores on the self-image/appearance domain and on the single-item general health; although significant, these differences were rather small (respectively 0.2 points on a 5-point scale and 7 points on a 100-point scale). In our study, patients scored around 4 points on a 5-point scale in the self-image/appearance domain, which implies that these patients were satisfied. Weinstein et al. concluded in their study that untreated AIS patients had cosmetic concerns[9]. Although different measures were used, it seems that treated patients are more satisfied with self-image than untreated patients. However, it is important to know that Cobb angles of the untreated

patients in the study by Weinstein et al. were much larger than Cobb angles in our study population.

Patients treated with a brace had a significantly higher mean score in the function/activity domain than patients treated surgically (whether or not being braced before surgery). However, there is a positive correlation between time span between surgery and filling out the questionnaire and function scores in the surgery group; after a longer time span function scores are higher (i.e. better), and there were no significant differences in function scores between patients of the B group and the S group who filled out the questionnaire at least 12 months after completing treatment. Obvious reasons for this short-term difference are that patients are recovering from a major operation and that initial restrictions in the patients' physical activities, enforced by their surgeon, are no longer required 6 - 12 months after surgery. These reasons might also explain the worse pain scores found in the surgery group. These findings are in accordance with the findings of Asher et al. in their study of responsiveness of change[16].

In line with our results, other studies also found no major impact of gender[17,20,21], Cobb angle[12,17] and curve type[12,15,17] on HRQoL after treatment.

In patients treated with a brace, orthopaedic surgeons who recorded their satisfaction with management were more satisfied than the patients themselves (difference not significant). A reason for this could be that patients have a different expectation about outcome than their orthopaedic surgeon. If this is the case, patients should be better informed about possible outcomes. However, surgeons agreed about management results with patients treated surgically. Although not all surgeons expressed their opinion about satisfaction with management for all their patients, this result supports the finding that patients treated with a brace are less satisfied with management than patients treated surgically.

Although the SRS-22 is not fully validated for children younger than 18 years old, mean domain scores in the present study corresponded with mean domain scores found by Asher et al.[14] and Bago et al.[18] Cronbach's alphas in the Dutch version were good to excellent and comparable with the original version, there were no floor effects and there were less ceiling effects than in the original version. For complete validation of the Dutch version of the SRS-22 Questionnaire, test-retest reliability and responsiveness to change should be further evaluated.

Our design was limited to a cross sectional assessment after treatment. It means we were not able to evaluate whether differences in HRQoL between the groups existed before treatment, nor were we able to evaluate whether these possible differences had influenced the results after treatment. For instance, patients in the brace group and the surgery group differ in some respects, e.g. Cobb angle at baseline differed significantly between the brace group and the surgery group. This difference is probably also responsible for different expectations and management issues and might have influenced HRQoL, and in particular satisfaction with management. Longitudinal data on different treatment groups (i.e. under observation, brace treatment, or surgery) could provide more insight into the impact of baseline characteristics, management issues and expectations on HRQoL.

In conclusion, the idea that conservative treatment is to be preferred to surgical treatment is not supported by differences in HRQoL after treatment in our adolescent patients with idiopathic scoliosis. On the contrary, patients treated with a brace were less satisfied with management results than patients treated surgically. At the start of the 21st century with changing adolescent culture and experience, such perceptions are very important in this particular phase in a teenager's life.

These findings should be taken into account in the debate about the preferred option for treatment in adolescent idiopathic scoliosis. Other issues are also important in this discussion, especially regarding a decisive conclusion about the degree of effectiveness of bracing[4,6]. Concerning HRQoL, further research on this debate should also focus on quality of life during brace treatment or observation, the pre-surgery period, and on the long-term follow-up after treatment, because short-term results are important, but not conclusive.

Acknowledgements

This study was funded by the Netherlands Organisation for Health Research and Development (ZonMw) Grant # 2200.0217.

References

1. Moe J, Lonstein J. Idiopathic scoliosis. In: Lonstein J, editor. Moe's textbook of scoliosis and other spinal deformities. 3th ed. Philadelphia: Saunders; 1995. p. 219-256.
2. Scoliosis Research Society. Morbidity and Mortality Committee report. Vancouver: Scoliosis Research Society; 1987.
3. Dickson RA, Weinstein SL. Bracing (and screening)--yes or no? *J Bone Joint Surg Br* 1999;81:193-8.
4. Donnelly MJ, Dolan LA, Weinstein SL. How effective is bracing for treatment of scoliosis? *Am Fam Physician* 2003;67:32.
5. Goldberg CJ, Moore DP, Fogarty EE, et al. Adolescent idiopathic scoliosis: the effect of brace treatment on the incidence of surgery. *Spine* 2001;26:42-7.
6. Korfage IJ, Juttmann RE, Das BV, et al. [Idiopathic scoliosis in adolescents; an inventory into the possibilities of studying the efficacy of screening and treatment] Idiopathische scoliose bij adolescenten; inventarisatie van mogelijkheden van onderzoek naar de effectiviteit van screening en behandeling. *Ned Tijdschr Geneeskd* 2002;146:1228-33.
7. Guyatt GH, Feeny DH, Patrick DL. Measuring health-related quality of life. *Ann Intern Med* 1993;118:622-9.
8. Higginson IJ, Carr AJ. Measuring quality of life: Using quality of life measures in the clinical setting. *BMJ* 2001;322:1297-300.
9. Weinstein SL, Dolan LA, Spratt KF, et al. Health and function of patients with untreated idiopathic scoliosis: a 50-year natural history study. *JAMA* 2003;289:559-67.
10. Ascani E, Bartolozzi P, Logroscino CA, et al. Natural history of untreated idiopathic scoliosis after skeletal maturity. *Spine* 1986;11:784-9.
11. Danielsson AJ, Nachemson AL. Back pain and function 22 years after brace treatment for adolescent idiopathic scoliosis: a case-control study-part I. *Spine* 2003;28:2078-85.
12. Danielsson AJ, Wiklund I, Pehrsson K, et al. Health-related quality of life in patients with adolescent idiopathic scoliosis: a matched follow-up at least 20 years after treatment with brace or surgery. *Eur Spine J* 2001;10:278-88.
13. Haher TH, Gorup JM, Shin TM, et al. Results of the Scoliosis Research Society Instrument for Evaluation of Surgical Outcome in Adolescent Idiopathic Scoliosis. A Multicenter Study of

244 Patients. *Spine* 1999;24:1435-1440.
14. Asher M, Min Lai S, Burton D, et al. The reliability and concurrent validity of the scoliosis research society-22 patient questionnaire for idiopathic scoliosis. *Spine* 2003;28:63-9.
15. Asher M, Min Lai S, Burton D, et al. Discrimination validity of the scoliosis research society-22 patient questionnaire: relationship to idiopathic scoliosis curve pattern and curve size. *Spine* 2003;28:74-8.
16. Asher M, Min Lai S, Burton D, et al. Scoliosis research society-22 patient questionnaire: responsiveness to change associated with surgical treatment. *Spine* 2003;28:70-3.
17. Climent JM, Bago J, Ey A, et al. Validity of the Spanish Version of the Scoliosis Research Society-22 (SRS-22) Patient Questionnaire. *Spine* 2005;30:705-709.
18. Bago J, Climent JM, Ey A, et al. The Spanish version of the SRS-22 patient questionnaire for idiopathic scoliosis: transcultural adaptation and reliability analysis. *Spine* 2004;29:1676-80.
19. Brooks R. EuroQol: the current state of play. *Health Policy* 1996;37:53-72.
20. Helenius I, Remes V, Yrjonen T, et al. Does gender affect outcome of surgery in adolescent idiopathic scoliosis? *Spine* 2005;30:462-7.
21. Sucato DJ, Hedequist D, Karol LA. Operative correction of adolescent idiopathic scoliosis in male patients. A radiographic and functional outcome comparison with female patients. *J Bone Joint Surg Am* 2004;86-A:2005-14.

Patients' preferences for scoliosis brace treatment: a discrete choice experiment

7

Eveline M Bunge & Esther W de Bekker-Grob*, Frans C van Biezen, Marie-Louise Essink-Bot, Harry J de Koning

Submitted

* Both authors contributed equally to this work

Abstract

Study Design: Discrete choice experiment.
Objective: To evaluate how effective brace treatment should be in preventing surgery for idiopathic scoliosis patients to consider the brace as a reasonable form of treatment during several years of puberty.
Summary of Background Data: The effectiveness of brace treatment in idiopathic scoliosis patients has not been established in randomized controlled trials. Treatment with a brace can be quite bothersome. Patients' preferences for brace treatment are unknown.
Methods: A total of 197 patients who had completed treatment (brace and/or surgery) for scoliosis were approached for the study, of which 135 gave informed consent. A discrete choice experiment was designed in which patients had to choose between hypothetical brace treatment profiles that differed in four treatment attributes: effectiveness, invisibility, comfort, and treatment duration. A multinomial logit regression model was used to analyze the relative importance of these treatment attributes. Subgroup analyses were conducted for brace-only patients, brace-surgery patients, and surgery-only patients.
Results: The response rate was 85.9% (116/135). All treatment attributes proved to be important for patients' choices. Patients were prepared to wear a Boston brace for at least three years if the brace would reduce the need for surgery by 25%.
Conclusions: The patients in our study stated to be prepared to undergo brace treatment. Effectiveness and comfort in wearing a brace played the most important role in their choices. These results are promising if randomized controlled trials would conclusively establish that bracing is effective in reducing the need for surgery.

Introduction

Idiopathic scoliosis (IS) is defined as a lateral curvature of the spine with a minimal Cobb angle of 10º of unknown origin. The Cobb angle is the angle between the upper most inclined vertebra and the lower most inclined vertebra. Besides a lateral curvature of the spine, there is a fixed rotation of one or more vertebrae, and a rotational deformation of that vertebra[1]. About 0.3% of all children aged between 10 and 16 years have IS that progresses to curvatures with Cobb angles over 20-25 degrees[2]. In this situation, the chance is small that the curvature will disappear spontaneously, and brace treatment is usually applied. Brace treatment is supposed to prevent further progression of the curvature and thereby the need for surgery, which is indicated when a patient has a Cobb angle of more than about 45-50 degrees[1]. Some authors conclude that bracing is effective[3,4], while others conclude that the effectiveness is doubtful[5,6]. The designs of these studies were however not convincing; no randomized controlled trials (RCTs) have been done[7]. In both the US and the Netherlands, an RCT on (Boston) bracing IS patients was designed; in the US the trial is currently running (BrAIST)[8].

Treatment with a brace, as well as surgical treatment for scoliosis, can be rather bothersome[9,10]. In case of brace treatment, patients (usually aged 10-16 years) have to wear the brace for 18-23 hours a day, during several years of puberty[1]. The brace can be (very) uncomfortable to wear, and is practically always visible to others. After treatment, no major differences in health-related quality of life (HRQoL) were found between patients who were treated by bracing or who needed surgery[11,12].

The aim of this study was to evaluate how effective brace treatment should be for IS patients to consider the brace as a reasonable form of treatment. A discrete choice experiment (DCE) was used. DCEs have increasingly been used in health care as an approach to elicit patient preferences[13-17]. We evaluated whether there were differences in preferences between patients who had completed treatment with a brace, patients who were treated with a brace followed by surgery, and patients who were only treated surgically.

Materials and Methods

The study was conducted according to the principles of the Declaration of Helsinki. Under Dutch law, observational health surveys are exempted from approval from a Medical Ethics Committee.

Study sample

The 197 patients who gave consent for participation in the former NESCIO (Netherlands Evaluation Study on Screening for scoliosis) study[11], were approached again for their consent to send them a new questionnaire. These patients had completed treatment with a brace, surgery, or with a brace followed by surgery, and were recruited in 12 Dutch hospitals. For the braced patients, Boston braces had been used. Four weeks after the first mailing, a reminder was sent. A total of 135 patients gave

informed consent regarding the questionnaire; for seven patients we had the incorrect address, one had moved to another country, and two did not give consent. The non-response rate at this stage of the study was 26.4%.

Variables

The following data concerning patient characteristics were collected: age at filling out the questionnaire, type(s) of treatment, highest current or completed education, Cobb angle at diagnosis, Cobb angle after treatment and, if applicable, total bracing period. Self-rated general health was assessed on a visual analogue scale (VAS) from 0 to 100, where 100 indicates the best possible health status and 0 indicates the worst possible health status[18].

Discrete Choice Experiment

DCEs assume that a given healthcare intervention or treatment can be described by its characteristics (attributes) and that any subject's preferences for an intervention or treatment are determined by the levels of the attributes[17]. Attributes should be identified beforehand as potentially important for the choice of an intervention or treatment[19]. The relative importance of attributes and the trade-offs patients make between these can be assessed when patients are offered a series of choices between brace treatment alternatives that have different combinations of attribute levels[20].

We identified four attributes of brace treatment, with specific focus on the attributes of the Boston brace. The attributes and the attribute levels were chosen based on literature, expert interview (specialist in orthopaedics), and personal interviews with patients who had experienced brace treatment and/or surgery for scoliosis (i.e., the target group). The attributes were: effectiveness of brace treatment, brace comfort, total treatment duration, and visibility of the brace (Table 7.1).

Table 7.1 Attributes and attribute levels for brace treatment

Attributes and attribute levels	Coefficients in regression analysis
Reduction in risk of undergoing surgery (%) (EFFECTIVENESS) 12.5 25 50 75	β_1
Invisible when worn (INVISIBLE) No (0) Yes (1)	β_2
Total treatment duration (years) (TIME) 2 4 6 8	β_3
Wearing comfort (WEARING) No (0) Yes (1)	β_4

	Brace treatment A	Brace treatment B	No brace treatment
Total treatment duration	4 years	6 years	0 years
Brace is invisible to wear	No	Yes	Not applicable
Risk of surgery	Reduces from 40% to 20%	Reduces from 40% to 10%	Remains 40%
Brace is comfortable to wear	Yes	No	Not applicable
Which brace do you prefer?	☐ A	☐ B	☐ None

Figure 7.1 Example of a choice set as presented in the questionnaire

The combination of attributes and attribute levels (2 attributes with 4 levels, and 2 attributes with 2 levels) resulted in 64 hypothetical brace treatment profiles ($4^2 * 2^2$). For practical reasons, not all of these could be used in a questionnaire. Therefore, we generated a sample of hypothetical brace treatment profiles from all these 64 brace treatment profiles for the questionnaire (i.e., we used a fractional factorial design)[21]. Such a sample must be large enough to estimate at least all main effects in a regression analysis. In our case, a sample of 16 hypothetical brace treatment profiles was sufficient to estimate at least all main effects in a regression analysis[22]. Based on these 16 profiles, choice sets were created. Each choice set consisted of two brace treatment profiles between which the patients could choose. If the patients considered both brace treatments as not acceptable, the patient could opt-out. Figure 7.1 shows an example. The first brace treatment profile (i.e. Brace treatment A) of each choice set was always one of the 16 hypothetical brace treatment profiles selected for the fractional factorial design. We created the second brace treatment profile (i.e. Brace treatment B) of each choice set by means of a specific technique (cycle 'fold-over') to ensure minimal overlap of attribute levels (i.e., Brace treatment A and Brace treatment B always had different attribute levels in each choice set). Too much overlap would reduce the information obtained on trade-offs between attribute levels.

Before participants started with the 16 choice sets of the DCE in the questionnaire, they were asked to rank the four attributes of a hypothetical brace treatment (total treatment duration of two years, 30% risk reduction of surgery, brace is comfortable to wear, and invisible under clothing) from most important to least important. The questionnaire included a detailed written description of each attribute and its levels. While answering the choice sets of the DCE, the patients had to imagine that they were an 11-year-old patient with scoliosis that is eligible for brace treatment. A dominant choice set was included in the questionnaire to test for rationality (i.e. a choice set including one brace treatment profile characterized by logically preferable levels on all attributes). Finally, patients who had been treated with a brace (whether or not

before surgery) were asked if they would choose for brace treatment again if they would face the same situation. The questionnaire was pilot tested to check for any problems in interpretation and face validity (n=10).

Analyses

Because some data were skewed and for some variables there were less than 30 patients in a subgroup, non-parametric tests (Mann Whitney U-test) were used to determine significant differences in age, education, Cobb angle, brace duration and VAS between the different subgroups.

Data from respondents who failed the dominant question in the DCE were excluded from further analyses. The DCE was analyzed by taking each choice among the three options (two brace treatment alternatives, and a no brace treatment option) as an observation. The remaining observations were analyzed by a multinomial logit regression model. Assuming that all attributes have an independent influence on a patient's preference, the following model was estimated:

$$V = \beta_0 + \beta_1 \text{TIME} + \beta_2 \text{ EFFECTIVENESS} + \beta_3 \text{INVISIBLE} + \beta_4 \text{COMFORT, where}$$

- V represents the observed utility for brace treatment as derived from the respondents' choice behaviour;
- β_0 is a constant reflecting the respondents' preference for receiving brace treatment relative to no brace treatment;
- β_1 to β_4 are coefficients that indicate the relative importance of each attribute (Table 7.1).

The absolute values of V have a relative interpretation, i.e., an observed utility for brace treatment with higher value of V is preferred over a brace treatment with lower value of V. A positive utility value of a specific brace profile indicates a preference for that treatment over no treatment. The sign of a coefficient reflects whether the attribute has a positive or negative effect on utility. The value of a coefficient indicates the relative contribution of the corresponding attribute to total utility. For a correct interpretation of the comparison of the coefficients of the attributes, we need to consider the different units of measurement.

A statistically significant coefficient indicates that the respondents considered the attribute important in their choices. A priori, we expected all attributes to contribute to patients' choices, and we expected that only the attribute 'total treatment duration' would have a negative effect (i.e., a negative sign). The utility from the no brace treatment option was normalized to zero.

Subgroup analyses were conducted by using interaction terms in the multinomial logit regression model to assess whether brace-only patients, brace-surgery patients, and surgery-only patients had different preferences.

Results

Respondents

The response rate was 116/135 i.e. 86%. In total, 113 of 116 patients (97%) passed the dominant question. Of these 113 respondents, 41 had been treated with a brace only (brace-only group), 41 had been treated with a brace followed by surgery (brace-surgery group), and 31 had been treated surgically only (surgery-only group). The respondents of each subgroup had a mean age of about 20 years at the time of completion of the DCE questionnaire. Table 7.2 shows the characteristics of the respondents. There were no significant differences between the subgroups, except, as expected, the Cobb angle at diagnosis. Table 7.3 shows the direct ranking of the attributes from most important to least important. Effectiveness and comfort of the brace were considered the most important attributes.

Table 7.2 Characteristics of the study population

	Brace-only (n=41)	Brace-surgery (n=41)	Surgery-only (n=31)
	n (%)	**n (%)**	**n (%)**
Girls	36 (87.8)	37 (90.2)	27 (87.1)
Lower educational level	4 (9.8)	7 (17.5)	2 (6.5)
Intermediate educational level	18 (43.9)	21 (52.5)	19 (61.3)
Higher educational level	19 (46.3)	12 (30.0)	10 (32.3)
	Mean (SD)	**Mean (SD)**	**Mean (SD)**
Age at survey (years)	20.2 (1.6)	19.5 (2.5)	19.7 (2.4)
Cobb angle at diagnosis (°)[a]	27 (10.3)[1,2]	34 (13.8)[1,3]	50 (15.5)[2,3]
Cobb angle after treatment (°)[a]	31 (10.2)	30 (13.3)	34 (10.1)
Total bracing period (years)[b]	2.7 (1.8)	2.1 (1.7)	NA
Self-rated health (VAS)[c]	77.0 (13.5)	78.4 (11.0)	74.8 (13.9)

[1,3] $p < 0.05$
[2] $p < 0.01$
[a] on average, 73.5% of the Cobb angles were available
[b] for five brace-only patients and five brace-surgery patients data on total bracing period were missing
[c] for one brace-only patient and for one brace-surgery patient data on self-rated general health were missing

Table 7.3 Direct ranking of the attributes from most important to least important

	Effectiveness %	Comfort %	Invisible %	Time %
Brace-only (n=39)	53.8	23.1	20.5	2.6
Brace-surgery (n=40)	35.0	40.0	22.5	2.5
Surgery-only (n=31)	51.6	25.8	9.7	12.9

Table 7.4 Preferences for brace treatment per patient group

Attributes	All patients		Brace-only patients (BO)		Brace-surgery patients (BS)		Surgery only patients (SO)		Differences between patients groups (p-value of the interaction)		
	Coefficient[a]	p-value	Coefficient[b]	p-value	Coefficient[c]	p-value	Coefficient[d]	p-value	BO versus BS	BO versus SO	BS versus SO
Constant (brace treatment)	0.79	**	1.99	**	0.60		-0.12		**	**	
Treatment duration (per 1 yr)	-0.35	**	-0.51	**	-0.33	**	-0.29	**	*	**	
Invisible	0.82	**	0.94	**	0.82	**	0.78	**			
Effectiveness (per 10% risk reduction of surgery)	0.40	**	0.56	**	0.35	**	0.40	**	**	*	
Comfort	1.16	**	1.29	**	1.20	**	1.05	**			

* $p < 0.05$
** $p < 0.01$
[a] Number of observations 5,376 (113 patients x 16 choices x 3 options per choice, minus 48 missing values)
[b] Number of observations 1,962 (41 patients x 16 choices x 3 options per choice, minus 6 missing values)
[c] Number of observations 1,956 (41 patients x 16 choices x 3 options per choice, minus 12 missing values)
[d] Number of observations 1,458 (31 patients x 16 choices x 3 options per choice, minus 30 missing value)

DCE results

Most patients indicated that they found the DCE questions (very) clear, and had no difficulties in completing the questionnaire. All coefficients were significant (Table 7.4, column 3); thus, all attributes were important for patients' choices, and all signs were consistent with a priori expectations. The positive constant term suggests that the patients preferred brace treatment over no brace treatment if all attributes were set to zero (i.e. without knowing the effectiveness, total treatment duration, comfort, and invisibility); thus, as a total group, our patients had an unconditionally positive attitude towards brace treatment.

Patients weighted comfortable wearing of a brace about 1.4 times more important than invisibility of wearing of a brace (Table 7.4, column 2; the ratio between 1.16 and 0.82 equals 1.4).

As an example, the utility of a hypothetical brace treatment (total treatment duration of 5 years, 25% reduction in the risk of undergoing surgery, brace is comfortable to wear, and invisible under clothing; using the coefficients of Table 7.4, column 2) for the participants in the present DCE can be estimated as:

V = 0.79 - 5*0.35(TIME) + 0.82(INVISIBLE) + 2.5*0.40(EFFECTIVENESS) + 1.16(COMFORT) = 2.02; i.e., a positive value, meaning that the participants prefer this particular brace treatment over no treatment.

Subgroup analyses

The results of multinomial logit regression modeling of data from the three subgroups and between the three subgroups are presented in Table 7.4 (columns 4-12). The constant term was only significant for the brace-only group (Table 7.4, columns 4-5); thus, brace-only patients had an unconditionally and significantly positive attitude towards brace treatment, while this was not the case for brace-surgery and surgery-only patients.

If the effectiveness of the brace treatment was 30% (just like the hypothetical brace treatment in our direct ranking exercise) the brace-only group and the surgery-only group considered the effectiveness of brace treatment to be the most important attribute with a coefficient magnitude of 1.68 (3*0.56) and 1.20 (3*0.40) respectively followed by comfort of the brace with a coefficient magnitude of 1.29 and 1.05 respectively (Table 7.4, columns 4 and 8). The brace-surgery patients considered comfort of the brace as the most important attribute with a coefficient magnitude of 1.20 followed by effectiveness of the brace treatment with a coefficient magnitude of 1.05 (3*0.35) (Table 7.4, column 6).

There were no significantly different preferences between brace-surgery patients and surgery-only patients (Table 7.4, columns 11-12). Brace-only patients were significantly less prepared to undergo long treatment duration compared to brace-surgery patients and surgery-only patients, but were more prepared to wear a less effective brace.

Brace-only patients chose significantly more often for brace treatment again if they would be in the same situation than did patients who were treated with a brace followed by surgery (70.0% vs. 24.4%, respectively).

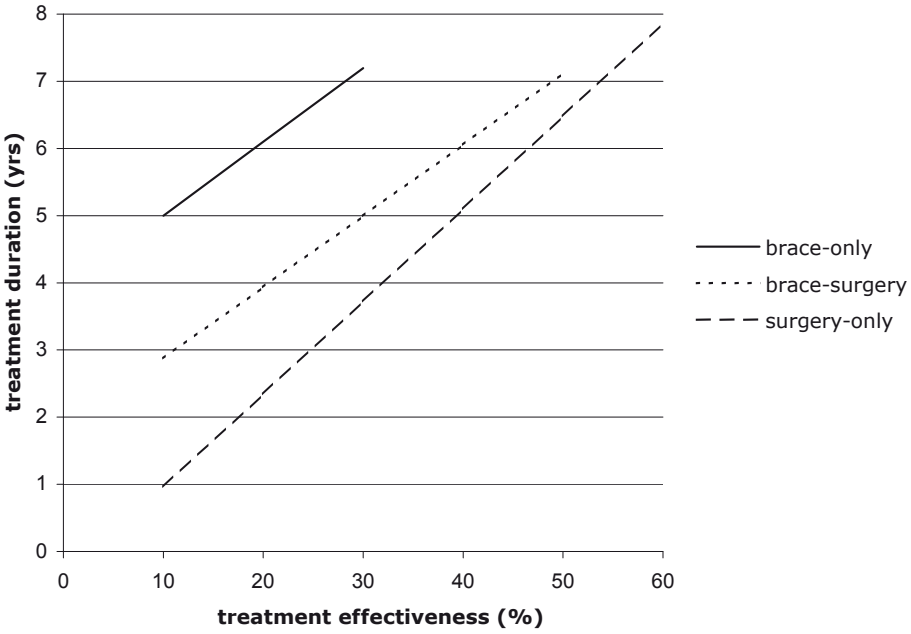


Figure 7.2 Regression lines showing the relationship between effectiveness (%) and acceptation of maximal treatment duration (years) of bracing for brace-only, brace-surgery, and surgery-only patients.

We estimated that our patients were prepared to wear a Boston brace for 5 years (from age 11 to 16 years) if the brace would reduce the risk of needing surgery by at least 24% and the brace was visible and uncomfortable to wear (0 (utility)=< 0.79(constant) - 5*0.35(total treatment duration) + 0*0.82(invisible) + 2.4*0.40(effectiveness) + 0*1.16(comfort)). If the brace would be invisible and comfortable to wear, they were prepared to wear it for over 10 years.

Figure 7.2 shows the relationship between effectiveness (%) of a brace and acceptance of maximal treatment duration (years) of bracing for brace-only, brace-surgery, and surgery-only patients. If the brace would reduce the risk of needing surgery by 25%, then brace-only, brace-surgery, and surgery-only patients were prepared to wear the brace for 6.6, 4.5, and 3.0 years, respectively. Or, the other way around, they were prepared to wear a Boston brace for 5 years if the brace would reduce the risk of needing surgery by 10%, 30% and 39%, respectively.

Discussion

The present study shows that our patients, including scoliosis patients who previously underwent surgery, stated to be prepared to undergo brace treatment. Effectiveness and comfortable wearing of a brace played the most important role in the patients' choices. These patients were prepared to wear a Boston brace for at least three years

if the brace would reduce the need for surgery by 25%. This result may seem dissimilar to other studies reporting that compliance with brace treatment is a problem[23,24]. Nevertheless our results are promising, especially if future research would establish that bracing is effective in reducing the need for surgery by at least 25%.

There are no previous DCEs investigating IS patients' preferences for brace treatment with which to compare our data. The present scores for general health might be somewhat lower than could be expected, based on an earlier study on HRQoL in almost the same patient group (74.8-77.0 vs. 80.9-87.6)[11].

The 'real' risk of progression and the need for surgery in case of no brace treatment is not well established. Surgical rates of 0-38% have been reported, with higher rates in not braced patients than in braced patients; however, these studies were not based on randomized controlled trials [25-27]. By including hypothetical levels of effectiveness we can extend the relative importance of the effectiveness of brace treatment in comparison with other attributes of brace treatment.

This study has illustrated the feasibility of DCE to elicit patients' preferences for brace treatment. A reasonable proportion of potential respondents agreed to participate in the investigation, and only 3 of 116 failed the dominant question. This study therefore adds to the available literature on the usefulness of DCE to investigate preferences for treatment[28-30]. Comparing our DCE results with the results of the direct ranking exercise in our questionnaire, in both methods the brace-only group and the surgery-only group considered the effectiveness of brace treatment to be the most important attribute followed by comfort of the brace, whereas the brace-surgery patients considered comfort of the brace as the most important attribute followed by effectiveness of the brace treatment. This result supports convergent validity of the DCE results.

A limitation is that we used a main effects only design, assuming that all attributes were value-independent of each other (i.e., all interactions between attributes were zero). This may, however, be reasonable since main effects typically account for 70-90% of the explained variance in DCE[22]. Another limitation is that this DCE used attributes of the Boston brace only, because that is the most used brace in the Netherlands at present. It is conceivable that other brace types, like SpineCor braces or TriaC may be preferred differently, because these are less rigid than the Boston brace.

All patients in our study population had experienced treatment for scoliosis and therefore knew what they were choosing for in this DCE. This strength is, however, also a limitation. These patients may have 'defended' their own treatment (i.e., cognitive discordance), and this may have biased the results. For example, brace-only patients had no experience of surgery and may have been more afraid of surgery than the surgery patients and may, therefore, have been more willing to wear a brace. Brace-surgery patients have experienced both forms of treatments; however, this group may have been disappointed in brace treatment because eventually they had to undergo surgery. Surgery patients might be too positive towards surgery, because their surgery had been successful. The differences in the preferences we found were in the expected directions, i.e., the surgery-only patients expressed the least positive preferences for brace treatment. However, all patient groups expressed posi-

tive preferences for brace treatment. Therefore, we may conclude that the general attitude for brace treatment was positive. Regardless of the differences between the patient groups in this study, new IS patients who have to decide about brace treatment might have other preferences. The current results could gain importance if it were possible to ask new IS patients what preferences they state and then compare their stated preference with their actual behavior later on.

In conclusion, this DCE shows that patients who had completed treatment for IS by brace, surgery, or both, were highly prepared to undergo brace treatment; effectiveness and comfort in wearing of a brace played the most important role in their choices.

Acknowledgments

The patients who participated in this study were initially recruited by the following orthopaedic surgeons (all in the Netherlands): HD Been, MD, PhD, Academic Medical Center, Amsterdam; LNJEM Coene, MD, PhD, HaGa Hospital, Den Haag; AJ de Gruijter, MD, PhD, Medical Center Alkmaar, Alkmaar; LWL de Klerk, MD, PhD, Erasmus MC – University Medical Center Rotterdam, Rotterdam; M de Kleuver, MD, PhD, St. Maartenskliniek, Nijmegen; PHJ Klop, MD, Ziekenhuis Walcheren, Vlissingen; HJA Kruls, MD, PhD, Amphia Ziekenhuis, Breda; PJM van Loon, MD, Rijnstate Hospital, Arnhem; F de Nies, MD, Onze Lieve Vrouwe Gasthuis, Amsterdam; JEH Pruijs, MD, PhD, University Medical Center Utrecht, Utrecht; MP Teeuwen, MD, Oosterscheldeziekenhuis, Goes, and University Hospital Maastricht, Maastricht.

We are very grateful to the patients who participated in this study.

References

1. Campbell W, Canale ST, Daugherty K, et al. Scoliosis and Kyphosis. In: ST C, editor. *Campbell's Operative Orthopaedics*. St. Louis, MO: Mosby, 2003:1751-1984.
2. Weinstein SL. Natural history. *Spine* 1999;24:2592-600.
3. Nachemson AL, Peterson LE. Effectiveness of treatment with a brace in girls who have adolescent idiopathic scoliosis. A prospective, controlled study based on data from the Brace Study of the Scoliosis Research Society. *J Bone Joint Surg Am* 1995;77:815-22.
4. Rowe DE, Bernstein SM, Riddick MF, et al. A meta-analysis of the efficacy of non-operative treatments for idiopathic scoliosis. *J Bone Joint Surg Am* 1997;79:664-74.
5. Dolan LA, Weinstein SL. Surgical rates after observation and bracing for adolescent idiopathic scoliosis: an evidence-based review. *Spine* 2007;32:S91-S100.
6. Goldberg CJ, Dowling FE, Hall JE, et al. A statistical comparison between natural history of idiopathic scoliosis and brace treatment in skeletally immature adolescent girls. *Spine* 1993;18:902-8.
7. Weinstein SL, Dolan LA, Cheng JC, et al. Adolescent idiopathic scoliosis. *Lancet* 2008;371:1527-37.
8. http://clinicaltrials.gov/ct2/show/NCT00448448.
9. Matsunaga S, Hayashi K, Naruo T, et al. Psychologic management of brace therapy for patients with idiopathic scoliosis. *Spine* 2005;30:547-50.
10. Tones M, Moss N, Polly DW, Jr. A review of quality of life and psychosocial issues in scoliosis. *Spine* 2006;31:3027-38.

11. Bunge EM, Juttmann RE, de Kleuver M, et al. Health-related quality of life in patients with adolescent idiopathic scoliosis after treatment: short-term effects after brace or surgical treatment. *Eur Spine J* 2007;16:83-9.
12. Danielsson AJ, Wiklund I, Pehrsson K, et al. Health-related quality of life in patients with adolescent idiopathic scoliosis: a matched follow-up at least 20 years after treatment with brace or surgery. *Eur Spine J* 2001;10:278-88.
13. Gyrd-Hansen D, Sogaard J. Analysing public preferences for cancer screening programmes. *Health Econ* 2001;10:617-34.
14. Ryan M, Hughes J. Using conjoint analysis to assess women's preferences for miscarriage management. *Health Econ* 1997;6:261-73.
15. Ryan M, Farrar S. Using conjoint analysis to elicit preferences for health care. *BMJ* 2000;320:1530-3.
16. Sculpher M, Bryan S, Fry P, et al. Patients' preferences for the management of non-metastatic prostate cancer: discrete choice experiment. *BMJ* 2004;328:382.
17. de Bekker-Grob EW, Essink-Bot ML, Meerding WJ, et al. Patients' preferences for osteoporosis drug treatment: a discrete choice experiment. *Osteoporosis Int* 2008;19:1029-37.
18. Brooks R. EuroQol: the current state of play. *Health Policy* 1996;37:53-72.
19. Farrar S, Ryan M, Ross D, et al. Using discrete choice modelling in priority setting: an application to clinical service developments. *Soc Sci Med* 2000;50:63-75.
20. Ryan M, Scott DA, Reeves C, et al. Eliciting public preferences for healthcare: a systematic review of techniques. *Health Technol Assess* 2001;5:1-186.
21. Hahn GJ, Shapiro SS. A catalog and computer program for the design and analysis of orthogonal symmetric and asymmetric fractional factorial experiments. Schenectady, NY, USA: General Electric Research and Development Center, 1966.
22. Louviere JJ, Hensher DA, Swait JD. *Stated choice methods: analysis and application.* Cambridge: Cambridge University Press, 2000.
23. DiRaimondo CV, Green NE. Brace-wear compliance in patients with adolescent idiopathic scoliosis. *J Pediatr Orthop* 1988;8:143-6.
24. Houghton GR, McInerney A, Tew A. Brace compliance in adolescent idiopathic scoliosis. *J Bone Joint Surg (Br)* 1987;69-B:852.
25. Danielsson AJ, Hasserius R, Ohlin A, et al. A prospective study of brace treatment versus observation alone in adolescent idiopathic scoliosis: a follow-up mean of 16 years after maturity. *Spine* 2007;32:2198-207.
26. Fernandez-Feliberti R, Flynn J, Ramirez N, et al. Effectiveness of TLSO bracing in the conservative treatment of idiopathic scoliosis. *J Pediatr Orthop* 1995;15:176-81.
27. Miller JA, Nachemson AL, Schultz AB. Effectiveness of braces in mild idiopathic scoliosis. *Spine* 1984;9:632-5.
28. Lloyd A, McIntosh E, Price M. The importance of drug adverse effects compared with seizure control for people with epilepsy: a discrete choice experiment. *Pharmacoeconomics* 2005;23:1167-81.
29. Mahadevia P, Shah S, Mannix S, et al. Willingness to pay for sensory attributes of intranasal corticosteroids among patients with allergic rhinitis. *J Manag Care Pharm* 2006;12:143-51.
30. Lancsar EJ, Hall JP, King M, et al. Using discrete choice experiments to investigate subject preferences for preventive asthma medication. *Respirology* 2007;12:127-36.

General discussion

8

Answering the research questions

Research question 1: Does screening for scoliosis lead to earlier detection and to a reduction in the need for surgery?

In a follow-up study amongst 125 patients with idiopathic scoliosis (IS), patients who were detected through screening, were detected in a significantly earlier stage of the clinical course (28° vs. 40° Cobb, $p < 0.01$), and were significantly younger at diagnosis (10.9 years ±2.5 vs. 13.1 years ±2.5, $p < 0.01$), than patients who were detected otherwise. This difference was clinically relevant, because patients with a Cobb angle of about 28° are still eligible for treatment with a brace to prevent further progression and thereby to prevent surgery, while patients with a Cobb angle of 40° have almost reached the criterion for surgery.

The screen-detected patients had a 73% lower chance on having had surgery than the otherwise-detected patients. This means that two prerequisites for an effective scoliosis screening programme have been met, namely earlier detection and less surgery for the screen-detected patients. This gives valuable information on the potential effectiveness of this screening programme. However, this design is susceptible to bias. Length bias can occur because patients with slow progressive curves have more chance on being detected by screening, and have less chance of needing surgery than patients with rapidly progressive curves. The patients with slow progressive curves will be overrepresented in the screen group and thereby the effect of screening will be overestimated. Over-treatment bias can occur, because in a screening situation more children with scoliosis will be detected than in a situation without screening. This can lead to unnecessary treatment of children who would not need treatment if they had not been screened.

Therefore, a case control study was performed to estimate the effectiveness of screening for scoliosis. The case group consisted of IS patients treated surgically and the control group consisted of a random sample of the source population. In the Netherlands, there is considerable variation in exposure to screening for scoliosis, which is a prerequisite for a case control study. If screening for scoliosis would be effective in reducing surgery, then one should expect that patients who needed surgery were less often screened than the general population. We could not establish that screening had resulted in a reduction in the need for surgery. The patients who needed surgery were not significantly differently screened than the control group (OR: 1.44; 95%CI: 0.77-2.68). This was found for screening at all ages: screening at 11 to 14 years of age, the age category in which screening is usually being advised, led to an OR of 0.64; 95%CI: 0.34-1.19.

Research question 2: What is the effectiveness of bracing patients with idiopathic scoliosis?

To establish the effectiveness of bracing patients with IS, a randomized controlled trial (RCT) was designed. We aimed at including 100 patients within one and a half years, 50 would be randomized to the intervention arm and 50 to the control arm. The intervention arm would be treated with a Boston brace for 18-23 hours a day. The control arm would initially not be braced. Every four months, each patient would have

a physical examination and an X-ray of the spine. The main outcomes would be the Cobb angle two years after inclusion, health-related quality of life and costs.

A pilot study had been performed to investigate whether patients and their parents would be willing to participate in such a trial. In total, 87% of 21 patients (95% CI: 57-91%) and 70% of the parents (95% CI: 48-85%) said they would be willing to participate in such a trial.

To our surprise, hardly any patients were included in the trial. One and a half year after the start, we had only included 4 patients in the trial; 15 patients refused to participate (of which one shortly after informed consent) and at least 7 patients had been missed to be invited to participate in the trial. A lot less eligible patients than anticipated and a much higher refusal rate to participate than found in our pilot study both contributed to the failure to include patients. Therefore, we could not answer our research question. This means that orthopaedic surgeons, patients and their parents are still not sure what brace treatment can do.

Research question 3: Do patients treated with a brace differ in health-related quality of life after treatment in comparison with patients who needed surgery?

Patients who completed brace treatment and patients who were operated on do not differ significantly in health-related quality of life (HRQoL) within the first two years after completing treatment. Patients treated surgically (whether or not being braced before surgery) were more satisfied with management than the patients who were only treated with a brace, despite Cobb angles after treatment being quite as large in both groups (32° vs. 33°). This difference might be partly explained by the fact that the surgically treated patients had a smaller Cobb angle after treatment than before surgery (diagnosis 39°, pre-surgery 54°, after surgery 32°), while the patients who were treated by bracing only had a larger Cobb angle at the end of treatment than at diagnosis (diagnosis 24° vs. after treatment 33°), i.e., the surgically treated patients 'improved' in Cobb angle after 'deterioration from diagnosis', while the braced patients 'only deteriorated'. There was however only a weak correlation between improvement in Cobb angle and satisfaction with management.

Research question 4: What are patients' preferences on treatment for scoliosis?

A discrete choice experiment was designed in which patients had to choose between hypothetical brace treatment profiles that differed in levels of four treatment attributes: effectiveness (i.e., reduction in the need for surgery, relative risk reduction between 12.5% and 75%), invisibility (yes or no), comfort (yes or no), and treatment duration (from 2 to 8 years)). A set of 16 choice sets was designed. Each choice set consisted of two brace treatment profiles and a 'no brace' treatment option. A total of 116 patients with IS participated in this study. All together, these patients stated to be highly prepared to undergo brace treatment as an attempt to avoid surgery. The effectiveness and comfort of the brace played the most important role in the patients' decisions. Patients who were only treated with a brace exhibited the highest willingness to accept brace treatment, while the patients who had undergone surgery were

more reluctant to accept brace treatment. If the brace would reduce the risk of needing surgery by 25%, the patients who were only treated with a brace were willing to wear that brace for 6.6 years, while the patients who underwent surgery were willing to wear that brace for 3.0 years. The patients who were treated with a brace followed by surgery were willing to wear that brace for 4.5 years.

It is now very important to know what the effectiveness of bracing patients in reducing the need for surgery is. If bracing proves to be effective, these results are very promising. There is however somewhat dissimilarity between the preferences and international results in practice, which suggest that compliance to brace treatment is rather low.

General discussion

This thesis deals with three important prerequisites for the justification of a screening programme: (1) screening must lead to earlier detection, (2) an effective early treatment is available and this treatment is more effective early than later, and (3) screening followed by treatment reduces the adverse outcome of the disease/condition being screened for[1,2]. The aim of screening for scoliosis is to detect patients in an early stage of the clinical course, in order to apply brace treatment to prevent further progression and ultimately the need for surgical treatment[1,3]. Although we established that screening for scoliosis leads to earlier detection[4], we did not find evidence that screening leads to a reduction in the need for surgery[5]. Unfortunately, we were unable to establish the effectiveness of bracing patients with an early stage of scoliosis, because we were unable to include substantial numbers of patients in our RCT[6].

There are a lot of uncertainties concerning idiopathic scoliosis. Probably most importantly, there is lack of knowledge on the natural history and aetiology of idiopathic scoliosis[7]. The cause of this condition is unknown, and it is not exactly known why the condition in some children progresses and why not in others[7,8]. Because of this lack of knowledge, all current treatment efforts are aimed at prevention and correction of the primary manifestation of the disorder, namely spinal deformity[7,8]. This also implies that the current screening test and especially the early treatment may not be the most appropriate ones.

We also don't have reliable data about incidence, the number of patients who need brace treatment per year, and the number of surgeries. Based on a questionnaire sent out to Dutch orthopaedic surgeons, and on literature, estimates for the yearly needed brace treatment in the Netherlands range from at least 200 (based on data from 25 Dutch hospitals, excluding the numbers of at least three large scoliosis clinics) to 500 or 600[9,10,11]. These estimates reported in the literature concern the number of children that would need brace treatment if a screening programme were performed. In the Netherlands however, not all Municipal Health Services (MHS) screen for scoliosis, so the number of patients that would be detected early enough to apply brace treatment is probably lower than those estimates. The number of patients needing surgery in the Netherlands per year are estimated to be 50[11]. Some

orthopaedic surgeons feel that the incidence of idiopathic scoliosis might be declining, but we do not have data to prove this nor to disprove this.

Screening

In an earlier ecological case-control study, also no beneficial effect of screening was found[12]. A critical note on that study was made, because exposure to screening was not measured at a personal level, but was based on the formal screening policy of the MHSs. Whether cases and controls were actually screened for scoliosis was not established. Furthermore, allocation of the cases to a MHS that did screen or that did not screen was based on the postal codes of residency at time of discharge after surgery. Because that was 2-6 years after screening, migration could have been a source of misclassification[13].

After we started the preparations of the brace trial, in 2004, the US preventive Services Task Force (USPSTF) recommended against the routine screening of asymptomatic adolescents for IS, because, as stated, "the harms of screening adolescents for idiopathic scoliosis exceed the potential benefits". The USPSTF did not find good evidence that screening asymptomatic adolescents leads to detection of IS at an earlier stage. They found fair evidence that treatment of IS during adolescence leads to health benefits (decreases pain and disability) in only a small proportion of people. Most cases detected through screening will not progress to a clinically significant form of scoliosis. Scoliosis needing aggressive treatment, such as surgery, is likely to be detected without screening. Furthermore, the USPSTF found fair evidence that treatment of adolescents with idiopathic scoliosis detected through screening leads to moderate harms, including unnecessary brace wear and unnecessary referral to specialty care[14]. The Academy of Orthopaedic Surgeons (AAOS), the Scoliosis Research Society (SRS), the Pediatric Orthopaedic Society of North America (POSNA) and the American Academy of Pediatrics (AAP) however, do not support any recommendations against screening. Although they recognize that scoliosis screening has limitations, they feel that the potential benefits that patients with IS receive from early treatment of their deformities can be substantial[15]. As far as we know, screening for IS is still legislated in about 20 states in the US.

In the Netherlands, about 50[5] (based on actual screenings as measured in the case control study) to 80[5,16] (based on policy of the MHSs late 1990s) % of the Municipal Health Services (MHS) screen for scoliosis. At the moment, there is no formal policy that recommends for or against screening. The advice given to the MHSs after the results of our case control study is that if a MHS screens for scoliosis, then the MHS should perform this screening according to the methodology 'screening for scoliosis', and if no screening is performed then the MHS should not implement screening. A policy decision on whether to screen for scoliosis or not would be made after the results of the brace trial[17].

Brace treatment

Until today, there is ongoing discussion whether bracing is effective or not, and a range of different types of brace are used worldwide to treat patients[7]. However, no results of RCTs are available[7,18]. Recently, Dolan et al. published a systematic review of clinical

data concerning surgical rates[19]. The pooled surgical rate was 23% after bracing and 22% in children after just observation. They concluded that this provides no evidence to recommend bracing over observation. The studies they used for this analyses were mostly level III and IV studies, since no RCTs have been done so far. At the moment, Weinstein and Dolan are running a RCT in the United States and Canada on the effectiveness of bracing[20]. They started early 2007 and aim to include 500 children with idiopathic scoliosis in the trial (among others: age 10-15 year olds; Cobb angle between 25 and 40 degrees; Risser sign 0, 1 or 2; pre-menarchal or post-menarchal by no more than 1 year). Patients who have a history of previous surgical or brace treatment are excluded. The primary outcome measures are progression of Cobb angle to greater than 50 degrees (proxy for surgical indication) and cessation of skeletal growth.

A non-randomized prospective study of brace treatment versus observation alone demonstrated that bracing was successful ($p < 0.0001$) in preventing six degrees of increase of the curvature until the patients were sixteen years old[21]. None of the patients who were primarily braced needed surgery, while 20% of the observation group needed brace treatment because of progression and another 10% needed surgery. After a mean follow-up of 16 years, just published in 2007, no additional patients needed surgery, and progression of the curvature was equal between the initially braced and observed patients. As 70% of the initially observed patients did not need any treatment, 70% of the braced patients can be regarded as being unnecessarily braced[22]. The authors maintained the conclusion that bracing prevents curve progression during adolescence, but they also wondered whether 'is it worth overtreating such a high percentage (70%) of patients to realize the goal of 'saving' only 10% of the patients from surgery[22]. The fact that none of the braced patients and only 10% of the initially not braced patients needed surgery is remarkable, since the pooled surgery rate after bracing was 23% (95% CI: 20-24) and after observation was 22% (95% CI: 16-29) in the overview study by Dolan et al.[19]

The idea that conservative treatment (i.e., brace treatment) is to be preferred to surgical treatment is not supported by differences in HRQoL after treatment in our adolescent patients with idiopathic scoliosis[23]. A 20 year follow-up study on HRQoL in patients treated with a brace and/or treated surgically patients also showed no major differences between these groups[24].

Methodological considerations

Case control study

Some of the reasons why we did not find a beneficial effect of screening on the reduction of surgery could be that bracing is not effective, or that the patients in the case control study were 'wrongly' treated with a brace or were non-compliant to brace treatment. Half of the surgically treated patients in the case control study had been treated with a brace for 2,5 years on average before surgery. It seems unlikely that these patients represent a group that was 'wrongly' treated with a brace, because they were treated by the same orthopaedic surgeons who also treated the 'successfully' braced patients in the patient follow-up study. There is, however, a lack of

detailed information on compliance to brace treatment in our study. The information we have on brace compliance is based on telephone interviews with the patients and their medical files. Literature shows that compliance to brace treatment is not optimal[25,26]. If brace treatment is effective, then non-compliance could indeed result in higher surgical rates, and could thereby have decreased the effect of screening, especially if 'not feeling like wearing the brace' is the reason for non-compliance. Another reason for non-compliance could be that a patient notices that in his/her case the brace does not prevent progression, and she/he therefore was discouraged to continue to wear the brace. These different reasons for non-compliance complicate a straightforward interpretation and conclusion.

Randomized controlled trial

From a methodological point of view, we used the best possible design, namely a RCT, to establish the effectiveness of bracing patients with IS. However, as in every study, some remarks in our protocol can be made. Firstly, the ultimate goal of bracing is preventing progression of the curvature(s) and thereby preventing surgery. A follow-up period of two years is too short to establish whether bracing can prevent patients from needing surgery. To determine this, a follow-up until maturity is needed. For the youngest patients in our trial (8 years old) that would imply a follow-up of about 8 years. However, a two-year follow-up could provide us with valuable intermediate information. If we would have found a difference of at least 5 degrees in favour of the brace group, then bracing is potentially effective. Further evaluation until maturity would then be necessary to establish whether bracing will eventually prevent patients from further progression and needing surgery, or whether bracing can slow down progression but is not able to prevent surgery in the end. On the contrary, if we would not have found any difference in mean progression between the brace group and the control group, apparently bracing can be postponed by at least two years in this group. The chance that a brace would be effective after those two years seems rather low, especially if the patients reached a more mature stage at that time (i.e., Risser >2, or one year post menarche), because the more skeletally mature patients are, the less chance of progression they have[7]. However, since the natural course of scoliosis has not been fully understood, we must be careful with this last conclusion.

Another limitation is that with the planned number of included patients, we possibly would not be able to make subgroup analyses on curve type, gender and dose-response effects.

In this trial, only Boston braces would be used. This means that we would only be able to draw conclusions on Boston bracing, and not for brace types that are based on another concept, like the SpineCor brace[27] or Triac brace[28]. We choose for the Boston brace, because this is the most used brace in the Netherlands at present.

Compliance to brace treatment is an important factor to include in a trial on the effectiveness of brace treatment. Lack of compliance can underestimate the effect of bracing in preventing curve progression. Literature shows that compliance with brace treatment appears to be rather marginal[25,26]. Patients overestimate the number of hours they wear the brace each day. In the trial, we would try to measure compliance to brace treatment by three different means (orthopaedic surgeons asking

the patients; checks for worn-out signs and a questionnaire filled in by the patient). These means, however, are still based on patients', parents' and orthopaedic surgeons' opinions. A more objective measurement, like using temperature sensors in the brace, would probably have resulted in a more accurate measurement of compliance. Due to practical reasons, this was not possible in our design.

Conclusion

In conclusion, two prerequisites for the justification of a screening programme for scoliosis have not convincingly been met (i.e., a more effective early treatment and a reduction in the need for surgery due to screening). Considering this, we feel that it is justified to discontinue screening for scoliosis. For now, instead of screening large numbers of asymptomatic children, the appropriate approach would be to only look at a child's back when there are indications that something is wrong. These children should be examined and if necessary, be referred to an orthopaedic surgeon. In case the orthopaedic surgeon feels that brace treatment should be applied, the patients and parents should be well informed that it is not clear whether brace treatment can help preventing the curvature from worsening[19]. If the US trial would establish that bracing is effective in reducing the need for surgery, then it would be worthwhile to assess which children could benefit from a screening programme, and how this screening should be organized.

Main conclusions

- Screening for scoliosis leads to detection at an earlier stage of the clinical course.
- We found no evidence that screening for scoliosis leads to a reduction in the need for surgery.
- There are no major differences in health-related quality of life after treatment between patients who were treated with a brace, with surgery or both.
- Patients say that they are very willing to accept brace treatment if they think this avoids surgery.

Recommendations

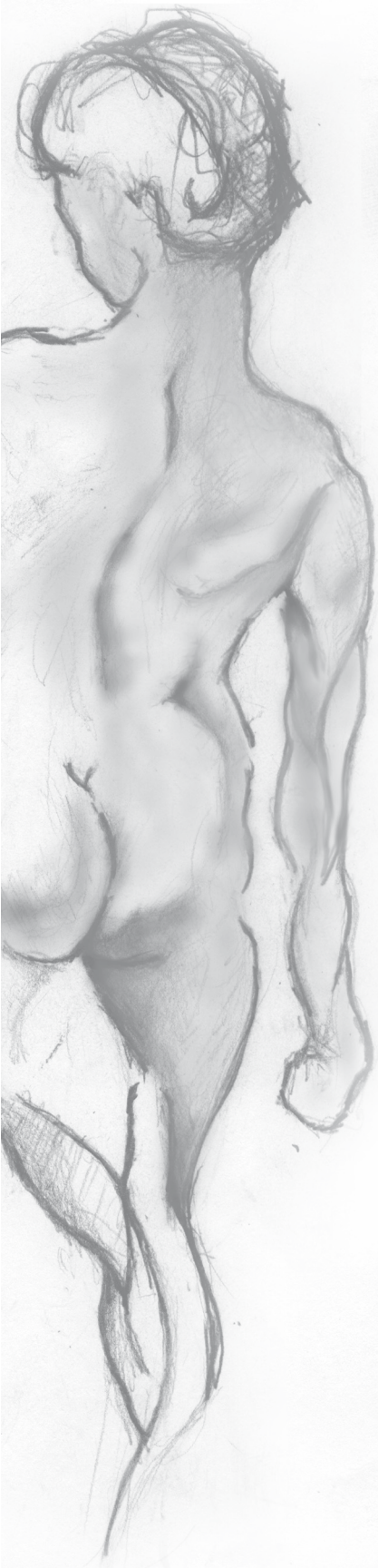
- In regions with a screening programme, continuing screening for scoliosis could only be considered if research that has sufficient power to detect a clinically meaningful benefit within a reasonable time is attached to the programme. We realise that it will be difficult to design and accomplish such a research component.
- The number of patients that require brace treatment or that fulfil the inclusion criteria for brace treatment each year in the Netherlands should be established, and, if possible, it should be evaluated whether this number has changed in the last two decades.

- The number of patients needing surgery per year in the Netherlands should be counted, and it should be evaluated whether this number has substantially changed in the last two decades.
- We recommend to evaluate whether there are differences in quality of life during treatment between brace treatment and observation.
- We should wait for the results of the RCT in the US on the effectiveness of bracing patients with idiopathic scoliosis.
- Trials on existing treatment should keep in mind that, possibly, it is harder to perform a RCT that abolishes or postpones an existing treatment than to perform a RCT that adds a new treatment.

References

1. US Preventive Services Task Force. Screening for adolescent idiopathic scoliosis. Review article. JAMA 1993;269(20):2667-72.
2. Wilson J, Junger C. Principles and practice of screening for disease: World Health Organization Public Health Paper 34; 1968.
3. Goldbloom RB. Screening for idiopathic adolescent scoliosis. In: Canadian Task Force on the Periodic Health Examination. Ottawa: Health Canada; 1994. p. 346-354.
4. Bunge EM, Juttmann RE, De Koning HJ, and the steering committee of the NESCIO Group. Screening for scoliosis: do we have indications for effectiveness? J Med Screen 2006;13(1):29-33.
5. Bunge EM, Juttmann RE, van Biezen FC, Creemers H, Hazebroek-Kampschreur AA, Luttmer BC, et al. Estimating the effectiveness of screening for scoliosis: a case-control study. Pediatrics 2008;121(1):9-14.
6. Bunge EM, Habbema JDF, De Koning HJ. A randomised controlled trial on the effectiveness of bracing patients with idiopathic scoliosis; failure to include patients. to be submitted 2008.
7. Weinstein SL, Dolan LA, Cheng JC, Danielsson A, Morcuende JA. Adolescent idiopathic scoliosis. Lancet 2008;371(9623):1527-37.
8. Goldberg CJ, Moore DP, Fogarty EE, Dowling FE. Scoliosis: a review. Pediatr Surg Int 2007.
9. Bunnell WP. Outcome of spinal screening. Spine 1993;18(12):1572-80.
10. Styblo K. Conservative treatment of juvenile and adolescent idiopathic scoliosis. A clinical, rontgenological and comparative retrospective study on the effects of conservative treatment by brace in 290 juvenile and adolescent consecutive patients.; 1991.
11. Korfage I, Das B, Juttmann R. Screening op scoliose, rapportage van de pilotstudy voor een kosteneffectiviteitsanalyse van Screening Op Houdingsafwijkingen in de jeugdgezondheidszorg (SOHO). Rotterdam; 2000.
12. Wiegersma PA, Hofman A, Zielhuis GA. The effect of school screening on surgery for adolescent idiopathic scoliosis. Eur J Public Health 1998;8:237-240.
13. Hazebroek-Kampschreur AAJM, Creemers H. The effect of school screening on surgery for adolescent idiopathic scoliosis: a comment. Eur J Public Health 1999;9:152.
14. US Preventive Services Task Force. Screening for Idiopathic Scoliosis in Adolescents: Recommendation Statement. Rockville. MD: Agency for Healthcare Research and Quality; June 2004.
15. Richards BS, Vitale MG. Screening for idiopathic scoliosis in adolescents. An information statement. J Bone Joint Surg Am 2008;90(1):195-8.
16. Korfage IJ, Juttmann RE, Das BV, Diepstraten AF, Hazebroek-Kampschreur AA, van der Maas PJ. [Idiopathic scoliosis in adolescents; an inventory into the possibilities of studying the efficacy of screening and treatment] Idiopathische scoliose bij adolescenten; inventarisatie van mogelijkheden van onderzoek naar de effectiviteit van screening en behandeling. Ned Tijdschr Geneeskd 2002;146(26):1228-33.

17. Richtlijnadviescommissie R. Overzicht richtlijnen. Bilthoven: RIVM Centrum Jeugdgezondheid; 2008.
18. Lenssinck ML, Frijlink AC, Berger MY, Bierman-Zeinstra SM, Verkerk K, Verhagen AP. Effect of bracing and other conservative interventions in the treatment of idiopathic scoliosis in adolescents: a systematic review of clinical trials. Phys Ther 2005;85(12):1329-39.
19. Dolan LA, Weinstein SL. Surgical rates after observation and bracing for adolescent idiopathic scoliosis: an evidence-based review. Spine 2007;32(19 Suppl):S91-S100.
20. http://clinicaltrials.gov. NCT00448448
21. Nachemson AL, Peterson LE. Effectiveness of treatment with a brace in girls who have adolescent idiopathic scoliosis. A prospective, controlled study based on data from the Brace Study of the Scoliosis Research Society. J Bone Joint Surg Am 1995;77(6):815-22.
22. Danielsson AJ, Hasserius R, Ohlin A, Nachemson AL. A prospective study of brace treatment versus observation alone in adolescent idiopathic scoliosis: a follow-up mean of 16 years after maturity. Spine 2007;32(20):2198-207.
23. Bunge EM, Juttmann RE, Kleuver de M, Biezen van F, Koning HJ de, and the NESCIO Group. Health-related quality of life in patients with adolescent idiopathic scoliosis after treatment: short-term effects after brace or surgical treatment. Eur Spine J 2007;16(1):83-9.
24. Danielsson AJ, Wiklund I, Pehrsson K, Nachemson AL. Health-related quality of life in patients with adolescent idiopathic scoliosis: a matched follow-up at least 20 years after treatment with brace or surgery. Eur Spine J 2001;10(4):278-88.
25. DiRaimondo CV, Green NE. Brace-wear compliance in patients with adolescent idiopathic scoliosis. J Pediatr Orthop 1988;8(2):143-6.
26. Houghton GR, McInerney A, Tew A. Brace compliance in adolescent idiopathic scoliosis. J Bone Joint Surg (Br) 1987;69-B:852.
27. Coillard C, Leroux MA, Zabjek KF, Rivard CH. SpineCor--a non-rigid brace for the treatment of idiopathic scoliosis: post-treatment results. Eur Spine J 2003;12(2):141-8.
28. Veldhuizen AG, Cheung J, Bulthuis GJ, Nijenbanning G. A new orthotic device in the non-operative treatment of idiopathic scoliosis. Med Eng Phys 2002;24(3):209-18.



Summary

Patients with idiopathic scoliosis (IS) have a lateral curvature of the spine, of unknown origin, with concomitant vertebral rotation. The severity of scoliosis can be assessed by X-ray and is expressed in sizes of the Cobb angle, which is the angle between the upper most inclined vertebra and the lower most inclined vertebra. Someone is being diagnosed with scoliosis when the Cobb angle is larger than 10 degrees. Progression of the curvature in IS usually occurs just before or during adolescent growth spurt, in girls before the menarche. Patients with Cobb angles larger than 20-25 degrees that have shown progression of at least 5 degrees, and who are not fully grown, are usually treated with a (Boston) brace to prevent further progression of the curvature. A brace is a close-fitting device applied to the trunk to correct (in brace), as much as possible, the lateral curvature of the spine. A brace should be worn for 18-23 hours a day and for about three to six years during adolescence. In case an immature patient has a Cobb angle of more than about 45-50 degrees, surgery can become necessary. With surgery, the spine is perpetually stabilized by rods. Severe cases of scoliosis with Cobb angles of more than 100-120 degrees may, besides cosmetic concerns and pain, lead to intrathoracal problems, which impede the well functioning of the heart and lungs. Besides medical problems for some patients, patients with IS can also suffer from psychosocial problems. IS can be a stigmatizing disorder, because a prominent rib 'hump' (hunchback), is visible in more severe cases. Furthermore, being treated with a brace is often visible for family, friends and peers.

To prevent patients with IS from needing surgery, screening for scoliosis was introduced in the USA and many other countries in the 1970s. The screening test for scoliosis is the Adam's forward bending test. A school physician examines the child's uncovered back while the child is bending forward; in case of scoliosis, a rib 'hump' is present. The screening aims at detecting patients early, in order to apply brace treatment to prevent progression and surgery. In 2000, a pilot study was performed to establish what kind of research was necessary in the field of screening and treatment for scoliosis. The main conclusion was that the effectiveness of both screening and early treatment with a brace had not been sufficiently established, and research on these topics was needed **(Chapter 1)**.

The following research questions are addressed in this thesis:

1. Does screening for scoliosis lead to earlier detection and to a reduction in the need for surgery?
2. What is the effectiveness of bracing patients with idiopathic scoliosis?
3. Do patients treated with a brace differ in health-related quality of life after treatment in comparison with patients who needed surgery?
4. What are patients' preferences on treatment for scoliosis?

Part I: Screening for idiopathic scoliosis

In **chapter 2** we tested whether two of the prerequisites for a screening programme

for scoliosis to be effective were met. These two prerequisites were 1) screen-detected patients should be detected in an earlier stage of the clinical course and 2) screen-detected patients should need less surgery than otherwise-detected patients (i.e. a more favourable outcome). The Cobb angle was used as a measure for the clinical course, and being treated with a brace only and not needing surgery was considered as the better outcome. Consecutive patients from 12 Dutch hospitals who completed treatment with a brace and patients who were operated on were asked to participate. Data on being screen-detected or not, age at detection and age at diagnosis, and Cobb angle at diagnosis were collected from 125 patients. We found that screen-detected patients had a significantly smaller Cobb angle at diagnosis than other patients (i.e., detected in an earlier stage of the clinical course). Furthermore, screen-detected patients had a 73% lower chance of having had surgery (i.e., a higher chance of a better outcome). This means that two prerequisites for an effective screening programme have been met. Definite proof of the effectiveness of the programme, i.e., less surgery due to screening and early treatment, still has to be established, because length-bias and overtreatment bias cannot be ruled out in this retrospective follow-up design of patients with IS. Length bias can occur because patients with slow progressive curves have more chance on being detected by screening, and have less chance of needing surgery than patients with rapidly progressive curves. The patients with slow progressive curves will be overrepresented in the screen group and thereby the effect of screening will be overestimated. Over-treatment bias can occur, because in a screening situation more children with scoliosis will be detected than in a situation without screening. This can lead to unnecessary brace treatment of children who would not need treatment if they had not been screened.

Chapter 3 describes our case control study on the effectiveness of screening for scoliosis. The case group consisted of 108 patients with IS who needed surgical treatment, and the control group consisted of a random sample of Dutch youth (n=216). Control subjects were matched to case subjects with respect to age and gender. For both case subjects and control subjects, we evaluated whether they had been exposed to screening. If screening for scoliosis would have been effective in reducing surgery, then one should expect that patients who needed surgery were less often screened than the general population. The patients who needed surgery however, were not significantly less often screened than the control group. This was true for both screening without taking into account the age at which a child was screened, and screening at the age of 11 to 14 years. The latter reflects the age category in which screening is usually being advised.

Part II: Treatment for idiopathic scoliosis

The effectiveness of bracing patients with IS in preventing progression of the curvature and thereby the need for surgery has not been convincingly established, due to a lack of randomized controlled trials. We therefore designed a RCT, of which the protocol is described in **Chapter 4**. In short, eligible patients for this trial were girls

and boys in the age group 8-15 years whose diagnosis of IS had been established by an orthopaedic surgeon, who had not yet been treated by bracing or surgery, and for whom further growth of physical height was still expected based on medical examination and maturation characteristics (Risser ≤ 2). The Cobb angle of the eligible patient should have either been minimally 22 and maximally 29 degrees with established progression of more than 5 degrees, or should have been minimally 30 and maximally 35 degrees; established progression for the latter was not necessary. A total of 100 patients were supposed to be included in this trial. The intervention group would have been treated with full-time Boston brace wear; the control group would not have been braced. Every four months, each patient would have had a physical and an X-ray examination. The main outcomes would have been the Cobb angle two years after inclusion and health-related quality of life.

Unfortunately, we were unable to include more than a few patients in the trial. In **Chapter 5** we describe how this could have happened, and which lessons can be learnt. After one and a half year of inclusion, we had included four patients only. We faced administrative difficulties in obtaining approval from the local Medical Ethics Committees, which caused a delay in starting the trial in some hospitals. More importantly however, we had significant problems in including patients in the trial. This happened because there were less eligible patients for the trial than counted on beforehand, and because a lower percentage of eligible patients were willing to participate in the trial than we had found in our pilot study. This teaches us that making a choice in a near-future situation can be something else than making a choice in the actual situation. Furthermore, we feel that it is harder to perform a RCT that abolishes or postpones a treatment than a RCT that adds a new treatment.

Part III: Quality of life and patients' preferences

In **Chapter 6** we evaluated whether there were differences in quality of life between patients who were treated with a brace and patients who were operated on. Patients (n=109) who had completed treatment with one of these treatments or both filled in the SRS-22 questionnaire (Scoliosis Research Society 22 item questionnaire), between 0 and 28 months after completing treatment. These patients did not differ significantly in health-related quality of life (HRQoL), within the first two years after completing treatment. Patients treated surgically (whether or not being braced before surgery) were more satisfied with management than the patients treated with a brace only.

We wondered how effective brace treatment in preventing surgery should be for patients with IS to consider the brace as a reasonable form of treatment during several years of puberty (**Chapter 7**). We performed a discrete choice experiment in which we evaluated this. A total of 116 patients with IS participated in this study. All together, these patients stated to be highly prepared to undergo brace treatment as an attempt to avoid surgery. The effectiveness and comfort of the brace played the

most important role in the patients' decision. The patients who were only treated with a brace showed the highest willingness to accept brace treatment. The patients who had undergone surgery were more reluctant to accept brace treatment, but still would be willing to wear the brace for 3 years if that reduces the risk on needing surgery with 25%.

In **Chapter 8**, the general discussion, the main findings are presented.

Firstly, screening for scoliosis leads to earlier detection and diagnosis, but we did not find evidence that screening resulted in a decrease in the number of patients that needed surgery.

Secondly, we designed a randomized controlled trial to evaluate whether bracing patients with scoliosis prevents the curvatures from progression. Unfortunately, we were unable to include more than a few patients in our trial, so this research question remains unanswered for now. We will have to wait for the results from the currently running US trial (NCT00448448) with a roughly similar design.

Thirdly, patients being treated with a brace only and patients who needed surgery did not differ in short-term health-related quality of life after treatment.

Finally, patients with IS were very willing to accept brace treatment if they think this avoids surgery.

We concluded that two prerequisites for the justification of a screening programme for scoliosis have not been convincingly met (i.e., a proven more effective early treatment and a reduction in the need for surgery due to screening). Considering this, we conclude that it is justified to discontinue screening for scoliosis. Only if the US trial would establish that bracing is effective in reducing the need for surgery, then it would be worthwhile to assess which children could benefit from a screening programme, and how this screening should be organised.

Samenvatting

Patiënten met idiopatische scoliose (IS) hebben een zijwaartse verkromming van de wervelkolom, waarbij de wervelkolom tevens om de eigen as is gedraaid, zonder bekende oorzaak. De ernst van de scoliose kan worden bepaald met behulp van röntgenfoto's en wordt uitgedrukt in de grootte van de Cobb hoek. De Cobb hoek is de hoek tussen de bovenste meest gekantelde wervel en de onderste meest gekantelde wervel. Wanneer de Cobb hoek tenminste 10 graden bedraagt, wordt de diagnose scoliose gesteld. Progressie van de verkromming treedt meestal op vlak voor of tijdens de puberteit, bij meisjes meestal voor de menarche. Patiënten die nog niet zijn uitgegroeid, die een Cobb hoek hebben die groter is dan 20-25 graden en die een progressie in de tijd heeft laten zien van tenminste 5 graden, worden meestal behandeld met een (Boston) brace om verdere progressie van de verkromming te voorkomen. Een brace is een nauwsluitend korset dat druk uitoefent op de romp om de zijwaartse verkromming zoveel mogelijk te corrigeren (in de brace). Een brace moet gedurende 18-23 uur per dag gedragen worden, gedurende 3 tot 6 jaar tijdens de puberteit. Indien een nog niet uitgegroeide patiënt een Cobb hoek heeft van meer dan 40-45 graden kan een operatie noodzakelijk worden. Met een operatie wordt de wervelkolom permanent gestabiliseerd met staven. Ernstige gevallen van scoliose waarbij de Cobb hoek groter is dan 100-120 graden kunnen naast cosmetische problemen en pijn leiden tot intrathoracale problemen die het goed functioneren van hart en longen kunnen belemmeren. Naast medische problemen kunnen IS patiënten ook psychosociale problemen hebben. IS kan een stigmatiserende aandoening zijn doordat een gibbus ('bochel') zichtbaar kan zijn in meer ernstige gevallen. Verder is behandeling met een brace vaak zichtbaar voor familie, vrienden en leeftijdsgenoten.

Om te voorkomen dat door de progressie van de scoliose patiënten een operatie nodig hebben, is gestart met screening op scoliose in de VS en veel andere landen in de jaren 70 van de vorige eeuw. De screening test voor scoliose is de Adam's buktest. Een schoolarts onderzoekt de rug van een kind terwijl het kind voorover buigt. Indien er sprake is van scoliose, wordt een gibbus zichtbaar. Het doel van de screening is patiënten vroeg op te sporen, zodat een brace behandeling kan worden gestart om daarmee een operatie te voorkomen. In 2000 is een pilotstudie uitgevoerd om vast te stellen welk onderzoek nodig was op het gebied van screening op en behandeling van scoliose. De hoofdconclusie was dat de effectiviteit van zowel de screening als de vroegtijdige behandeling met een brace niet voldoende was vastgesteld, en dat onderzoek op dit gebied nodig was (**Hoofdstuk 1**).

De volgende onderzoeksvragen worden in dit proefschrift behandeld:

1. Leidt screenen op scoliose tot een eerdere opsporing en tot een reductie in de noodzaak tot opereren?
2. Wat is de effectiviteit van brace behandeling van patiënten met idiopatische scoliose?
3. Zijn er verschillen in kwaliteit van leven tussen patiënten die met een brace behandeld zijn en patiënten die geopereerd zijn?
4. Wat zijn patiëntvoorkeuren met betrekking tot scoliose behandeling?

Deel I: Screenen op idiopatische scoliose

In **hoofdstuk 2** onderzochten we of aan twee voorwaarden voor een effectief screeningsprogramma op scoliose werd voldaan. Deze twee voorwaarden waren 1) door screening ontdekte patiënten zouden in een eerder stadium ontdekt moeten worden en 2) door screening ontdekte patiënten zouden minder vaak een operatie nodig moeten hebben dan anderszins ontdekte patiënten (d.w.z. een meer gunstige uitkomst). De Cobb hoek werd gebruikt als maat voor klinisch stadium. Met een brace behandeld zijn waarbij geen operatie nodig was, werd beschouwd als de gunstige uitkomstmaat. Opeenvolgende patiënten uit 12 Nederlandse ziekenhuizen die hun behandeling met een brace hadden voltooid en patiënten die waren geopereerd werden gevraagd om deel te nemen. Van 125 patiënten werden gegevens verzameld over de wijze van opsporing (door screening of anderszins), leeftijd van ontdekking en diagnose, en de Cobb hoek bij diagnose. We vonden dat de patiënten die door screening waren ontdekt een significant kleinere Cobb hoek bij diagnose hadden (d.w.z. dat deze waren opgespoord in een eerder klinisch stadium) dan andere patiënten. Bovendien hadden de door screening ontdekte patiënten 73% minder kans om geopereerd te moeten worden (d.w.z. ze hadden een grotere kans op een gunstige uitkomst).

Dit betekent dat aan twee voorwaarden voor een effectief screening programma wordt voldaan. Definitief bewijs van de effectiviteit van het programma, dat wil zeggen minder operaties als gevolg van screening en een vroegtijdige behandeling, moet echter nog worden vastgesteld, aangezien length bias en overbehandelingsbias niet kunnen worden uitgesloten in dit retrospectieve follow-up design van patiënten met IS. Length bias kan optreden omdat patiënten met een langzaam progressieve scoliose meer kans hebben om door screening te worden ontdekt en een kleinere kans hebben op een operatie dan patiënten met een snel progressieve scoliose. De patiënten met een langzaam progressieve scoliose zullen oververtegenwoordigd zijn in de door screening ontdekte groep en daardoor wordt het effect van screening overschat. Overbehandelingsbias kan optreden omdat in een screeningssituatie meer kinderen met scoliose ontdekt zullen worden dan in een situatie zonder screening. Dit kan leiden tot onnodige behandeling van kinderen die geen brace behandeling nodig hadden gehad als ze niet door screening waren ontdekt.

Hoofdstuk 3 beschrijft ons patiënt-controle onderzoek naar de effectiviteit van screenen op scoliose. De patiëntengroep bestond uit 108 patiënten met IS die een operatie hadden gehad. De controlegroep bestond uit een willekeurige steekproef van Nederlandse jongeren (n=216). Controles werden gematcht met de patiënten met betrekking tot leeftijd en geslacht. Voor zowel de patiënten als de controles gingen we na of ze in het verleden waren gescreend. Als screenen op scoliose effectief is in het reduceren van operaties, dan zouden we verwachten dat patiënten die een operatie nodig hadden minder vaak gescreend zouden zijn dan de algemene populatie. De patiënten die geopereerd waren, bleken echter niet significant minder vaak gescreend dan de controle groep. Dit was zowel het geval voor screening zonder rekening te houden met de leeftijd waarop screening plaatsvond, als voor screening

in de leeftijd van 11 tot 14 jaar. Dit laatste is de leeftijdsgroep waarbinnen screening meestal wordt geadviseerd.

Deel II: Behandeling van idiopatische scoliose

De effectiviteit van behandeling van IS patiënten met een brace om progressie van de verkromming te voorkomen is niet overtuigend vastgesteld, doordat gerandomiseerde gecontroleerde onderzoeken (randomised controlled trial, RCT) ontbreken. We hebben daarom een RCT opgezet, waarvan het protocol is beschreven in **hoofdstuk 4**. Geschikte patiënten voor deze trial waren meisjes en jongens in de leeftijdsgroep 8-15 jaar, bij wie de diagnose IS was vastgesteld door een orthopedisch chirurg, en die nog niet behandeld waren met een brace of een operatie en bij wie nog lichamelijke groei te verwachten was. Dit laatste was gebaseerd op medisch onderzoek en rijpingskenmerken (het zogenaamde teken van Risser ≤ 2). De Cobb hoek van geschikte patiënten moest of tussen minimaal 22 en maximaal 29 graden zijn met aangetoonde progressie van meer dan 5 graden, of zou tussen minimaal 30 en maximaal 35 graden moeten zijn. Voor de laatstgenoemde groep was aangetoonde progressie niet nodig. In totaal zouden 100 patiënten in de trial moeten worden geïncludeerd. De interventie groep zou behandeld worden met een Boston brace die ze fulltime moesten dragen, de controle groep zou niet met een brace worden behandeld. Elke patiënt zou iedere 4 maanden door een orthopeed worden onderzocht en zou röntgenonderzoek krijgen. De belangrijkste uitkomstmaten zouden de Cobb hoek 2 jaar na inclusie en kwaliteit van leven zijn.

Helaas konden we slechts enkele patiënten includeren in de trial. In **hoofdstuk 5** beschrijven we hoe dit kon gebeuren, en welke lessen hieruit geleerd kunnen worden. Na een inclusieperiode van anderhalf jaar waren er slechts vier patiënten geïncludeerd. We hadden te maken met administratieve problemen bij het verkrijgen van goedkeuring van alle locale Medisch Ethische Commissies wat er voor zorgde dat we een vertraagde start hadden in enkele ziekenhuizen. Veel belangrijker echter is dat we significante problemen hadden met het includeren van patiënten in de trial. Dit kwam omdat er minder geschikte patiënten waren dan van tevoren was ingeschat en omdat er een lager percentage patiënten wilde deelnemen aan de trial dan uit onze pilotstudie was gebleken. Dit leert ons dat een beslissing nemen voor een toekomstige situatie iets anders kan zijn dan een beslissing nemen in de werkelijke situatie. Bovendien denken wij dat het moeilijker is om een RCT uit te voeren waarbij een behandeling wordt uitgesteld of afgeschaft dan een RCT waarbij een nieuwe behandeling wordt toegevoegd.

Deel III: Kwaliteit van leven en patiëntvoorkeuren

In **hoofdstuk 6** onderzochten we of er verschillen in kwaliteit van leven bestonden tussen patiënten die met een brace waren behandeld en patiënten die geopereerd

zijn. Patiënten (n=109) die een van deze behandelingen of beide hadden voltooid, vulden de SRS-22 vragenlijst (Scoliosis Research Society 22 item questionnaire) in tussen 0 en 28 maanden na het einde van hun behandeling. Deze patiënten verschilden niet significant in kwaliteit van leven gedurende de eerste twee jaar na het einde van hun behandeling. Patiënten die geopereerd waren (al dan niet met brace behandeld voor operatie) waren meer tevreden met hun behandeling dan de patiënten die alleen met een brace waren behandeld.

We vroegen ons af hoe effectief behandeling met een brace moet zijn voordat IS patiënten behandeling met een brace gedurende enkele jaren tijdens de puberteit als acceptabel beschouwen (**hoofdstuk 7**). We voerden een discreet keuze experiment uit om dit na te gaan. In totaal deden 116 patiënten mee aan deze studie. Samengevat verklaarden deze patiënten zeer bereid te zijn om behandeling met een brace te ondergaan als poging om een operatie te voorkomen. De effectiviteit en het comfort van de brace speelden de belangrijkste rol in de keuze van de patiënten. De patiënten die alleen met een brace waren behandeld bleken het meest bereid om behandeling met een brace te accepteren, terwijl patiënten die geopereerd waren minder bereidwillig waren om brace behandeling te accepteren. Deze laatste groep was wel bereid om een brace gedurende drie jaar te dragen als dat de kans op een operatie zou beperken met 25%.

In **hoofdstuk 8**, de algemene discussie, worden de belangrijkste bevindingen gepresenteerd.

Ten eerste, screenen op scoliose leidt tot eerdere opsporing en diagnose, maar we vonden geen bewijs dat screenen leidt tot een afname in het aantal patiënten dat een operatie nodig heeft.

Ten tweede, we hebben een RCT opgezet om vast te stellen of het met een brace behandelen van IS patiënten progressie van de verkromming voorkomt. Helaas konden we niet meer dan een paar patiënten in de trial includeren, waardoor deze onderzoeksvraag voorlopig onbeantwoord blijft. We zullen moeten wachten op de resultaten van de nu lopende RCT in de VS (NCT00448448) met ongeveer dezelfde studieopzet.

Ten derde, patiënten die met een brace zijn behandeld en patiënten die geopereerd zijn verschillen niet in kwaliteit van leven op korte termijn na behandeling.

Ten slotte, IS patiënten zijn zeer bereidwillig om behandeling met een brace te accepteren als ze denken dat dit een operatie voorkomt.

We concludeerden dat aan twee voorwaarden voor de rechtvaardiging van een screeningsprogramma voor scoliose niet overtuigend wordt voldaan, te weten een bewezen meer effectieve vroege behandeling en een reductie in de noodzaak voor operaties. Dit in overweging nemende concluderen wij dat het gerechtvaardigd is om screenen op scoliose af te schaffen. Alleen als in de toekomst uit de trial in de VS zou blijken dat behandeling met een brace effectief is in het voorkomen van een operatie, dan is het waardevol om te bepalen welke kinderen voordeel zouden kunnen hebben bij een screeningsprogramma, en hoe deze screening georganiseerd zou moeten worden.

Dankwoord

Pfff, het is af!! Met plezier heb ik aan dit proefschrift gewerkt, al had ik uiteraard graag gezien dat we in hoofdstuk 5 de effectiviteit van de brace trial hadden kunnen bespreken…

Er zijn heel veel mensen die direct of meer indirect een bijdrage aan dit proefschrift hebben geleverd. Via deze weg wil ik graag een aantal van hen hiervoor bedanken.

Allereerst wil ik mijn promotoren Harry de Koning en Dik Habbema bedanken. Harry, vanaf het begin van het traject, toen het nog niet per se de bedoeling was dat ik zou gaan promoveren, ben jij als mijn begeleider betrokken geweest. Onze samenwerking heb ik als zeer prettig ervaren. Ik bewonder je kennis en heb veel van je geleerd. Bovendien waardeer ik het zeer dat je mij deze kans hebt gegeven. Dat ik nu de eer heb om als eerste bij jou te promoveren vind ik extra leuk! Dik, jij bent vooral bij de laatste fase van mijn promotietraject betrokken geweest. Onze besprekingen waren altijd zeer constructief. Door een paar scherpe vragen kon ik weer verder en heb ik mijn proefschrift kunnen afronden. Veel dank daarvoor!

In dit rijtje wil ik ook Rikard Juttmann, begeleider in de eerste fase van het traject, noemen. Rikard, jij hebt me wegwijs gemaakt in de jeugdgezondheidszorg en leerde me hoe we NESCIO het beste konden aanpakken. Ook jij veel dank voor je belangrijke bijdrage aan dit proefschrift. Nadat je ergens anders in het Erasmus MC bent gaan werken, heb je vaak geïnformeerd hoe alles ging en toonde je nog steeds je betrokkenheid, wat ik erg waardeer.

Ik dank ook de leden van de kleine commissie, professor Verhaar, professor Hira Sing en professor Koes voor het lezen en beoordelen van het manuscript.

Dit boekje had er niet gelegen als we geen medewerking hadden gekregen van de orthopeden die patiënten hebben aangemeld. Dr. H.D. Been, F.C. van Biezen, dr. L.N.J.E.M. Coene, dr. A.J. de Gruijter, J.P.W. van Jonbergen, dr. L.W.L. de Klerk, dr. M. de Kleuver, P.H.J. Klop, dr. H.J.A. Kruls, P.J.M. van Loon, F. de Nies, dr. J.E.H. Pruijs, dr. L.W. van Rhijn, M.P. Teeuwen en P.B.J. Tilman, hartelijk dank hiervoor. De orthopeden van het Erasmus MC, Frans van Biezen en Luuk de Klerk, wil ik in dit kader nog even apart noemen. Frans, hartelijk dank voor alle scoliose-educatie en het meedenken over een aantal artikelen. Luuk, hartelijk dank voor je input bij de aanvraag van de brace trial.

Mijn dank is ook groot dat alle GGD'en in Nederland aan NESCIO hebben willen meewerken. Hierbij gaat mijn dank in het bijzonder uit naar alle JGZ-artsen en verpleegkundigen die dossiers van patiënten en controlekinderen hebben opgezocht en aan de hand hiervan vragenlijsten hebben ingevuld.

En natuurlijk gaat mijn dank en waardering uit naar alle patiënten die hun medewerking hebben verleend door hun verhaal te vertellen en door vragenlijsten in te vullen!

De leden van de NESCIO begeleidingscommissie, Frans van Biezen, Huub Creemers,

Alice Hazebroek-Kampschreur, Bert Luttmer en Auke Wiegersma, hartelijk dank voor jullie inzet om mee te denken over NESCIO en de praktische hulp bij de uitvoer daarbij.

In de rustige perioden tijdens de scolioseonderzoeken heb ik uitstapjes kunnen maken naar niet-scoliosegerelateerde onderwerpen. Hein, met jou heb ik mijn eerste artikel geschreven. Dank voor je enthousiaste begeleiding hierin. Marie-Louise, bij drie projecten hebben we met elkaar te maken gehad. Ik heb veel van je geleerd over kwaliteit-van-levenonderzoek, en natuurlijk over de DCE. Ik waardeer je vrolijke en directe manier van begeleiden.

Collega's van MGZ, reuze bedankt voor die leuke en gezellige tijd! Ik heb met veel plezier de afgelopen jaren op MGZ gewerkt en daar hebben jullie een belangrijke bijdrage aan geleverd. Een paar collega's wil ik in het bijzonder noemen. Esther de Bekker, we staan samen als eerste auteur bij het DCE-artikel, wat een mooi voorbeeld is van samenwerking en aanvulling van elkaars kennis. Dank je voor je inzet hiervoor, maar natuurlijk ook dank voor alle leuke gesprekken die wat minder werkgerelateerd waren. Karien, mijn uitstapje naar NELSON was erg leerzaam, mede door jou. Je was een leuke collega en ik heb fijne herinneringen aan onze samenwerking. Kamer- en ganggenoten Elsbeth, Fanny, Judith, Carola, Heleen, Nicole en Suzie, dank voor jullie gezelligheid, fijne discussies en wijze raad. Arry, de screensectie boft met zo'n collega als jij! Je bent een leuke, gezellige en behulpzame collega en ik heb met veel plezier met je samengewerkt.

Suzanne, je bent een geweldige collega geweest. Zowel voor persoonlijke als voor werkgerelateerde zaken sta je altijd klaar om te luisteren, of om advies te geven. Willemieke, je was een zeer gezellige overbuurvrouw. Ik denk met veel plezier terug aan onze vele gesprekjes, jouw onderzoeksadviezen en onze uitjes naar De Doelen. Ashna, dank voor alle gezellige momenten. Nog even en jouw boekje ligt er ook! Heel veel succes met de laatste loodjes.

En tot slot, het secretariaat en de helpdesk, wat fijn dat jullie altijd klaar stonden om te helpen!

En ook mijn collega's bij Pallas, dank voor jullie interesse in de vorderingen rondom mijn proefschrift. Judith, veel dank dat ik de layout van dit proefschrift mocht uitbesteden. Anna (Zoiets Communicatie), bedankt voor de uitvoering hiervan. Ik ben er erg blij mee!

Lieve familie en vrienden, jullie zijn erg belangrijk voor mij en ik prijs me erg gelukkig met jullie. Een aantal wil ik hier even in het bijzonder noemen. Mijn lieve vriendinnetjes uit Kampen, ik ken jullie al sinds de lagere of middelbare school en ik vind het heel bijzonder en fijn dat we elkaar nog zo regelmatig spreken en dat we zo betrokken zijn bij elkaars leven, ook al wonen we daar niet allemaal meer. Huisgenootjes uit Groningen, Roelien in het eerste huis en Sofie in het tweede huis, wat ben ik blij met jullie en onze hechte vriendschap! En Nienke, dat onze moeders vriendinnen zijn en wij dat ook werden van jongs af aan is wel heel bijzonder. Lieve familieleden, dank

voor jullie interesse in de vorderingen van dit proefschrift en jullie bemoedigende woorden!

Paranimfen Corry en Tinneke, wat fijn dat jullie vandaag naast mij willen staan! Corry, sinds Bewegingswetenschappen in Groningen zijn wij dikke vriendinnen. Wat fijn dat we na onze studie een paar honderd kilometer verderop toch weer dicht bij elkaar wonen. Ik vind het heerlijk om bij jou, en natuurlijk Bart en Liv, te komen aanwaaien. Tinneke, vijf jaar lang hebben we op de kamer (onderzoeks-) lief en leed gedeeld. Dat we vaak in ongeveer dezelfde fase van onderzoek zaten, zorgde ervoor dat we een aantal zaken echt samen konden uitvogelen. Verder was het uitermate gezellig met jou op de kamer. Fijn dat dit contact zo is gebleven na MGZ.

Ten slotte wil ik graag mijn ouders, Jeroen en Sietske bedanken, en daarbij ook Dirk. Lieve pap en mam, ik heb niet de meest rechtstreekse onderwijs- en opleidingsroute gevolgd, en ik ben blij dat jullie mij steunden toen ik nog een tweede studie wilde doen. Jullie vertrouwen in mij is voor mij zeer belangrijk en waardevol! Jeroen en Siets, ik bof enorm met jullie als broer en zus, beter kan ik niet wensen! Jeroen, onze inhoudelijke discussies over mijn proefschrift, en Siets jouw onafgebroken belangstelling voor de vorderingen in het onderzoek (“En, weet je al wat er uitkomt?”) zijn zeer belangrijk voor mij geweest.

Eveline

About the author

Eveline Bunge was born on November 19, 1975 in Rotterdam, the Netherlands. In 1994, she completed her secondary education (HAVO) at the Almere College in Kampen. From 1994 – 1998 she studied Nutrition and Dietetics at the Hanze University Groningen, applied sciences. As a part of this study she wrote her thesis on the nutritional intake of the Dutch top gymnastics girls. Subsequently, she studied Human Movement Sciences at the University of Groningen. During the first year of that study, she was appointed as a dietician at the Isala klinieken, Zwolle. To complete this study, she wrote a thesis on the effects of an exercise programme on motor fitness and some CHD risk factors in a high risk population. She graduated in 2001. In March 2002 she started working as a junior researcher at the Department of Public Health of the Erasmus MC, University Medical Center Rotterdam. She performed the research that is described in this thesis , and was involved in a project on quality of life in lung cancer CT screening. Since May 2008, Eveline is appointed as a senior researcher at Pallas, health research and consultancy.

List of publications

Bunge EM, Essink-Bot ML, Kobussen MP, van Suijlekom-Smit LW, Moll HA, Raat H. Reliability and validity of health status measurement by the TAPQOL. *Arch Dis Child* 2005;90:351-8.

Bunge EM, de Koning HJ. Selective screening for scoliosis. *Clin Orthop Relat Res* 2006;445:277-8.

Bunge EM, Juttmann RE, de Koning HJ, and the steering committee of the NESCIO group. Screening for scoliosis: do we have indications for effectiveness? *J Med Screen* 2006;13:29-33.

Bunge EM, Juttmann RE, de Kleuver M, van Biezen FC, de Koning HJ, and the NESCIO group. Health-related quality of life in patients with adolescent idiopathic scoliosis after treatment: short-term effects after brace or surgical treatment. *Eur Spine J* 2007;16:83-9.

Bunge EM, de Koning HJ. Answer to the Letter to the Editor of I. Aprile et al. concerning "Health-related quality of life in patients with adolescent idiopathic scoliosis after treatment: short-term effects after brace or surgical treatment" (by Bunge EM et al. Eur Spine J 16: 83-89, 2007). *Eur Spine J* 2007;16:1964.

Bunge EM, Juttmann RE, van Biezen FC, Creemers H, Hazebroek-Kampschreur AAJM, Luttmer LCF, Wiegersma PA, de Koning HJ for the NESCIO group. Estimating the effectiveness of screening for scoliosis; a case control study. *Pediatrics* 2008;121:9-14.

Bunge EM, de Koning HJ, and the brace trial group. Bracing patients with idiopathic scoliosis: design of the Dutch randomized controlled treatment trial. *BMC Musculoskeletal Disord* 2008;9:57

Bunge EM, de Koning HJ. Estimating the effectiveness of screening for scoliosis. In reply. *Pediatrics* 2008;121:1297-8.

Van den Bergh KAM, Essink-Bot ML, Bunge EM, Scholten ET, Prokop M, van Iersel CA, van Klaveren RJ, de Koning HJ. Short-term impact of lung cancer CT screening on participants in a randomized controlled trial (NELSON). *Cancer* 2008;113:396-404.

Bunge EM, van den Bergh KAM, Essink-Bot ML, van Klaveren RJ, de Koning HJ. High affective risk perception associated with more lung cancer-specific distress in CT screening for lung cancer. *Lung Cancer* 2008;62:385-90.

Bunge EM, de Bekker-Grob EW, van Biezen FC, Essink-Bot ML, de Koning HJ. Patients' preferences for scoliosis brace treatment: a discrete choice experiment. 2008 *submitted*.

Bunge EM, Habbema JDF, de Koning HJ. A randomised controlled trial on the effectiveness of bracing patients with idiopathic scoliosis; failure to include patients and lessons to be learnt. 2008 *submitted*.

PhD Portfolio Summary

Summary of PhD training and teaching activities

Name PhD student: Eveline Bunge
Erasmus MC Department: Public Health

PhD period: 2002-2008
Promotor(s): Prof.dr. H.J. de Koning and prof.dr. J.D.F. Habbema

	Year	Workload (Hours/ECTS)
1. PhD training		
Research skills		
Erasmus Summer Programme, Erasmus MC Rotterdam:		
- Current concepts in epidemiologic study design	2002	1.4 ECTS
- Methods of Public Health Research	2002	0.7 ECTS
- Methods of Health Services Research	2002	0.7 ECTS
- Case-control studies	2003	0.7 ECTS
- Regression Analysis	2005	1.4 ECTS
Nihes, Erasmus MC Rotterdam:		
- Planning and evaluation of Screening	2003	1.4 ECTS
Dept. Of Public Health, Erasmus MC Rotterdam:		
- Health related quality of life of children in practice and research of paediatrics, general practice and youth health care	2003	3 hours
Presentations		
Research meeting youth health care, Utrecht:		
- Screening for scoliosis: early detection and a better outcome?	2005	20 hours
Youth health care symposium: Evidence based youth health care 0 – 19 years, Rotterdam:		
- Reduction in the need for surgery by screening?	2006	24 hours
4th International Conference Conservative Management of Spinal Deformities, Boston, US:		
- Idiopathic scoliosis: screening and bracing	2007	20 hours
Research meeting, dept. Public Health, Erasmus MC Rotterdam:		
- Idiopathic scoliosis: screening and bracing	2008	20 hours
International conferences		
4th International Conference Conservative Management of Spinal Deformities, Boston, US	2007	4 days
Seminars and workshops		
Attending seminars of the department of Public Health	2002-2008	120 hours
2. Teaching activities		
Lecturing		
Nihes course 'Planning and evaluation of screening', Erasmus MC Rotterdam:		
- Evaluation of youth health care screening programmes	2004	32 hours
	2005	16 hours
	2006	16 hours
	2007	16 hours
Curriculum medical students, 4th year, Erasmus MC Rotterdam:		
- Theme 4.2: The population as a patient	2006	60 hours
	2007	60 hours