

CHAPTER 8

GENERAL DISCUSSION



This thesis describes the content of the PRO-FIT project. Our aim was to develop an individually tailored lifestyle intervention (the PRO-FIT intervention) for people with Familial Hypercholesterolemia (FH), and to evaluate the effect on biological cardiovascular disease (CVD) risk indicators and lifestyle behaviors, and to link these effects to the process of intervention delivery and healthcare-related costs. In the preceding chapters, existing evidence on computer-tailored physical activity and nutrition education was reviewed (chapter 2), and the design and evaluation of the PRO-FIT intervention were reported (chapter 3). Next, the results of studies on the effects of the PRO-FIT intervention on specific lifestyle behaviors (chapter 4) and biological CVD risk indicators (chapter 5) were reported. Finally, the effects of PRO-FIT were linked to the process of intervention delivery (chapter 6) and healthcare-related costs (chapter 7).

In this chapter, we reflect on the results and implications of the PRO-FIT project. First, we will briefly summarize the development of the PRO-FIT intervention and the related evaluation plan. Next, the effects of the intervention are described and compared with those from other relevant studies. The results are explained from various perspectives and recommendations are formulated for the design and evaluation of future interventions. Finally, the actual contribution of the results of the project for practice is discussed.

THE PRO-FIT PROJECT

The development of the PRO-FIT intervention

In chapter 3, insights into important CVD risk factors and changeable behavioral determinants among people with FH were given. Based on these factors, the PRO-FIT intervention was developed to address both biological and behavioral CVD risk factors, as well as determinants of the I-Change model. According to this model, we hypothesized that for people with FH, the intervention would: 1) improve awareness of CVD risk, 2) improve motivation with respect to a healthy lifestyle regarding smoking, physical activity, saturated fat intake, fruit and vegetable intake, and compliance to statin medication, 3) induce adoption and maintenance of a healthy lifestyle, and 4) lower LDL cholesterol (LDL-C) levels and CVD risk. The PRO-FIT intervention was developed using strategies shown in Table 1. The strategies included a combination of tailored and web-based lifestyle advice (*PRO-FIT** advice) and face-to-face counseling (using Motivational Interviewing (MI) techniques) complemented by telephone booster sessions. Results from our systematic review (chapter 2) confirmed the previously reported consistent effects of computer-tailored physical activity and nutrition education. In this review, we compared the recent scientific evidence in the field with an original review by Kroeze et al. published in 2006 [1], and verified whether recommendations from the previous review were still relevant. In addition, our review now also documented consistent evidence for the promotion of physical activity. However, the effects were generally restricted to studies with short- and medium-term follow-up and the effect sizes remained small.

Table 1: Intervention strategies to address each stage of the behavioral change process in the I-Change model and determinants

Behavioral change determinants	Intervention strategy
Genetic predisposition, current lifestyle, personal characteristics and information factors <i>Predisposing determinants</i>	Tailored feedback Tailoring the information on CVD risk factors and lifestyle counseling to the genetically predisposed risk of people with FH and their personal characteristics (age, gender, household characteristics) and current lifestyle behavior.
Knowledge, risk perception, cues to action <i>Awareness phase</i>	Risk communication Educating people on their current CVD risk factors, with regard to size and changeability of these factors. Then, translating this knowledge to opportunities for behavioral change in their personal situation. Motivational Interviewing Raising awareness by providing personal and normative behavioral feedback following Motivational Interviewing techniques.
Attitude, social support and self-efficacy <i>Motivation phase</i>	Tailored feedback Giving personal feedback to participants' self-reported attitude, social support and self-efficacy and involving people's social environment when making action plans.
Self-efficacy, action planning, skills, barriers <i>Action phase</i>	Motivational Interviewing Stimulating people to make action plans and discussing how to overcome barriers to behavioral change.

The evaluation of the PRO-FIT intervention

As outlined in chapter 3, the PRO-FIT project was designed as a randomized controlled trial (RCT). Individuals, recently genetically diagnosed with FH by the national cascade-screening program of the Dutch Foundation for Tracing Hereditary Hypercholesterolemia (StOEH), were recruited from the StOEH client database. Adult clients with an increased LDL-C (>95th percentile, age- and gender-corrected) who were willing to participate were randomly assigned to either the intervention or the control group that received usual care. Outcomes on blood pressure, glucose, body mass index (BMI), waist circumference and lipids (LDL-C, HDL-C, total cholesterol (TC), triglycerides), as well as lifestyle behaviors were measured at baseline and after 12 months. In addition, the process of the PRO-FIT intervention delivery was evaluated according to a process evaluation plan (chapter 6). Reach, dose (delivered and received) and MI fidelity (20 counseling

sessions) were measured using the recruitment database, website/coaching logs and the MI Treatment Integrity (MITI 3.1.1.) code. Further, an economic evaluation was conducted from a healthcare perspective consisting of an analysis of the cost differences in the development and implementation of the intervention and between the intervention and control group. The incremental costs of the intervention group compared to the control group were divided by the incremental effect for the improvement in LDL-C and quality adjusted life years (QALYs).

MAIN FINDINGS

Results showed that after 12 months, the PRO-FIT intervention was not superior to usual care for changes in both multiple lifestyle behaviors (chapter 4) and biological CVD risk indicators (chapter 5). Post-hoc analyses showed that the most obvious reductions in LDL-C and TC levels were among participants who used no statins. For both groups, no significant improvements in any targeted lifestyle behavior was found. However, post-hoc subgroup analyses showed a significant decrease in saturated fat intake among women.

Results of the process evaluation in chapter 6 showed a sufficiently delivered dose of all intervention components. However, the extent to which participants engaged in using *PRO-FIT** advice as planned proved to be disappointing; none of the 20 evaluated counseling sessions was fully completed according to MI methodology. Weak non-significant positive associations were found between intervention dose and LDL-C and lifestyle behaviors.

As described in chapter 6, the PRO-FIT intervention is not cost-effective in comparison with usual care.

COMPARING OUR FINDINGS WITH RECENT LITERATURE

The lack of interventional effects on the biological CVD risk indicators and lifestyle behaviors found in the PRO-FIT project are not in accordance with the latest published evidence. In their review, Blokstra et al. showed that multifactorial lifestyle interventions could have favorable effects among individuals with a high risk for CVD. [2] The authors found improvements in blood pressure (-2-4 mmHg), nutrition, physical activity and smoking (-25-40%). Studies on other high-risk populations also showed that biological changes can be achieved, though often small and not significant in the long term (> 6 months). [3,4] However, the three cited studies were not conducted with FH subjects. In a recent review by Shafiq (2011), no differences were reported between a cholesterol-lowering diet compared to no intervention or other dietary interventions in people with FH. [5] However, in this review and recent literature, there was a noted lack of RCTs, which makes it hard to compare the findings to ours.

The absence of effects on compliance to statin therapy in our study is in concordance with earlier studies in non-FH samples. According to recent evidence, the effects of compliance-improving interventions for statins are generally small (only about 50% of the interventions proved to be efficacious) and effects on treatment outcomes (e.g. LDL-C) were often absent. [6,7]

No published studies were found that evaluated the cost-effectiveness of a lifestyle intervention compared to usual care in a FH sample. However, lifestyle interventions appeared cost-effective in reducing the long-term risk of type II diabetes and CVD, particularly interventions on both diet and physical activity in high-risk samples in one study. [8]

EXPLAINING THE LACK OF EFFECTS FROM VARIOUS PERSPECTIVES

There are several explanations for the lack of efficacy of the PRO-FIT intervention when compared to usual care, which can be broadly divided as: 1) explanations related to the PRO-FIT intervention, and 2) explanations related to the execution of the PRO-FIT project.

EXPLANATIONS RELATED TO THE PRO-FIT INTERVENTION

Targeted behavioral determinants

We assumed that selecting our target population in the PRO-FIT project by using a specific genetic predisposition, we would have a homogenous sample of individuals derived from FH families with prevalent CVD who were at a high-risk for CVD and therefore motivated to improve their lifestyle behavior. One of the strengths of this 'high-risk approach' is that it is more appropriate for the individual, and the clinician (or

health promotion worker) is more motivated, compared to the 'population approach'. [9]

However, identifying a high-risk sample, such as people with FH, for a health-promoting intervention is not a stand-alone guarantee for success. This approach requires a thorough pre-assessment of inter-individual variation in the determinants of the targeted behavioral change. In the PRO-FIT project, we did attempt to account for inter-individual variation by using computer-tailored lifestyle advice modules based on the assessment of the following variables: (awareness of) lifestyle behavior, knowledge, motivation to change, outcome expectations, attitude and self-efficacy. These modules were based on existing tailored information modules of the 'Healthy Life Check'. [10] The choice for the inclusion of these existing modules was supported by the already proven efficacy of the 'Healthy Life Check' in a healthy population, as well as the promising effects of computer-tailored education in healthy individuals as concluded in chapter 2. Since we assumed that the 'classical' motivational determinants addressed in these tailoring modules play a role in both healthy and at-risk populations, we considered the disparity between our sample and a healthy sample to be small. An obvious question now is: "Was it right to only target the determinants that were responsible for inter-individual variation in lifestyle behaviors among healthy people?" My answer is "no". In retrospect, additional FH-specific determinants should have been considered.

For example, it could be that the lipid metabolism of people with FH with certain mutations are more/less susceptible to environmental alterations, such as lifestyle improvements. [11,12,13] Research has shown that the type of mutation does not fully explain the variability in clinical symptoms in heterozygous patients. [14] It is still unclear whether there could be gene alleles that interact with environmental factors to influence the phenotype or the response to cholesterol-lowering treatment. So far, more than 800 mutations of the LDL receptor gene are known, and other mutations have been identified in clinical FH patients (e.g. in *APOB*, *PCSK9* and *LDLRAP1*). [15] Within the PRO-FIT trial, data were present on the mutation type, medication use and baseline lifestyle behavior. However, these data were not taken into account in the development of the intervention strategy, e.g. as tailoring variables.

Further, since statins provide the most effective treatment in reducing LDL-C levels in people with FH, variation in the effects of a lifestyle intervention was to be expected between statin-users and non-statin-users. In the PRO-FIT project including recently (<2 years ago) diagnosed participants, approximately 70% in both the intervention and the control group used statins at baseline. It is challenging to determine the actual cause of CVD risk reduction when both statins and lifestyle advice are given. Post-hoc analysis of the PRO-FIT data showed no substantial difference in lifestyle behavioral changes between statin-users and non-statin users. However, interactions between both treatment options (i.e. statin therapy and lifestyle) are realistic, since Hunninghake et al. showed that intensive dietary therapy has more promising effects when it is added

to statin therapy (-32% LDL-C reduction), compared to statin therapy alone (-27% LDL-C reduction) or dietary therapy alone (-10% LDL-C reduction).

Thus, the interventional effects that were small and non-significant may have been 'fragmented' or partly obscured by the underlying heterogeneity of the sample. Taking this heterogeneity into account or even transferring it into a strength by using a web-based individually tailored intervention and targeting behavioral determinants that proved to be effective in a healthy sample, was clearly not sufficient in this study. It is unquestionable that people with FH need a 'high-risk approach', due to their disproportionately high mortality risk. However, within this approach, an intervention may need to consider the above-mentioned determinants, in addition to the tailoring the variables that were already used. Inclusion of these factors will enable the development of an even more individually tailored intervention, that should also be FH- and CVD risk-tailored.

The underlying behavioral change theory

The I-Change model is an integrated model for explaining motivational and behavioral change that was derived from established health behavior models and theories such as the Theory of Planned Behavior, the ASE model, and stages of change models. [16,17] The I-Change model was used as a theoretical framework for the development of the PRO-FIT intervention. [18] This model emphasizes the intention-behavior pathway, wherein behavioral determinants of the awareness-, motivational- and action-phases, such as risk perception, attitude and self-efficacy form the backbone of the model. [19] Although the more-or-less 'reasoned action' intention-behavior pathway is important for changing behavior, there are determinants that might have been under-recognized in the model. Aside from determinants related to the intention-behavior pathway, behavior is most often also influenced by determinants derived from a broader context than the individual, such as the physical and social-cultural environment in which the behavior takes place, as well as by biological and unconscious or automatic drivers of behavior.

The physical environment is the presence of facilities and the possibility to adopt health behavior, e.g. the availability of sport facilities. [20] Accessibility to and availability of 'healthy' locations have been found to be positively associated with physical activity, but since changing the environment in an intervention study is difficult, changing a participant's perceived environment, i.e. the awareness of the facilities and possibilities, could be a useful target as well. Van Stralen et al. gave early indications of the relevance of environmental perceptions as a determinant for changing physical activity. [21] Despite promising developments in this field, evidence regarding access to and availability of health and unhealthy food choices is still contentious. [22] In a 2.0 version of the PRO-FIT intervention, tailoring of environmental determinants might be realized

by linking a Geographic Information System (GIS), designed to present all types of geographically referenced data, with Google earth, to provide suggestions for 'healthy' locations (e.g. sport school, fruit and vegetables shop) in a participant's neighborhood. [23]

Since the diagnosis of FH also has implications for family members who might have inherited the same disorder, targeting the direct social environment of people with FH seems useful. Family members can have a beneficial or harmful effect on a family member's physical health as well, e.g. through a biological pathway by sharing the same toxic environment (smoking) or the same genes. [24] Also, the behavioral pathway can play a role, since family members often share lifestyle habits regarding smoking and dietary intake and may influence each other via subjective and descriptive norms, social support and social pressure. [25] Family interventions can be useful to improve health outcomes. The British Family Heart Study, for example, showed the benefits of family-based counseling by a trained nurse that resulted in a significant reduction in smoking, blood pressure, cholesterol levels and CVD risk after a 1-year follow-up. [26] The PRO-FIT intervention was designed to target individuals, although family members were included in the face-to-face counseling session if requested. However, a real family-based approach would entail household group sessions of MI and thus empower family members to provide support for participants to achieve lifestyle improvement.

In addition to the contribution of motivational, environmental and social determinants, recent research indicates that engaging in healthy behavior may also be strongly influenced by genes. Recent twin studies, for example, indicate that the likelihood of engaging in sport activities versus sedentary behaviors is more strongly explained by genes than by environmental differences. [27,28,29] Smoking behavior and alcohol intake also appear to have a genetic component. [30] Additionally, it is well documented that people differ in their innate preferences for sweet and fatty foods and their dislike of bitter foods. [31,32] More insight in the consequences of these findings for intervention development is needed, as models like I-Change predominantly generally focus on conscious motivational factors, while the substantial genetic influence on health behavior might influence people's response to health behavior change interventions.

In short, further examination of environmental and social determinants in longitudinal and intervention studies, as well as genetic influences in twin studies, will increase the understanding of how these factors actually relate to the health behaviors of people with FH. This would enable the development of intervention programs that are tailored to individual, environmental, social and genetic determinants to effectively promote health behaviors.

Intervention strategies

During the development of the PRO-FIT intervention, we focused on the behavioral determinants that were identified mainly according to the I-Change model. Therefore, employed strategies and intervention components were based on these determinants (see Table 1). In the forthcoming paragraphs, the contribution of the key intervention strategies to the results of the project will be discussed.

Risk communication

Based on the assumptions of the I-Change model, (un)awareness of an increased CVD risk was defined as a pre-motivational determinant. In the PRO-FIT project, participants were presented with online CVD risk information to improve their risk perception, emphasizing the contribution of the various CVD risk factors and their changeability, as well as cues about how to change risk behaviors. Despite the absence of an interventional effect on lifestyle behaviors and biological CVD risk factors, an effect on an intermediate such as risk awareness could be indicative for the development of future lifestyle interventions targeting high-risk populations. So far, no comparable experimental study has been done with an FH sample. A non-experimental study, by Van Maarle et al., showed that people who were FH-positive correctly perceived a higher risk of having a CVD compared to those who were FH-negative. [33]

Computer tailoring

There are two main advantages of using internet-delivered interventions: they can be personalized by the use of computer tailoring and they can reach a large audience at a relatively low cost. The PRO-FIT intervention was personalized by tailoring the lifestyle advice to demographic information and the most important behavioral determinants: awareness, motivation to change, outcome expectations, attitude and self-efficacy, as well as personal performance level (e.g. level of physical activity). In retrospect, in addition to my doubts about whether we targeted the right determinants (see: 'targeted behavioral determinants'), another concern regarding the computer-tailored approach for the PRO-FIT intervention requires consideration.

On the *PRO-FIT** advice website, participants could choose what/how many advice modules to go through. As a consequence, we actually do not know the underlying reasons why people chose specific modules. For example, did a participant choose the module on fruit intake because he/she was eating too little fruit, or because the advice module had a less extensive screening questionnaire? Maybe changing fruit intake was perceived as more easy to achieve than stopping smoking? In concordance with our argument for a more specific approach towards high-risk populations, the content and structure of *PRO-FIT** advice could also be adjusted for a high-risk population, e.g. by providing better guidance in the choice for an advice module on *PRO-FIT** advice, instead of our 'free choice' approach. Adding a short pre-screening questionnaire prior to

the advice modules could assist in guiding the participant in the 'right' direction. 'Right' would be defined as the advice module that connects with the behavior that should be changed in order to reduce CVD risk.

Motivational interviewing (MI)

MI was chosen as the counseling method for the face-to-face and telephone counseling sessions, because of its effectiveness in facilitating health behavioral changes across a range of domains [34], including CVD rehabilitation practice. [35,36] Three comments can be made when reconsidering this approach, taking into account the results of the PRO-FIT trial.

When lifestyle coaches explore a client's readiness to change, two conditions should be met: recognition of the importance of a problem, and the belief in one's ability to change the problem. [37] However, Miller discussed that even when a client recognizes the importance of change and has the confidence to change, he/she may still not take action because they think the behavioral problem is not worth 'solving'. [38] Therefore, false CVD risk perceptions, e.g. the belief that CVD risk is 'uncontrollable', in this study might have blocked the change of lifestyle behavior; although this explanation remains speculative. If this insight holds true, more emphasis before actual counseling has started should be placed on the effective communication of CVD risk factors and their changeability, to optimize the impact of MI in future interventions.

Opportunities for the initiation of behavioral change will then arise, as people will not put effort into behavioral change programs if they are not convinced that such programs will contribute to improved disease status.

One assumption of MI is that the counselor should allow the client to be autonomous in the decision-making process. But the preference for autonomy varies from person to person. Studies on this topic are scarce. Our data did not show an association between the level of a need for autonomy and the efficacy of MI. However, it is not unthinkable that people with an elevated CVD risk simply want to be told what to do to reduce their risk. Resnicow et al (2008) showed that individuals with a low preference for autonomy responded to both directive and autonomy-supporting health messages. [39] More studies on this topic are needed, including the assessment of an individual's preference for autonomy linked to MI fidelity and the effects on health outcomes to gain insight into whether MI is suitable for individuals with no need for autonomy.

In the literature, MI has repeatedly been viewed as particularly useful and effective for people who are reluctant or ambivalent to change their behavior. [34] The majority of the study participants in the PRO-FIT trial had met the recommendations on physical activity and smoking behavior at baseline (physical activity: 78%; non-smokers: 81-85%). Miller and Rollnick defined MI as a useful approach for people in the action or maintenance stages as well, but this requires improvement of self-efficacy and reinforcement of

accomplishments, both of which are important in sustaining long-term change. [38] Of course, MI might have been successful in achieving maintenance of behavioral change for these participants.

Multi-channel approach

The delivery of the PRO-FIT intervention by the internet, face-to-face meetings and telephone, i.e. the multi-channel approach, had several advantages. From a communicative perspective, addressing both interpersonal and mediated channels maximized the impact of the intervention. Assuming that each individual prefers a distinct approach, the chances to reach each participant increased by our multi-channel approach, since the type of approach was accompanied by a specific communication style, e.g. straightforward and directive online feedback versus participant-centered face-to-face contact. Another advantage was that face-to-face counseling complemented *PRO-FIT** advice when needed. For example, when no online action plan was formulated, this was addressed during the first part of the counseling session. Participants' questions regarding *PRO-FIT** advice could be answered by the lifestyle coaches. On the other hand, using the first part of the counseling session to address questions about *PRO-FIT** advice may have been at the expense of MI counseling. The multi-channel approach might have been more successful if *PRO-FIT** advice had complemented MI counseling by including counselor support on the website through an interactive communication board/forum and a place for counselors and participants to communicate.

Intervention delivery

Computer-tailoring

Despite the high level of the delivered dose of *PRO-FIT** advice, the extent to which participants actively engaged in using the website as intended was disappointing. Suboptimal exposure to web-based interventions has already been pointed out as a major concern in health promotion studies. [40] Results from other process evaluations have confirmed that despite the potential of *PRO-FIT** advice (or web-based interventions in general) to be delivered at a high dose, achieving an acceptable use of the intervention remains challenging and less controllable. Based on previous research and the results of the PRO-FIT trial, two additional strategies may improve the use of *PRO-FIT** advice. First, the burden of filling in (screening) questionnaires should be minimized in order to keep participants motivated, as the significant overlap between the screening and evaluative questionnaires might have annoyed participants. The creation of a joint questionnaire, for both evaluative and tailoring purposes, could be more motivating. Second, the length of a visit at *PRO-FIT** advice internet site can be prolonged by using more interactive website components, such as a discussion board. Third, the use of SMS messaging can be an effective method for supporting computer-tailored education, as it allows a two-way communication and research has shown a doubling of the log-on frequency. [41,42] Because of these advantages and given the massive increase in use of

smartphones worldwide, mobile technologies should be considered more often to promote lifestyle changes. [43]

Counseling

The results of the process evaluation showed that none of the 20 evaluated counseling sessions were delivered according to MI methodology as assessed with the MITI 3.1.1. [44] Other studies on MI counseling also have reported below-threshold scores. [45,46,47] An underlying reason for these low scores was probably that a 3-day MI workshop was too short, since the skills required for effective MI may take longer to develop. [48,49] Despite the inclusion of role-play with professional actors, the workshop did not include real-time components. In addition to the counseling sessions for practice that took place in the pilot study, further 'coaching-on-the-job' would have been valuable to teach and correct MI skills more effectively and to provide ad-hoc feedback on pitfalls.

Another explanation for the low MI fidelity is that, in addition to an MI protocol, the application of the intervention protocol probably indirectly forced the counselor to structure the sessions in a non-MI methodology by asking closed questions. This could have explained the insufficient reflections to questions ratio, since asking questions can structure a conversation in a specific way.

By providing a 3-day workshop and an intervention protocol to both lifestyle coaches, we attempted to have consistent delivery of MI throughout the sessions. Nevertheless, despite all efforts, differences in background, demographics and other personal characteristics (e.g. counseling style) were unavoidable, and undoubtedly affected the counseling performance. It has been argued that a workshop is too brief to change existing counseling habits, leading to closed questions that result in low MI fidelity. [50] Clinicians and nurses are often taught to efficiently lead conversations in a short timeframe by asking closed questions to arrive at a differential diagnosis and treatment plan. For counselors with a medical/nursing background, changing these habits was an additional challenge. In accordance, the analyzed face-to-face sessions showed that the life coach with a more extended and diverse counseling history performed more poorly than the coach with a more limited (though lifestyle counseling) background. We should always keep in mind that in real-life settings, counselors also differ in background and counseling style.

EXPLANATIONS RELATED TO THE EXECUTION OF THE PRO-FIT PROJECT

In the 'hierarchy of evidence', an RCT is regarded as the gold standard, particularly when a researcher wants to find out whether a treatment is efficacious or not. [51] The PRO-FIT intervention was thus evaluated with the appropriate research design to provide a controlled setting; so observed effects could best be attributed to the treatment conditions that were compared. However, there were important issues related to an

evaluation in a controlled setting that merit attention.

Measurement issues

The assessment of the multiple lifestyle behaviors by self-report could have led to inaccurate responses and/or socially desirable answers due to recall or social desirability bias. Though, if this had been the case, it would have occurred in both the intervention and the control group. By using validated questionnaires for the assessment of saturated fat, fruit and vegetable intake and compliance to statin therapy (as described in chapter 1 and in chapter 3) we aimed to reduce the inaccuracy of self-report to a minimum. The SQUASH questionnaire and the short questionnaire on fat intake have shown acceptable reliability and validity, compared to 'computer science and applications' (CSA) activity monitors, 7-day diet records and biomarkers. [52,53,54] In contrast to more objective physical activity measures (e.g. the accelerometer), the SQUASH questionnaire has certain advantages: it provides a detailed oversight of the type, duration and intensity of physical activity, and does not face incompatible conditions or placement issues. The short questionnaire on fruit and vegetable intake has been validated using blood levels of carotenoids and vitamin C correlations reported in the literature.[55] However, despite the validation of study questionnaires, potential misclassifications should be kept in mind when interpreting the results of the PRO-FIT trial.

Despite good reliability and validity, the five-item Medication Adherence Report Scale (MARS-5) used to measure self-reported compliance to statin therapy, also has limitations.[56] Scores on five items were combined to give a total score ranging from 5 (lowest) to 25 (highest). The items documented whether participants: always (1) / never (5) forgot or stopped their medication, decided to miss a dose, took less medication than instructed or altered their dose without consulting a medical doctor and/or pharmacist. Participants with a score of ≥ 24 were categorized as compliant to statin therapy, others (score < 24) as non-compliant. This rather strict and arbitrary cut-off criterion was based on a review by Haynes et al. in which compliance was defined as being low if one or more doses were missing.[6] Weakening this cut-off criterion by defining participants with a score below 23 as non-compliant alters the results of our study; more participants would then be considered as compliant. As an alternative, continuous electronic monitoring of compliance is considered as the golden standard, with the use of a microprocessor in the cap of a medication bottle that records the date and time it is opened; however this was not used in this study.

Despite the lack of self-report biases, the objective instruments that were used, e.g. the Cholestech LDX analyzer to assess lipids and glucose levels, also have drawbacks. Despite the Cholestech LDX having self-calibration options, user-friendliness and being compact to transport, LDL-C was determined indirectly by using HDL-C and triglycerides concentrations (also measured by the Cholestech LDX). [57] For this reason,

and because of the limited range of the Cholestech LDX analyzer, not all LDL-C levels could be calculated. Fortunately, it is unlikely that this limitation led to a measurement flaw, since no differences in effects were seen between the complete case dataset and the dataset in which the missing LDL-C values were calculated through multiple imputations.

Extrapolation to CVD risk

Reflecting on the I-Change model as it used in the PRO-FIT project, we could not confirm or reject whether improvements of biological CVD indicators were caused by behavioral improvements. Although we checked the interventional effects on the main outcomes for confounding or interaction with behavioral (more proximal) determinants (e.g. risk perception and motivation), we do not have insight into the efficacy of the PRO-FIT intervention and whether the interventional effects mediated behavioral change. In my opinion, the inclusion of more than one follow-up measurement in our research design could have enabled analyses to measure intermediary changes in the presumed determinants of the risk factors. It would have been useful to assess those intermediates by using a longitudinal design with longer follow up and multiple measures. The addition of follow-up measurement points to the current data of the PRO-FIT project could still provide insight into the working mechanisms within the I-Change model and in general.

As described in chapter 1 and in chapter 3, we assessed the most relevant CVD risk indicators according to ATP III guidelines. [58] The collective contribution of small improvements of these risk factors could be cumulative, and larger than the CVD risk reduction associated with a single risk indicator. Unfortunately, we were not able to integrate these risk indicators into one CVD risk estimate. To date, no CVD risk prediction tool, such as those derived from the Framingham Heart Study, is available for FH populations. Professional guidelines discourage a CVD risk prediction tool, as it is likely to underestimate the CVD risk [58, 59], since unlike the rest of the population, people with FH have had high levels of cholesterol since birth that probably increase their relative risk. [60] However, such a tool would have been beneficial for the interpretation of our results, and moreover, it would have enabled us to identify people with severely increased CVD risk.

Furthermore, to draw conclusions about the interventional effect on morbidity and mortality, trials with longer follow-up periods and larger sample sizes are needed. A hypothetical sample size calculation indicates that a RCT would require approximately 1000 participants to detect a reduction of 5% or more in the incidence of CVD over 10 years in the intervention group, compared to usual care, at a power of 80% and a significance level of 0.05. Consequently, trials with longer follow-up periods and larger sample size would lead to more valid conclusions regarding intervention cost-effectiveness, as the large variability in the use of resources and cost measures should be minimized. [61] To illustrate this, the cost-savings we found in the

cost-effectiveness analyses must have been coincidental, because it seems unlikely that the PRO-FIT intervention was able to positively affect hospital admissions within the time frame of 12 months of this study, for example. Extrapolation of cost-effectiveness over an extended period of time by means of modeling studies is recommended. [62]

SO WHAT?

The PRO-FIT intervention did not change behavioral and biological outcomes in people with FH when compared to usual care. In short, both the underestimated heterogeneity of the sample used in this study and the lack of full implementation of the intervention probably contributed to the lack of efficacy. The lack of effects of this lifestyle intervention provokes the following question: “Should we forget about the promotion of a healthy lifestyle, and only prescribe cholesterol-lowering medication to all people with FH?” My answer is “yes” and “no”. “Yes” because it is irrefutable that statins are the most effective treatment to reduce LDL-C levels, particularly in people with FH, since minimal reductions of 50% are required to reach an LDL-C target of 2.5 mmol/l. [63] My answer is “no” because 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.

According to the NICE guideline, lifestyle advice should be a component of the treatment of FH, though it should not replace lipid-modifying drug therapy. [64] There is consensus on lifestyle recommendations for people with FH; however, a recommended format to effectively deliver these is still lacking. Results from the PRO-FIT trial showed that the implementation of a lifestyle-advice intervention remains challenging, and that various factors can interfere. The implications from this project for the development and evaluation of future comparable interventions can contribute to a consensus on an effective delivery of lifestyle advice to FH patients.

Emphasis on improving compliance to statins

The NICE guidelines are specific with regard to cholesterol-lowering medication and lifestyle advice. However, no recommendations on compliance to medication were formulated. Within the PRO-FIT project, baseline and follow-up LDL-C concentrations still did not reach the recommended treatment target concentration in our study (≤ 2.5 mmol/l for non-FH high risk populations). Clearly, there is a need for the improvement of compliance to statin therapy, as underlined by the outcomes described in chapter 5 and in the literature. The baseline self-reported compliance to statin therapy in our project (38-44%) was comparable to those reported by other studies. In addition to cholesterol-lowering medication and lifestyle advice, increasing compliance to medication should become a major target for intervention. Therefore,

effort should be put into the identification of potential barriers to compliance, in order to develop more successful compliance-improving interventions for high-risk individuals with FH. Meta-analyses already suggest that the most effective compliance-enhancing interventions should be initiated early in therapy [65], and should contain combinations of more convenient care, counseling, reminders, reinforcement and other forms of supervision or attention. [6,66,67] Since the idea that medication has clinical benefits is a key predictor of compliance [68], emphasis should also be put on the communication of CVD risk and the potential benefits of compliance to statin therapy.

RECOMMENDATIONS FOR FUTURE INTERVENTION STUDIES

Based on the above-mentioned explanations and insights, I would formulate the following critical recommendations for anyone organizing a comparable project in the future. These recommendations are related to either the content of the intervention (PRO-FIT 2.0), or to the execution of the PRO-FIT project 2.0.

The PRO-FIT intervention 2.0

- ★ Select the improvement of compliance to statin therapy as the major target of the intervention.
- ★ Use computer-tailored education with tailoring on both individual (e.g. self-efficacy) and environmental (e.g. availability/accessibility, social environment) determinants of lifestyle behaviors.
- ★ Systematically involve household members in counseling sessions to empower them to provide family support to participants.
- ★ Guide participants in their choice for an online computer-tailored advice module by adding a short pre-screening questionnaire, instead of a 'free choice' approach.
- ★ Emphasize the effective communication of CVD risk factors and their changeability, before the actual counseling session begins to increase the impact of counseling.
- ★ Use a multi-channel approach, since online and face-to-face channels can work complementarily. Optimize this approach by including online counselor support through an interactive discussion board/forum.
- ★ Reduce the burden of filling in online screening questionnaires in order to generate computer-tailored advice by creating a joint questionnaire, for both evaluative and tailoring purposes.
- ★ Uplift the website with computer-tailored advice modules by including a discussion board/forum in order to prolong the participants' visits.
- ★ Use SMS messaging to support the computer-tailored advice modules.
- ★ Teach counseling skills to counselors by a 'coaching on the job' workshop.

The execution of the PRO-FIT project 2.0

- ★ Include more than one follow-up measurement with the assessment of potential mediators of the effect on lifestyle behaviors and CVD risk indicators (e.g. risk perception) and more distal outcomes (e.g. morbidity, mortality).
- ★ Aim to merge all CVD risk factors into one CVD risk estimate.
- ★ Put emphasis on a thorough power and sample size calculation, including both health- and cost-related outcomes.

GENERAL IMPLICATIONS FOR RESEARCH

A strong focus is needed on the development and testing of behavioral change models including personal *and* environmental determinants, assuming that behavior is the result of rather automatic responses to environmental cues on one hand, and of systematically built beliefs and decisions on the other hand. With the inclusion of environmental clues, opportunities for the development of future lifestyle interventions will increase. Further, understanding is needed of the causal pathways of behavioral change, particularly, the 'awareness – motivation – behavior' pathway. By means of mediation analyses, clues could be provided for the development of future personally relevant lifestyle interventions. This also requires the development of valid and reliable instruments to assess lifestyle behaviors, particularly compliance to statin therapy, as well as its determinants. Furthermore, to draw valid conclusions about the effects of a lifestyle intervention on morbidity and mortality, as well as on cost-effectiveness, trials with longer follow-up periods and larger sample sizes than those used in this study are needed.

CONCLUSIONS

Despite a theory- and evidence-based 'high-risk approach', lifestyle behaviors and biological CVD indicators could not be changed in a sample of people with FH. It is irrefutable that statins are the most effective treatment in reducing LDL-C levels. A joint strategy is needed to reduce CVD risk in people with FH, 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.

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