Injuries in sports and physical activity are a worldwide health problem, with ankle sprains as the most common type of sports injury. Ankle sprain incidence rates have been shown to range from an average 1.00 to 2.00 per 1,000 sporting hours, with peaks of 7.56 per 1,000 soccer match hours. Intrinsic and extrinsic risk factors and the interaction between them make the athlete susceptible to an ankle sprain. Exposure to an index ankle sprain can cause alterations in athlete's intrinsic risk factors, such as strength deficits, impaired neuromuscular control, and impaired proprioception. Furthermore, previous injury and inadequate rehabilitation of an injury can make the athlete more susceptible to re-injury.

To prevent ankle sprains from occurring, preventive measures are warranted. These preventive measures should be aimed at improving effects of modifiable risk factors through the introduction of appropriate and timely ankle sprain prevention strategies. Research has shown that a 50% ankle sprain risk reduction can be achieved through proprioceptive balance board training. However, a preventive effect has only been found for subjects with previous ankle sprains. Since this secondary preventive effect was based on sub-group analyses of large study samples, loss of power and recall bias could have occurred.

With these methodological issues in mind and the fact that previous ankle sprains and inadequate rehabilitation of ankle sprains are the most important risk factors of an ankle sprain, an extensive randomized controlled trial (RCT) on preventing ankle sprain recurrences is warranted. This thesis deals with the abovementioned methodological issue in previous studies and with both risk factors by presenting a large RCT on athletes who recently sustained an ankle sprain and by supplying an intervention after usual care and thus testing adequacy of rehabilitation. More specifically, the main goal of this thesis was to establish the effectiveness on ankle sprain recurrences of an unsupervised home-based proprioceptive training programme given in addition to usual care.

Chapter 2

This chapter described the design of a RCT on an eight-week proprioceptive training programme aimed at the prevention of ankle sprain recurrences. The development of the RCT is depicted in this chapter. Athletes who had recently sprained their ankle were included in this study and after baseline measurements were randomly assigned to the intervention group or the control group. Intervention group athletes received an eight-week proprioceptive training programme after finishing usual care, whereas control group athletes received usual care only. As it was shown that athletes have a twofold risk for re-injury within the first year after an index ankle sprain, a follow-up time of one year was chosen. The training programme was a modification of a proven effective programme on top-level volleyball players. It consisted of general exercises on and off the balance board and had to be carried out individually. The programme prescribed three training sessions per week, with a maximum duration of 30 minutes per session. Exercises gradually increased in difficulty and training load during the eight-week programme. The primary outcome of the study was the number of recurrent ankle sprains in both groups within one year after the inclusion ankle sprain. A total of twelve monthly questionnaires were sent to each participating athlete. Per training session or match the total minutes of participation, type of sports and participation percentage of total session duration were registered. During the training programme, the intervention group received a supplement to the monthly questionnaire, which consisted of questions on the subjective response to the proprioceptive training programme, and a question on compliance to the programme. In case of an ankle sprain recurrence a web-based ankle sprain registration form was completed. Furthermore, athletes received a cost-diary, which registered all direct and indirect costs from the moment of injury onwards until full recovery.

This trial is the first RCT to study the effect on ankle sprain recurrences of an unsupervised home-based proprioceptive training programme given in addition to usual care.

Chapter 3

The objective of the RCT described in chapter 3 was to determine whether unsupervised home-based proprioceptive training, as described in chapter 2, was effective in reducing ankle sprain recurrence risk. For this purpose 522 male and female athletes of all types and levels of sports were followed prospectively for one year. Athletes were randomized to the intervention or control group, with stratification for gender, way of enrolment, and ankle sprain treatment. Both groups received treatment according to usual care. Athletes allocated to the intervention group received an eight-week proprioceptive training programme in addition to usual care. During one year, 145 athletes reported an ankle sprain recurrence: 56 (22%) athletes in the intervention group and 89 (33%) in the control group. The number needed to prevent one ankle sprain recurrence was 9. The intervention programme was associated with a 35% ankle sprain recurrence risk reduction compared to the control group. Cox regression analysis showed significantly fewer recurrent ankle sprains in the intervention group compared to the control group. This effect was found for self-reported recurrent ankle sprains (relative risk 0.63; 95% confidence interval 0.45 to 0.88), for recurrent ankle sprains leading to loss of sports time (0.53; 0.32 to 0.88), and for recurrent ankle sprains resulting in health care costs or lost productivity costs (0.25; 0.12 to 0.50). No significant differences were found between intervention group athletes who medically treated their inclusion ankle sprain and medically treated controls. Non-medically treated intervention athletes showed lower recurrence risk compared to non-medically treated controls. It was concluded that the use of a proprioceptive training programme after usual care of an ankle sprain is effective for the prevention of ankle sprain

recurrences. Furthermore, it was shown that such a programme should be advocated specifically in athletes, who non-medically treated their inclusion ankle sprain.

Chapter 4

After evaluating secondary preventive effectiveness of proprioceptive training in chapter 3, this chapter evaluated the costs associated with this eight-week programme. The cost data were registered in line with the prospective study described in chapter 3. If an athlete sustained an ankle sprain recurrence a cost-diary was completed for the duration of the injury. Costs related to ankle sprain recurrences were measured from a societal perspective using these cost-diaries. Bootstrapping was used to analyze the cost-effectiveness data. Statistically significant decreases in total costs were found per athlete (mean difference −€103; 95% confidence interval −€253 to −€23) and per injured athlete (−€332; −€741 to −€62) in favour of the intervention group. Cost-effectiveness planes showed that the intervention was dominant (i.e. larger effects and lower costs). Cost-effectiveness acceptability curves showed that the intervention was cost-effective in comparison with control for various ceiling ratios. From these results was concluded that the use of a proprioceptive training programme after usual care of an ankle sprain is cost-effective for the prevention of ankle sprain recurrences in comparison with usual care alone. In the Netherlands, an estimated annual €24,102,000 in medical and lost productivity costs can be saved solely by advocating a proprioceptive training programme as in the present study.

Chapter 5

Poor levels of compliance with a trialled intervention can influence estimates of its effectiveness. This chapter investigated the difference in outcome effect of a proprioceptive training programme aimed at preventing ankle sprain recurrences when analysed by means of intention-

to-treat (ITT) versus per-protocol (PP) principles. PP analysis was based on self-rated compliance with the training programme. Separate Cox regression analyses on ankle sprain incidence were performed according to the ITT and the PP approaches. Twenty-three percent of the intervention group indicated to have fully complied with the proprioceptive training programme, whereas 35% was classified as not compliant. Compliance to the training programme was unknown for 13% of the intervention group. Significantly fewer recurrent ankle sprains were found in the fully compliant group compared to the group that was not compliant (relative risk 0.63; 95% confidence interval 0.43 to 0.99). Significantly fewer recurrent ankle sprains were found in the intervention group compared to the control group when analysed according to the ITT principle (0.63; 0.45 to 0.88). A PP analysis on fully compliant athletes versus control group athletes showed that ankle sprain recurrence risk was over threefold higher in favour of the intervention group compared to when ITT analysis was utilized for the complete intervention group (0.19; 0.07 to 0.53). It was therefore recommended that a PP analysis is presented alongside ITT analysis in a paper to provide more insight into the effectiveness of the intervention in only those who adopt the intervention as per the protocol specifications. A PP analysis is only possible if measurement of compliance to the intervention programme is undertaken. Therefore, it was highly recommended that RCTs incorporate proper compliance measurement strategies.

Chapter 6

The review described in chapter 6 summarized the current literature on the effect of sensorimotor training on morphological and neurophysiological ankle characteristics and on measurable functional properties in subjects with a previous ankle sprain. An attempt was made to establish the pathway through which training leads to lower ankle sprain recurrence risk. Twelve studies met criteria set for design and

methodology and were reviewed in this chapter. From the reviewed studies can be concluded that effects on morphological, neurophysiological, and functional properties of the ankle after sensorimotor training were minimal, and in most studies more likely attributable to a learning effect of repeated measures than to the training itself. The pathway through which sensorimotor training reduces re-injury risk remains unclear. To create more insight in this pathway, future studies should (1) differentiate between morphological, neurophysiological, and functional changes, (2) use larger sample sizes with a priori sample size calculations, (3) ensure correspondence between training and test method, (4) use other measures than postural sway closer linked to functional stability, and (5) use a longer follow-up period than six weeks.