

## SUMMARY



The aim of this thesis was to describe the development and evaluation of an individually tailored lifestyle intervention (the PRO-FIT intervention) for people with Familial Hypercholesterolemia (FH).

**In chapter 1**, a general background and rationale for the PRO-FIT project was provided. Familial Hypercholesterolemia (FH) is associated with elevated LDL cholesterol (LDL-C) levels and an elevated risk of cardiovascular disease (CVD), the leading causes of premature death in Western countries. There is evidence that statin therapy reduces LDL-C levels and CVD risk in people with FH. In this chapter it was emphasized that to prevent the incidence of CVD, an intervention should target at both biological and behavioral CVD risk factors. Two strategies to achieve an optimal CVD risk reduction were suggested: 1) addressing multiple CVD risk factors, and 2) reducing LDL-C by improving adherence to statin therapy. The development of the PRO-FIT intervention was described, taking into account the most important risk factors and determinants, that are described in the I-Change model, that assumes that at least three stages in the behavioral change process can be distinguished: awareness, motivation and action. Consequently, the goals of the intervention were outlined: 1) to improve awareness of the CVD risk, 2) to improve motivation with respect to a healthy lifestyle, regarding physical activity, dietary behavior, smoking and compliance to medication, 3) to induce adoption and maintenance of a healthy lifestyle, and 4) to lower LDL-C levels and CVD risk.

**Chapter 2** included an update of a systematic review on the effectiveness of computer-tailored physical activity and nutrition education. A database search for randomized controlled trials aimed at primary prevention in adults, published from September 2004 through June 2011, resulted in fifty publications. It was concluded that, compared to the findings of the 2006 review, a larger proportion of studies found positive effects for computer-tailored programs compared to generic or no information, including those for physical activity promotion. The positive results were generally for short- or medium-term follow-up and effect sizes were small. Further, results showed that more studies with long-term follow-up were conducted, particularly on dietary behavior and that objective outcome indicators were most often used in physical activity studies. The authors concluded that future interventions should focus on establishing larger effect sizes and sustained effects, and should use more objective measurements in studies on dietary behavior, use more generic health education control groups, and include longer follow-up.

The process of the development, as well as the evaluation plan of the PRO-FIT intervention was described in **chapter 3**. In a randomized controlled trial, individuals with FH were assigned randomly to a control or intervention group. In the intervention group, participants received a personalized intervention, which entailed a combination of web-based tailored lifestyle advice and personal counselling by a lifestyle coach using Motivational Interviewing (MI). The control group received care as usual. Primary outcomes were biological indicators of CVD risk: systolic blood pressure, glucose, body mass index, waist circumference and lipids (triglycerides, total, LDL and HDL cholesterol). Secondary outcomes were: healthy lifestyle behaviour (with regard to smoking, physical activity, dietary pattern and compliance to statin therapy) and psychological correlates and determinants of healthy lifestyle behaviour (knowledge, attitude, risk perception, social influence, self-efficacy, cues to action, intention and autonomy). Measurements were planned to take place at baseline, and at 3 and 12 months after randomisation.

**Chapter 4** incorporated a description of the interventional effects on smoking, physical activity, saturated fat intake, fruit and vegetables intake, and compliance to statin therapy. Regression analyses were conducted to examine between-group differences. In both groups, non-significant improvements in all lifestyle behaviours were found. Post-hoc analyses showed a significant decrease in saturated fat intake among women in the intervention group ( $\beta=-1.03$ ; CI -1.98/-0.03). The results showed that individually tailored feedback was not superior to usual care regarding changes in multiple lifestyle behaviours in people with FH.

**Chapter 5** described the effects of the intervention on biological CVD risk indicators, namely systolic blood pressure, glucose, body mass index, waist circumference and lipids. Regression analyses were conducted to examine differences between both groups. After 12 months, no significant between-group differences of cardiovascular disease (CVD) risk indicators were observed. LDL-C levels had decreased in both the intervention and control group. This difference between intervention and control group was not statistically significant. The results suggested that an individually tailored lifestyle intervention did not have an additional effect in improving CVD risk indicators among people with FH.

The results from the point view of the process of the intervention delivery and its association with the observed intervention effects were highlighted in **chapter 6**. According to a process evaluation plan, intervention reach, dose delivered and received, and MI fidelity were assessed using the recruitment database, website/counselling logs and the Motivational Interviewing Treatment Integrity (MITI 3.1.1.) code. Regression analyses were conducted to explore differences between

participant and non-participant characteristics, and the association between intervention dose and change in LDL-C, and multiple lifestyle behaviours. A 34% (n = 181) representative proportion of the intended intervention group was reached during the recruitment phase; participants did not differ from non-participants (n = 623) on age, gender and LDL-C levels. Of the participants, 95% received a PRO-FIT\*advice log on account, of which 49% actually logged on and completed at least one advice module. Nearly all participants received a face-to-face counselling session and on average, 4.2 telephone booster calls were delivered. None of the face-to-face sessions were implemented according to MI guidelines. Overall, weak non-significant positive associations were found between intervention dose and LDL-C and lifestyle behaviours. Conclusively, implementation of the PRO-FIT intervention in practice appeared feasible, particularly PRO-FIT\*advice, since it could be relatively easily implemented with a high dose delivered. However, only less than half of the intervention group received the complete intervention-package as intended.

The cost-effectiveness and cost-utility of the PRO-FIT intervention was reported in **chapter 7**. Thereto, LDL-C, quality of life and cost data were measured at baseline and after 12 months. Missing data were multiply imputed and cost-effectiveness analyses were performed from a healthcare perspective. Uncertainty around the incremental cost-effectiveness ratios (ICERs) was graphically presented with cost-effectiveness planes and cost-acceptability curves based on 5000 bootstrap samples. Non-significant decreases in LDL-C and QALYs were found in the intervention group compared to usual care. The mean difference in costs between the intervention and control group was €-237 (95% CI: -1386;130). In conclusion, results of the cost-effectiveness analyses showed that the intervention was not (cost-)effective in comparison with usual care.

**Chapter 8** was a summative and general discussion chapter in which the results of the PRO-FIT project were explained from a variety of perspectives and recommendations were formulated for the design and evaluation of future interventions. It was concluded that despite a theory- and evidence-based 'high-risk approach', lifestyle behaviours and biological CVD indicators could not be changed in a sample of people with FH. No published studies have ever been evaluated the (cost-)effectiveness of a comparable lifestyle intervention compared to usual care in a FH sample, but these results are not in accordance with the latest published evidence regarding other high-risk samples. Explanations for the lack of efficacy of the PRO-FIT intervention are described, broadly divided as: 1) explanations related to the PRO-FIT intervention, and 2) explanations related to the execution of the PRO-FIT project. In short, both the underestimated heterogeneity of the sample used in this study and the lack of full implementation of the intervention probably have contributed to the lack of efficacy. It was concluded that it is irrefutable that statins are the most effective treatment in reducing LDL-C

levels. Though, the fact that we were unable to determine any (additional) effects of a lifestyle intervention compared to usual care does not necessarily mean that promoting a healthy lifestyle cannot have an additional value. A joint strategy to reduce CVD risk in people with FH was suggested, incorporating five chronological steps: 1) screening of under-diagnosed FH patients, 2) initiating cholesterol-lowering treatment, 3) communicating CVD risk and the contribution of (modifiable) risk factors, 4) optimizing compliance to cholesterol-lowering therapy, and 5) providing individually-tailored *and* FH-specifically tailored lifestyle advice.