PROMOTING A HEALTHY LIFESTYLE IN PEOPLE WITH FAMILIAL HYPERCHOLESTEROLEMIA

KAREN BROEKHUIZEN

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THE DEVELOPMENT AND EVALUATION OF AN INDIVIDUALLY TAILORED INTERVENTION

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Karen Broekhuizen

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CHAPTER 1

GENERAL INTRODUCTION

The number of people with chronic diseases is increasing worldwide and it is inevitable that every individual will —in the long run—face a health problem during their lifetime. Broadly, in order to reduce the burden of any health problem, four approaches in public health are available: health promotion/disease prevention, early disease detection and early treatment, disease cure, and disease management. [1, 2] Health promotion and disease prevention are often regarded together in one sentence and are defined as the aggregate of purposeful activities to promote personal and public health. [3] During the past 25 years, public, private and professional interest in health promotion/disease prevention have increased as there has been: an epidemiologic transition from infectious to chronic diseases as the leading causes of death worldwide, a demographic transition as populations age, a rapid escalation in health care costs, and new data linking individual behaviors to increased risk of morbidity and mortality. [4] Given this perspective, prevention of chronic disease is of eminent importance, and cardiovascular disease is amongst the main chronic disorders.

This thesis reports on a number of studies examining various aspects of the PRO-FIT project, a project aimed at the early prevention of cardiovascular disease (CVD). More specifically, this project focused on the development and evaluation of an innovative intervention to reduce CVD risk by promoting a healthy lifestyle among people with Familial Hypercholesterolemia (FH). This introductory chapter provides a general background and rationale for the PRO-FIT project. At first, the health problem and related biological and behavioral risk factors are introduced.

THE HEALTH PROBLEM: CARDIOVASCULAR DISEASE

Cardiovascular diseases are the leading causes of premature death in Western countries and are responsible for a substantial number of 'healthy years lost' (DALYs) worldwide—10% in low- and middle-income countries and as high as 18% in high-income countries. [5] CVD accounts for the second highest health-care related costs in the Netherlands.[6] Atherosclerosis is characterized by a progressive build up of a plaque (containing fatty deposits and other cells) in artery walls, and is the main cause of CVD and is triggered by such factors as high blood lipid levels, high blood pressure and infectious processes. [7]

Biological risk factors

Dyslipidemia, hypertension and diabetes mellitus have been appropriately highlighted as established biological CVD risk factors. [8] Elevated levels of low-density lipoprotein cholesterol (LDL-C) (≥ 2.5 mmol/l) and triglycerides (≥ 1.7 mmol/l), as well as low levels of high-density lipoprotein cholesterol (HDL-C) (≤ 1.3 mmol/l), play a dominant role in the initiation and progression of atherosclerosis. [9] In

particular, high serum LDL-C levels are significantly implicated in the development of atherosclerosis and its consequences.[10] Further, both clinical and experimental data have shown that high blood pressure
(≥ 140/90 mmHg) enhances the development of atherosclerosis due to the mechanical injury to arterial walls. In addition, type 2 diabetes mellitus often occurs with obesity and is a risk factor for CVD. High blood sugar levels can lead to blood lipid abnormalities, hypertension and systemic inflammation all of which predispose people to atherosclerosis and thus to CVD. [11]

Familial Hypercholesterolemia

Familial Hypercholesterolemia (FH) is associated with elevated LDL-C levels. This inherited disorder affects around one in 500 individuals in the heterozygous form. [12] It is caused by a mutation in the LDL-C receptor gene, leading to an approximately two-fold elevation in plasma LDL-C levels. Excess plasma LDL-C deposits in tendons and arterial walls contribute to tendon xanthomas (see Figure 1), atherosclerotic plagues and an increased risk of premature CVD. If left untreated, 50% of the male heterozygotes will develop a myocardial infarction before the age of 50, and 30% of the women will do so before the age of 60. [13] People with untreated FH usually have LDL-C levels in the range of 5-10 mmol/l. [14]

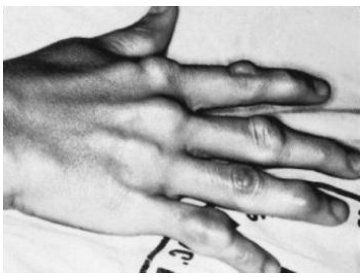

Figure 1: Xanthoma formation as a result of high LDL-C levels from FH

Behavioral risk factors

Targeting biological CVD risk factors alone to prevent the incidence of CVD, excludes important underlying risk factors, such as unhealthy lifestyle behaviors. Research has shown that the prevalence of obesity, dyslipidemia, hypertension and diabetes mellitus is much lower among populations with more healthy lifestyle behaviors. [15,16,17,18]

Dietary behavior and physical activity affect established biological risk factors, such as dyslipidemia, hypertension and diabetes mellitus, as well as other intermediate risk factors, such as obesity.[8]

Particularly modest consumption of oily fish [19], low or no trans-fat consumption [20,21] and replacing saturated fat intake with unsaturated fats are associated with a lower CVD risk. Consumption of whole grains, legumes and cereal fiber [22], and fruits and vegetables [23] may have additional CVD risk benefits. The benefits of physical activity are also important, as it raises HDL-C, lowers LDL-C and triglycerides, lowers blood pressure, improves fasting and postprandial glucose-insulin homeostasis, induces and maintains weight loss and facilitates smoking cessation. [24,25,26] The harmful effects of smoking and the benefits of smoking prevention and cessation are also well established, and declines in smoking have substantially reduced cardiovascular events in some populations. [27,28] In contrast to the other CVD risk factors, poor adherence to medication (i.e. not using medication as prescribed) is often considered as a hidden behavioral CVD risk factor. [29] After all, despite the proven effects of statin therapy, regimens can only be effective at reducing the risk for CVD if patients follow them.

Determinants of exposure to risk factors

Determinants of exposure to the above-mentioned risk factors are causal factors that induce an individual to be exposed to a particular risk factor. In order to develop an effective lifestyle intervention, it is important to identify the determinants most strongly related to lifestyle behaviors that can be changed. In this process, behavioral change models can be of assistance. In short, many social cognitive models of health behavior (such as the Theory of Planned Behavior [30] and the Precaution Adoption Theory [31]) state that an individual's intention or motivation is an important and proximal determinant of engaging in (un)healthy lifestyle behaviors. The Theory of Planned Behavior and similar models then posit that intention or motivation is influenced by three important categories of determinants: a weighing of the expected pros and cons (attitude), self-efficacy or perceived behavior control, and perceptions of the social environment (e.g. subjective and/or descriptive norms). Additionally, stage-based models of behavior change such as the Transtheoretical Model and Precaution Adoption Process Model claim that the importance of various determinants of behavior change may vary according to the stage of change the individual is in, and that behavioral change interventions should thus be stage-of-change-specific. [32] The I-Change model is an example of an integrative stage model that integrates determinants and stages of change. [33] The model assumes that at least three stages in the behavioral change process can be distinguished: awareness, motivation and action. For each phase, particular determinants are defined as relevant (see Figure 2).

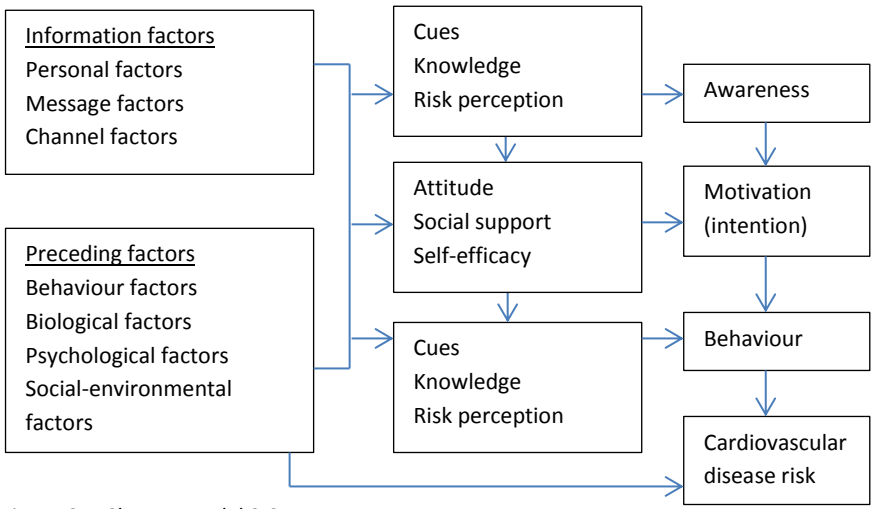

Figure 2: I-Change model 2.0

In the 'pre-motivational' awareness phase, people need to become aware of their risk behavior. Determinants to proceed through this phase according to I-Change are knowledge, risk perceptions, and cues that prompt people to become aware. In the motivational phase, people should become motivated to change their behavior. Determinants in this phase according to the I-Change model are attitudes, social support and self-efficacy expectations. Proceeding through the motivational phase results in a positive intention to change one's behavior. In the action phase, people need to translate intentions into actual behavior change. In this phase, several preparatory actions to facilitate behavior change must be planned and executed. People should convert their more global goal intentions into specific action plans with relevant strategies that will enable them to attain their goal. Finally, the I-Change model assumes that these processes are determined by various predisposing factors such as behavioral factors (e.g. lifestyle behaviors), psychological factors (e.g. personality), biological factors (e.g. gender, genetic predisposition), social and cultural factors (e.g. the price of cigarettes, policies), and information factors (the quality of messages, available channels and sources). [34]

The I-Change model has been used to study determinants of CVD risk behaviors in a range of

populations and this research has found general support for the importance of the presumed determinants. [33,35,36,37]

ADDRESSING THE HEALTH PROBLEM

Now that the health problem, as well as its determinants and risk factors are analyzed in the sections above, the next step is the development of intervention strategies to address the health problem. At first, a description of the current 'usual care' for people with FH is given in the following two paragraphs.

Management of Familial Hypercholesterolemia in the Netherlands

Screening for FH has been ongoing in the Netherlands since 1994. Cascade-wise, family members of individuals who are diagnosed with FH by their general practitioner and/or medical specialist (indexes) are traced by the Dutch Foundation for FH screening (in Dutch: StOEH). By this method, 23.668 family members with FH have been found and genetically diagnosed in the Netherlands so far. In 2010, of the 4654 investigated family members, 1685 (36.2%) proved to have FH according to DNA diagnostics. [38] Overall, this approach proved to be a (cost-) effective way to identify persons who have FH in the Netherlands. [39,40,41]

Dutch guidelines recommend a LDL-C treatment target of ≤ 2.5 mmol/l for people with FH. [42] The treatment of FH entails both pharmaceutical treatment and lifestyle modifications. There is consensus on statin treatment as the primary treatment for people with FH [42], and several studies have shown that statin therapy reduces LDL-C levels and CVD risk. [43,44,45,46,47] However, significant CVD risk persists despite effective LDL-C lowering statin treatment. [48]

Intervention strategies in addition to statin therapy

Since CVD risk reduction by effective lipid-lowering statin therapy is not optimal, two additional strategies remain to achieve an optimal CVD risk reduction: 1) addressing multiple CVD risk factors, and 2) reducing LDL-C by improving adherence to statin therapy. In order to develop an intervention to further reduce CVD risk among people with FH by promoting a healthy lifestyle, the most important CVD risk factors and determinants should be translated into intervention strategies. According to the I-Change model, for each stage in the behavioral change process—awareness, motivation and action—and accompanying determinants, specific intervention strategies are needed

(see Table 1).

Table 1: Intervention strategies to address each stage of the behavioral change process in the I-Change model and determinants [34]

BEHAVIORAL CHANGE DETERMINANTS	INTERVENTION STRATEGY
Genetic predisposition, current lifestyle, personal characteristics and information factors *Predisposing determinants*	**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 *Awareness phase*	**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 *Motivation phase*	**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 *Action phase*	**Motivational Interviewing** Stimulating people to make action plans and discussing how to overcome barriers to behavioral change.

Risk communication

Unfortunately, just telling people that they are at risk of developing a disease is rarely sufficient to change behavior. [49,50] However, effective risk communication can improve awareness of health risks and promote risk-reducing behavior in support of health promotion and disease prevention. [51] Research has shown that risk communication is most effective in motivating people to make behavioral changes when the problem is perceived to be severe and personally relevant enough to

warrant action, the behavior change is perceived to be effective in reducing the risk, and the behavior change is perceived as doable. [52] Risk communication should preferably include an assessment of the risk (perception), and should be framed in terms of relative risk and natural frequencies (instead of in terms of absolute risk and proportions). [53] [54]

Computer tailoring

Previous research has shown that computer-tailored education is an innovative and promising method to motivate people to change their physical activity and dietary behaviors, and it has shown better effects than generic health education. [55,56,57,58,59,60] The fact that computer-tailored health education provides people with personalized feedback and advice is probably the main determinant of its effectiveness. [61] Unlike interpersonal counseling, it has potential for wide distribution at relatively low costs. At the same time, individualized feedback can be given based on (awareness of one's) personal performance levels (i.e. dietary intake or physical inactivity), personal motivation, outcome expectations, self-efficacy and other behavioral determinants. In the past years, significant steps were made in the field of computer-tailoring and numerous reviews have been published that show the effectiveness of computer-tailored education, although such effects are mostly based on self-report measurers and the effect sizes have been generally small. [55,56,57,58,59,60]

Motivational interviewing

Motivational Interviewing (MI) has been found to be useful intervention strategy in behavioral-change interventions. [62] MI is directive, but client-centered and its main goal is to help the client to identify and mobilize or her intrinsic values and goals related to the targeted behavioral changes. Meta-analyses indicate that MI can be effective in facilitating health behavioral changes across a range of domains. [63,64] The five main principles of MI are: 1) showing empathy, 2) avoiding discussion, 3) rolling with resistance, 4) supporting self-efficacy, and 5) raising awareness of a dissonance between actual behavior and behavioral goals. The main MI interviewing strategies are: asking open-ended questions, showing empathy, reflecting on the client, confirming and summarizing. [65] A review by Rubak has shown that approximately 75% of the studies did obtain an effect, regardless of whether the problems were psychological or physiological. [62]

The PRO-FIT intervention

According to the above-mentioned intervention strategies, taking into account the most important risk factors and determinants, the PRO-FIT intervention was developed. It involved a combination of tailored web-based lifestyle advice and face-to-face counseling, based on MI, and complemented

with telephone booster sessions. Its goals were to: 1) improve awareness of the CVD risk, 2) improve motivation with respect to a healthy lifestyle, regarding physical activity, dietary behavior, smoking and compliance to medication, 3) induce adoption and maintenance of a healthy lifestyle, and 4) lower LDL-C levels and CVD risk.

The evaluation of the PRO-FIT intervention

The PRO-FIT intervention was evaluated in a randomized controlled trial in which individuals with FH were randomly assigned to a control or intervention group. Participants were individuals who were diagnosed with FH by StOEH from January 1st 2007 to April 15th 2009. Participants were included in the project if they: 1) were aged 18-70 years, 2) were sufficiently fluent in Dutch, 3) had given informed consent, 4) had a LDL-C level that was >75th percentile (corrected for age and gender), 5) lived in a 150 km radius of Amsterdam, and 5) had access to the internet. The participants in the intervention group received the PRO-FIT intervention. The control group received care as usual. In order to investigate the intervention effect on lifestyle behaviors and biological CVD risk indicators, the following outcomes were assessed: smoking, physical activity, saturated fat intake, fruit and vegetable intake, compliance with medication, systolic blood pressure, glucose, body mass index (BMI), waist circumference and lipids (triglycerides, total, LDL and HDL cholesterol). Measurements were taken at baseline and 12 months after randomization.

According to a process evaluation plan, intervention reach, dose delivered and received, and counseling fidelity were assessed using the recruitment database, website/counseling logs and the Motivational Interviewing Treatment Integrity (MITI 3.1.1.) code. [66] In addition, the association between the intervention dose and change in LDL-C and multiple lifestyle behaviors was investigated.

An economic evaluation was conducted from a healthcare perspective, including an analysis of differences in intervention development and implementation costs 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). Costs data were collected using a 12-month retrospective questionnaire and quality of life was measured with the EQ-5D questionnaire at baseline and after 12 months. [67]

Outline of the thesis

A short description of the background and rationale is presented in this introductory chapter. Chapter 2 includes an update of a systematic review on the effectiveness of computer-tailored physical activity and nutrition education. The process of the development and the evaluation plan of

the PRO-FIT intervention is described in chapter 3. Chapter 4 incorporates the interventional effect on smoking, physical activity, saturated fat intake, fruit and vegetables intake, and compliance to statin therapy. Chapter 5 describes the effects of the intervention on biological CVD risk indicators, namely systolic blood pressure, glucose, BMI, waist circumference and lipids.
The results from the point view of the process of the intervention delivery and its association with the observed intervention effects is highlighted in chapter 6. Next, the cost-effectiveness and cost-utility of the PRO-FIT intervention is reported in chapter 7. Chapter 8 is a summative and general discussion chapter in which the results are compared with those from other relevant studies. In this chapter, the results are explained from a variety of perspectives and recommendations are formulated for the design and evaluation of future interventions. Finally, the actual contribution of the results of the project to practice is discussed.

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CHAPTER 2

A systematic review of randomized controlled trials on the effectiveness of computer-tailored physical activity and dietary behavior promotion programs: an update

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Background
Since the first systematic review of randomized controlled trials (RCTs) on the effectiveness of computer-tailored physical activity (PA) and dietary behavior promotion programs was performed in 2006, additional studies have been published, thus necessitating an update.

Purpose
To summarize the latest evidence on the effectiveness of computer-tailored PA and nutrition education programs, and to compare the results to the 2006 review.

Methods
Databases were searched for RCTs evaluating computer-tailored PA and nutrition education aimed at primary prevention in adults, published from September 2004 through June 2011.

Results
Fifty publications were identified. Compared to the findings in 2006, a larger proportion of studies found positive effects for computer-tailored programs compared to generic or no information, including those for PA promotion. The positive results were generally for short- or medium-term follow-up and effect sizes were small). There were also more studies with long-term follow-up, particularly on dietary behavior. Objective outcome indicators were most often used in PA studies.

Conclusions
The results of the 2006 review were confirmed and reinforced. 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.

INTRODUCTION

The potential impact of physical activity (PA) and healthy dietary habits on the prevention of a range of chronic conditions is substantial. [1,2] Effective PA and dietary promotion interventions are needed. Successful intervention strategies and techniques to motivate and guide people to adopt healthy choices need to be identified. Over the last decades, computer tailoring has proven to be an innovative and promising health education technique. [3-12] A computer-tailored intervention mimics interpersonal counseling using a computerized process, but, unlike interpersonal counseling, it can be widely distributed through interactive media channels at a relatively low cost. Computer tailoring allows for individualized feedback and advice on personal behavior, personal motivation, outcome expectations, self-efficacy, social and physical environmental opportunities, and other behavioral determinants.

In recent years, a number of systematic reviews and meta-analyses have been published on the effectiveness of computer-tailored health education covering a range of behaviors. [5,9,10,13-15] The effects of tailoring may, however, be behavior-specific. It has been argued that computer tailoring may be especially promising for complex health behaviors, such as PA and dietary behaviors. [16] Examples of complex health behaviors are gaining increased awareness of personal behavioral patterns, comparing one's own behaviors with recommendations, and setting and monitoring progress towards behavior change goals. The first systematic review that explicitly focused on the effectiveness of computer-tailored health education on PA and dietary behaviors was published in 2006 and included intervention studies published up to September 2004. [3] In concordance with other more narrative reviews on computer-tailored health education [16,17], the authors concluded that computer tailoring was promising, especially for dietary behaviors, although the effect sizes were small. The authors made key recommendations for improving research on computer tailoring, i.e., using objective outcome measures instead of self-report or using generic health education (HE) comparison groups instead of or in addition to no-intervention control groups. The latter would allow more precise evaluation of the effects of tailoring health education interventions. Finally, it was concluded that longer follow-up was needed to assess the sustained effects in all studies.

Since many original studies have been published since 2004, a review update is needed to document evidence regarding the effectiveness of computer-tailored PA and nutrition education programs. Furthermore, responding to recommendations made in 2006, comparing effects and specific study and intervention characteristics over time is additive to other systematic reviews and meta- analyses. This review update aims to: 1) review the evidence on computer-tailored PA and nutrition education from studies published since September 2004, 2) compare the evidence from this review update to that derived from the

original review regarding intervention characteristics, study characteristics and effects, and 3) provide updated recommendations for further research and practice.

METHODS

This paper reports on a second systematic review conducted using the study protocol of the original 2006 review. This protocol was based on guidelines extracted from the Cochrane Reviewers' Handbook. [18]

Search strategy and data sources

For the original review, intervention studies published from 1965 to September 2004 were identified through a structured computerized search of PubMed, PsychInfo and Web of Science. For this update, a nearly identical search was conducted from September 2004 to June 2011. The review differed from 2006 as we added the search engines' most recent thesaurus terms, resulting in the following search terms for nutrition: ((nutrition OR feeding OR food OR diet OR dietary OR intake OR nutritional status OR feeding behavi* OR food consumption) AND (education OR behavior OR behavio* OR education)) AND (tailored OR tailoring OR tailor* OR expert system) and for PA: (exercise OR motor activity OR sports OR leisure activities OR (physical* AND active) OR (physical* AND activity) OR (physical* AND activities) OR exercis* OR walking OR cycling OR sport* OR leisure activit* AND (education OR behavior OR behavio* OR education) AND (tailored OR tailoring OR tailor* OR expert system). No limitations for age or study design were added.

Selection of studies

Just as in the original 2006 review, new studies had to examine a computer-tailored intervention aimed at promoting healthy PA or dietary behaviors for primary prevention of chronic diseases in apparently healthy adults. Evaluation studies that used an RCT were included. Tailoring was defined by Kreuter (1999) as "the intention to reach one specific person, based on characteristics that are unique to that person, are related to the outcome of interest, and have been derived from an individual assessment". [19] Interventions were considered to be computer-tailored if the tailored advice was generated through a computerized process. RCTs were included if: 1) published in a peer reviewed scientific journal, 2) published in English, and 3) conducted in an adult sample (18+ years). Studies were excluded if the tailored intervention was part of a larger intervention program that made it impossible to isolate the effect of tailoring components from the other intervention components.

Data extraction

Detailed information was extracted only from new studies that met the aforementioned inclusion criteria. Two reviewers independently summarized the new studies for content and methods. The following intervention characteristics were extracted: theories used for intervention development, variables used to

tailor the computer-tailored information, the 'tool' that was used to provide individual feedback, frequency of tailored feedback, and additional health-education activities. Extracted study characteristics were: the country where the study was conducted, size and source of the study population, eligibility criteria, intervention modes, and primary outcome measures. Results from single and multiple post-test measurements were extracted. The outcomes included all PA and dietary behavior measures. To interpret and compare results from the studies that used differing measures to assess PA and dietary outcomes, effect sizes (ESs) were calculated if significant effects were found (provided the data were available). The effect size, Cohen's ES, was calculated by dividing the difference between two means at follow-up by their pooled standard deviation. [20,21] Cut-off points for ESs were 0.2-0.5 for small ES, 0.5-0.8 for moderate ES and >0.8 for large ES. [22] The findings were summarized per behavioral outcome (PA, fat intake, fruit and vegetable consumption and other dietary behaviors) and separately for short- (<3 months), medium- (3-6 months), and long-term (>6 months) follow-up.

Apart from reporting the results found in the current review, we compared these with the results of the original 2006 review. In order to check whether recommendations from the original review were met, we compared intervention and study characteristics of the present review with the original one. Frequencies on the number of studies that found significant effects, as well as the number of studies that used objective outcome measures, various types of comparison groups (generic HE versus no-intervention control groups) and long-term follow up, as well as delivery mode (printed versus electronically) are listed in Table 2, linked to the original or current review.

RESULTS

Study selection

The initial cross-database search resulted in 2590 publications. After eliminating duplicates, 1562 remained. Titles and abstracts were reviewed for eligibility criteria, resulting in 141 publications that were fully considered. Fifty publications were finally included: 29 studies on PA and 34 on dietary behaviors, 21 on fat consumption, 18 on fruit and vegetable consumption and 14 on other dietary topics. Other dietary topics included: energy/carbohydrates intake, the consumption of sugar, dairy, fiber, whole-grain, and body fat, as well as weight and waist circumference. Thirteen studies in the current review evaluated interventions that targeted both PA and diet. Some publications reported on the characteristics and effects of one intervention using various follow-up measurements (e.g. short- and long-term effects) [23-28], effects in a variety of study samples [29-32], effects on other types of outcomes (e.g. fruit intake and variety of fruit intake) [34-37], or the effects of various doses of the intervention (e.g. delivered at once or at multiple time points). [38,39] As a consequence, this review update reports on the characteristics and effects of 25 interventions targeted at PA, 27 interventions targeted at dietary behavior, and 10 interventions for both behaviors. Of

the 27 interventions on dietary behavior, 17 were directed at fat reduction, 14 at increasing fruit and vegetable intake, and 12 at other dietary behaviors. The main reasons for exclusion were: the age of the study population was not in the required range, lack of RCT design, no focus on primary prevention, absence of behavioral outcomes, or the computer tailoring was part of a multi-component intervention that made it impossible to isolate the effect of tailoring.

Intervention characteristics

Characteristics of the interventions from studies in the current review are summarized in appendix 1. Both PA and nutrition education interventions were predominantly guided by the Trans Theoretical Model and Social Cognitive Theory. Most interventions (81% of PA, 84% of nutrition) provided tailored feedback on self-reported behavior. Two interventions (4%) also provided feedback based on more objective data obtained from pedometers [40] or accelerometers. [41] Most interventions (92% of PA, 68% of nutrition) were tailored on presumed behavioral determinants such as intention, motivation and stage of change, as well as self-efficacy and skills. Regarding nutrition education interventions, equal numbers of interventions provided print-delivered and electronically tailored feedback; however, the majority of PA interventions used electronic feedback formats (see also Table 2). Some interventions using electronic feedback had additional online discussion/message boards [42-44] (6% of all interventions) or an e-buddy system (2% of all interventions). [23,44] Electronic feedback was given on-screen (41% of all interventions), by email reports (10%), CD-ROM (4%) or by mobile phone(2%). Approximately one third of the interventions provided additional information such as booklets or information sheets. One intervention included weekly home visits. [45,46] Less than half of the interventions provided tailored feedback more than once for dietary behaviors (48%) and 65% did so for PA.

Appendix 1: Intervention characteristics

See end of chapter.

Study characteristics

The characteristics and effects for studies in the current review are shown in Table 1. The majority of studies were conducted in the US, followed by the Netherlands and Belgium, the UK, and several other countries. Studies in the US predominantly assessed PA with the validated 7-day PA Recall (PAR) [47-50]; this was the most commonly used tool. The next most common tool was the validated Short QUestionnaire ASsessing Health-enhancing PA (SQUASH) [51] predominantly used by Dutch researchers. The International PA Questionnaire (IPAQ) [52,53] was the third most commonly used assessment tool. Six studies (21%) included objective assessments of PA, i.e. pedometer, actigraph or accelerometer. Five studies (17%) measured aerobic fitness by either a (1 mile) walking test [54,55], the Chester step test [56] or the submaximal exercise

treadmill test. [57]

Fat reduction was most often assessed using food frequency questionnaires. In the US, the Block questionnaire was used most frequently [58] and in the Netherlands, a questionnaire developed by Van Assema et al. [59] Two studies obtained data from either an electronic scanner [60] or shopping receipts [40] in a supermarket setting. Data on fruit and vegetable consumption was obtained from questionnaires (the Block questionnaire in the majority of studies); one study also used shopping receipts. [40] Studies that included measures of weight or BMI either used self-report [44,61] or measured. [25,29,30,40,62,63] Fiber, grain, energy or added sugars intakes were assessed by food frequency questionnaires. [64,65]

Table 1: Study characteristics and effects found in the studies included in the review.
See end of chapter.

Effects on physical activity (section A, Table 1)

Of the 29 studies on PA, 20 (69%) showed significant differences in favor of the computer-tailored intervention. Five studies looked at short-term effects [42,43,75-77], of which four found significant effects for the tailored intervention [42,43,75,76] with small effect sizes, compared to no intervention. In one study, this applied to participants who did not comply to the PA guidelines at baseline. [76] Of the 17 studies with medium-term follow-up periods, 12 found significant effects with small effect sizes: six compared to no intervention [23,42,67,78-80], five compared to generic HE [25,38,39,81,82] and one compared to a health risk assessment. [61] Studies that investigated two computer-tailoring techniques [23,61,78,82] found significant effects for both tailoring conditions. Six of the 13 studies with long-term follow-up found significant effects of the tailored intervention. [24,26,38,40,80,82] Effect sizes were small except for one study that reported medium effect size for one of the two computer-tailored interventions investigated. [82] Of the eight studies that assessed effects at various follow-up periods, four studies reported no effects at either short-, medium- or long-term [36,41,77,83], six studies reported sustained effects over time[23,24,26,40,42,80,82] and one study reported no effect at short-term but a significant effect at medium-term. [67]

Effects on fat consumption (section B, Table 1)

Of the 21 studies on fat consumption, 17 (81%) showed significant differences in favor of the computer-tailored intervention. Six studies tested short-term effects, and reported significant effects of tailoring compared to no intervention [42,76,84,85], or generic HE [86,87] with small effect sizes. Two of those studies (also) targeted an at-risk population. [76,86] At medium-term, all eight studies found significant

effects compared to no intervention [42,33,84], or generic HE. [33,39,86-88] One of those studies targeted a low-income ethnically diverse population [88] and a second study also found a significant effect among risk consumers (i.e. people with fat intake levels higher than recommended at baseline). [86] Ten studies tested the long-term effects of an intervention and five found significant effects for tailoring compared to no intervention [31,32,84] or generic HE [25,38] with small effect sizes. Two of the ten studies (also) targeted high-risk populations [31,32], and another study targeted women aged 50-69 years. [25] Multiple measurements in time were reported for seven studies, of which five studies reported sustained significant effects [26,42,84,86,87], one study reported a significant effect at short-term [45] that was not sustained in the long-term [46] and one study reported no effects at both medium- and long-term time periods. [37]

Effects on fruit and vegetable consumption (section C, Table 1)

Of the 18 studies on fruit and vegetable consumption, 15 (83%) showed significant differences in favor of the computer-tailored intervention. Two of these studies measured the short-term effects of a computer-tailored intervention, and both found significant effects compared to no intervention [42,85] with small effect sizes in a general population. Six studies measured medium-term effects, of which five found significant effects compared to no intervention [35,42,80] or generic HE [39,88] with small effect sizes. One study investigated the effects of two intervention conditions (either delivered in one or four installments) compared to generic HE and measured the effects of retailored feedback. [88] The latter measured the effect of retailored feedback provided in four installments. Eight of the twelve studies that tested the long-term effects of an intervention found significant effects for tailoring interventions compared to no intervention [34,40,89,80] or generic HE. [25,38,90,91] The eight studies found small effect sizes, except for one that had targeted church members, which found a large effect size over the long-term. [34] Two studies with effective long-term interventions targeted populations who were over 50 years of age. [25,63] Heimendinger and colleagues found a significant effect of (re)tailored advice when spread across four booklets, as opposed to no effect when the advice was delivered in a single booklet. [91] Nine studies reported multiple measurements in time, and seven of these reported sustained effects. [26,35,38,40,42,80,88] One of the nine studies reported no medium-term effect but a significant long-term effect [89], and one study reported no medium- or long-term effect. [37]

Effects on other diet-related behaviors (section D, Table 1)

Of the 14 studies on other dietary behaviors, eight (57%) showed significant differences in favor of the computer-tailored intervention. Four interventions for weight loss found significant effects including: one short-, medium- and long-term[30], one medium- and long-term [44], and two long-term only. [40,62] Effect sizes were small [40,62], medium [30], or large. [44] Of the three interventions on energy intake, one

reported a significant short- and medium-term effect. [86] The corresponding effect size was small for the general study population and medium among risk consumers in the short-term. In addition, at medium-term, only the effect of print-based advice (as opposed to delivery through CD-ROM) was of significance in the general population with a small effect size. Both studies considering fiber consumption found significant short-, medium-term effects [84], and long-term effects [40] with small effect sizes. The intervention on grain intake showed no significant effect, nor did an intervention aimed at reducing added sugar. No significant effect was observed for the intervention to change dairy consumption. [92]

A comparison between the present update and the original 2006 review

The present review, included 50 publications over just under seven years, while the original review in 2006 included 30 publications over 13 years, showing an apparent increase in studies on PA and tailored nutrition education. This increase was most obvious for PA (29 studies in the present review, 11 in the original review).

Since 2004, the number of computer-tailored interventions electronically delivered has increased, particularly in PA studies (see Table 2). New delivery modes, such as mobile phone and CD-ROM were introduced since 2004. Similar to the original review, in the majority of studies included in the present update, a no-intervention control group was included without a generic HE comparison group. Most studies continue to lack objective assessments of effects of nutrition interventions, but PA intervention studies often used objective assessments for behavior changes. As recommended in the original 2006 review, more nutrition intervention studies included long-term follow-up.

In this update, the majority of studies reported significant effects of computer-tailoring, both for dietary and PA behavior (the largest increase). However, effects sizes remained small in general for dietary as well as PA behavior.

Table 2: Study characteristics and effects of studies from the original (<2004) and updated review (>2004) compared

See end of chapter.

DISCUSSION

The present review update confirms and further strengthens the evidence that computer-tailored PA and nutrition education is likely to be effective [5,9,10,14,15,93], although effect sizes related to tailored PA and nutrition education interventions are likely to be small. The evidence for long-term effects of computer-tailoring remains inconclusive.

The present review is an update of a 2006 review of the literature published up to September 2004. A number of differences in the results of the original and updated review are noteworthy. First, both for PA and dietary behavior, the number of published studies has increased substantially. In addition, a larger proportion of published studies reported favorable effects of tailored interventions in the update period than in the original review. Evidence on the efficacy of computer-tailored education is now also apparent for PA promotion. Second, the use of objective outcome measurement instruments increased in studies on PA education, but not for nutrition education studies. Third, overall there was no increase in comparisons of interventions with generic HE since 2004. Fourth, remarkably more studies with long-term follow-up were performed in the past years, particularly on nutrition education. Finally, the electronic delivery of feedback increased, particularly in studies on PA promotion; discussion boards/forums were frequently added to interventions.

The observed differences over time for the use of objective outcome measurements and various types of control groups, follow-up periods and delivery modes require more attention. Since 2004, a larger number of objective measures have been included in tailoring studies, especially regarding PA education. In this field, accelerometers and pedometers have grown in popularity, due to increased usability and feasibility. [94] In the field of nutrition, no such development was seen. The objective measurement of dietary intake can be achieved by monitoring biologic dietary indicators, such as serum cholesterol and serum carotenoids. [95] However, the assessment of biologic indicators is relatively expensive and these indicators are subject to genetic differences. Alternatively, two studies used shopping receipts and electronic shop scanners as objective indicators of food purchases. [40,60] In addition, anthropometrics and waist circumference were the most frequent objective indicators.

The fact that the evidence in favor of computer-tailored PA and nutrition education is now stronger than based on the studies published up to 2004 is promising and important. However, the most evidence comes from studies that compared tailored interventions to no-intervention control groups. Thus, these studies could not assess the effects of tailoring compared to non-tailored interventions. Significant effects were most often found in studies with a no-intervention control group. These findings do not different from the results of the original review or other comparable reviews. [3,6-8,14] Therefore, the evidence is stronger for a comparison between tailored interventions and with no intervention than with generic HE. However, this is probably because of the larger number of studies that included a no-intervention control group. If generic HE control groups were included in a study, the evidence was quite consistently in favor of tailoring. If this review had been restricted only to comparisons between tailored interventions with generic HE comparison groups, it would have focused specifically on the additional effects of tailoring in health education.

Nevertheless, we believe that the comparison with no intervention control conditions is also important, because it shows that tailored interventions are likely to be effective—because of the tailoring or other factors—and that is important information for health education practice. In addition, further exploration of the effectiveness of computer-tailored interventions compared to other control conditions, such as theory-based or personalized interventions, would be valuable to verify whether individually-tailored education is better than theory-based and/or personalized education.

For PA and nutrition interventions to have an effect on health, the effects should be sustained over long periods of time. [97] The present review update shows that since 2004 more studies with long-term follow-up (>6 months) have been published. However, the positive effects of these studies were generally observed at short- and medium-term follow-up. Lack of long-term effects of health education interventions has been reported before. In a meta-analysis of computer-tailored interventions, Krebs and colleagues also found a significant trend of decreasing effect size when follow-up time increased. [4] Some evidence suggests that 'dynamic tailoring' with more tailored feedback moments throughout a long intervention period may improve effects beyond the short term. The present updated review further shows that iterative feedback and tools supporting self-regulatory skills (e.g. goal setting activities, self-monitoring tools, skills building activities, e-mail reminders, booster sessions and interactive activities) are ways to realize such repeated tailoring. [4,5,16,98]

Not only has the number of electronically delivered interventions grown since 2004, but evidence for effectiveness has too. Before 2004, only a third of these 'second-generation' dietary interventions were effective, compared to 60% after 2004. For effective promotion of PA, the likelihood of effect appears not to be dependent on delivery mode. Furthermore, mobile phones were a delivery mode that was not yet available in the studies in the original 2006 review. A study by Haapala et al. indicates that mobile phone delivery can be an effective method for supporting weight loss. By allowing for two-way communication and showing a log-on frequency that is twice the rate of other web-based programs [99,100], mobile phones have potential for the future. Because of these advantages and given the massive increase of the use of smartphones worldwide, mobile technologies will and probably should be used more often to promote lifestyle changes. [101]

Overall, studies published since 2004 appear to have partially taken into account the recommendations for further research in the original review. Although more objective outcome measurement instruments were used in studies published after 2004, this was restricted to interventions on PA. Further, despite the increased number of studies, the proportion of comparisons with generic HE has not increased since 2004. Long follow-ups have been included more frequently in more recent studies, but only in nutrition

interventions. Comparisons with generic HE, instead of no-intervention control groups, are most important because they provide information on the effects of tailoring. Therefore, we repeat and strongly advocate the recommendation to study tailoring as compared to other intervention methods, such as generic HE. Long-term follow-up should remain a priority, as well as the inclusion of objective outcome measures including their use in nutrition intervention research.

This review update has limitations. We used the same review protocol as was applied in the original 2006 review. Therefore, potential limitations such as the non-blinding of reviewers to authorship or the journal of the reviewed publications also applied to the present review. A lack of unequivocal scientific evidence that blinding is essential to obtain valid review results, was already discussed in the original 2006 review. [3,102,103] In addition, a new independent reviewer assessed eligibility of the studies for the present update, which could have led to some differences in decisions and interpretations. Previous research has shown that updating a review can affect both the direction and the precision of the outcome. [104,105] Yet, two reviewers who were involved in the reviewing process of the original 2006 review were also part of the present update team. No risk of bias and/or quality assessments evaluations were performed for either the original and updated review; although the use of such tools has been recommended for systematic reviews. [18] Fortunately, because only RCTs were included, the variety in methodological quality was small. Nevertheless, the methodological quality of the studies included in this review could have had an impact on estimates of effects, which might have affected the validity of the conclusions. Finally, as any review of published literature, the present update may have been affected by publication bias that may have caused an overestimation of the positive findings.

Notwithstanding these potential limitations, this review importantly updates the systematic overview of developments and evidence regarding computer-tailored PA and nutrition education over the past years. Furthermore, this review update provides the most recent overview of the content and effects of computer-tailored interventions in the field of PA and nutrition. Reviews of the literature need to be updated regularly in order to provide up-to-date overviews of the evidence-base to inform health promotion practice, and to provide new recommendations for research to further strengthen the evidence base. This comparison is strengthened by our use of comparable reviewing methods at two time points, 2006 and 2011, giving us the opportunity to compare effects, intervention and study characteristics over time. Such updating of reviews using similar methodology is advocated and common practice in review consortia such as the Cochrane collaboration.

On the whole, from this updated review it can be concluded that the evidence on computer-tailored interventions for the promotion of PA and dietary change has become stronger and now is also convincing

for PA promotion. However, this effect particularly accounted for studies with no-intervention control groups, effect sizes were generally small and the evidence is generally restricted to rather short-term effects, i.e. up to 3 months follow-up. Further, it remains unclear whether the effect of tailored interventions is caused by tailoring as such or by the fact that tailored interventions are more likely to be carefully designed and based on behavioral theory. Previously formulated recommendations regarding the use of objective outcome measurements, generic HE control groups and long-term follow-up periods for the development of computer-tailored interventions were only partially met. Based on the present review, the use of computer-tailored interventions in PA and healthy nutrition promotion can be advocated, but future interventions should especially focus on: 1) establishing larger effect sizes and sustained effects, 2) using more objective measurements in studies on dietary behavior, 3) using more generic HE control groups, and especially control groups in which the generic HE is also carefully designed and theory-based in order to distinguish the effect of tailoring from the effects of theory-based intervention development, and 4) including more long-term follow-up measurements. Future research should also focus on why and how computer-tailored PA and nutrition interventions are effective, by conducting mediation analyses [24,106], and supporting large-scale dissemination of such interventions. [107]

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Table 1: Study characteristics and effects found in the studies included in the review

First author(s)[1] ***reference number(s)***	**Country**	**Study population [N]**	**Intervention modes[2]**	**Validated question-naire**	**Outcome measurement instruments**	**Outcome measurement units**	**Results[3] and Effect Size[4] at short- (ST), medium- (MT) or long-term (LT)[5]**
A. PHYSICAL ACTIVITY							
Adachi, 2007 [30] *154* Tanaka, 2010 [29] *369*	JAP	Overweight Japanese women [205] recruited from the general population (Adachi, 2007) Overweight Japanese men [51] recruited from the general population (Tanaka, 2010)	**C** Self-help booklet **EXP1** C + self-monitoring of weight and walking **EXP2** CT advice **EXP3**[6] CT advice + self- monitoring of weight and walking	?	15-item Pedometer	Self-rated physical activities (points 1 (bad) – 3 (good) Daily walking steps	**LT** No significant effects
Carroll, 2010 [66] *488*	USA	Inactive participants [394] recruited through primary care providers	**C** Generic HE **EXP1** CT advice	Yes	7-Day PA Recall (7-Day PAR)	Leisure-time PA (min/wk) Non leisure-time PA (min/wk)	**MT** No significant effects
Dunton, 2008 [67] *599*	USA	Women [156] (21-65) recruited from the general population	**C** No intervention **EXP1** CT advice	Yes	Standardized activity inventory	MVPA (min/wk) Walking (min/wk)	**ST** No significant effects **MT** Significant effect on MVPA ES: 0.24 **MT** Significant effect on Walking ES: 0.21
Hageman, 2005 [81] *768*	USA	Women [31] (50-69 yrs) recruited through newspaper advertisement	**C** Generic HE **EXP1** CT advice	Yes	Modified 7-Day Activity Recall (PAR) Fitness Walking Test Sit and reach test	MVPA (min/wk) Calories expended daily Aerobic fitness (VO2max in ml/kg/min) Flexibility (cm)	**MT** Significant effect on VO2 max ES: 0.42
Hurling, 2007 [43] *691*	UK	Participants [77] (30-55 yrs) recruited through market research recruitment agency	**C** No intervention **EXP1** CT advice	Yes	IPAQ Accelerometer	Overall PA (MET min/wk) Leisure-time PA (MET min/wk) Overall sitting time (hours/wk) Weekday sitting time (hours/wk) Weekend sitting time (hours/wk)	**ST** Significant effect on leisure-time PA <u>Accelerometer data</u> Significant effect on MPA (3-6 MET range) ES: N/A
Jacobs, 2004 [68] *884*	USA	Women [511] (50-64) recruited from nutrition and PA program (WISEWOMAN)	**C** Generic HE **EXP1** CT advice	?	31-item PAA questionnaire	Score from 31-item scale : Not very active (0) – Very active (42)	**LT** No significant effect on PA score

First author(s)[1] *reference number(s)*	Country	Study population [N]	Intervention modes[2]	Validated question-naire	Outcome measurement instruments	Outcome measurement units	Results[3] and Effect Size[4] at short- (ST), medium- (MT) or long-term (LT)[5]
A. PHYSICAL ACTIVITY (cont)							
Marcus, 2007 [82] *679*	USA	Sedentary participants [239] (18-65) recruited from the general population	**C** Generic HE **EXP1** CT advice (print-based) **EXP2** CT advice (telephone-based)	Yes	7-Day PAR Actigraph Submaximal exercise threadmill test	MPA/VPA (min/wk) Aerobic fitness (VO2max in ml/kg/min)	**MT** Significant effect on PA in EXP2 compared to C ES: 0.46 **MT** Significant effect on PA in EXP1 compared to C ES: 0.39 **MT** No significant difference between EXP1 and EXP2 **LT** Significant effect on PA in EXP2 compared to C ES: N/A **LT** No significant effect on PA in EXP1 compared to C **LT** No significant difference between EXP1 and EXP2
Marcus, 2007 [83] *690*	USA	Sedentary participants [249] (18+) from the general population	**C** Generic HE **EXP1** CT advice (internet) **EXP2** CT advice (print-based)	Yes	7-Day PAR Submaximal exercise threadmill test	MPA/VPA (min/wk) Aerobic fitness (VO2max in ml/kg/min)	**MT/LT** No significant effect on MVPA.
Napolitano, 2006 [36] *724*	USA	Sedentary women [280] recruited from the general population	**C1** Generic HE **C2** Self-help booklet **EXP2** CT advice	Yes	7-Day PAR	MPA/VPA (min/wk)	**MT/LT** No significant effect on MVPA.
Oenema, 2008 [76] *86*	NL	Participants [2159] (> 30) recruited from online research panel	**C** No intervention **EXP1** CT advice	Yes	Short version of IPAQ	Self-rated PA level (scale from −2 to +2) % compliant to PA guideline (moderate intensity PA for at least 30 min/day in at least 5 days/wk)	**ST** Significant effect on % compliant to PA guideline in at-risk group (those who did not comply with the PA guidelines at baseline) ES: 0.16
Pekmezi, 2009 [69] *529*	USA	Sedentary Latinas [93] (18-65) recruited from the general population	**C** Generic HE **EXP1** CT advice	Yes	7-Day PAR	MPA/VPA (min/wk)	**MT** No significant effect on MVPA.
Prochaska, 2008 [61] *654*	USA	Participants [1400] at risk for at least one risk behavior (exercise, stress, BMI > 25 kg/m^2 and smoking) recruited from a major medical university	**C** Health Risk Assesment **EXP1** C + coaching **EXP2** C + TTM-based feedback	Yes	Self-reported level of exercise	% exercising moderately 30 min/day for at least 5 days/wk	**MT** Significant effect on % exercising moderately 30 min/day for at least 5 days/wk in EXP1 and EXP2 compared to C ES: N/A

First author(s)[1] *reference number(s)*	Country	Study population [N]	Intervention modes[2]	Validated questionnaire	Outcome measurement instruments	Outcome measurement units	Results[3] and Effect Size[4] at short- (ST), medium- (MT) or long-term (LT)[5]
A. PHYSICAL ACTIVITY (cont)							
Quintiliani, 2010 [75] *176*	USA	Female college students [408] recruited from universities/colleges	**C** Generic HE **EXP1** CT advice (topic by choice) **EXP2** CT advice (topic by expert)	Yes	US Behavioral Risk Factor Surveillance Survey	MVPA (min/wk) VPA (min/wk)	**ST** Significant effect on VPA in EXP2 compared to C ES: 0.41
Slootmaker, 2009 [41] *550*	NL	Participants [102] (20-40 yrs) recruited from worksites	**C** Generic HE **EXP1** CT advice	?	AQuAA[70] Chester Step Test	LPA[a] / MPA[a] / VPA[a] (MET min/wk) Aerobic fitness (VO2max in ml/kg/min)	**MT/LT** No significant effects
Smeets, 2007 [39] *126* De Vries, 2008 [38] *72*	NL	Participants [2827] (18-65) recruited from companies and the general population	**C** Generic HE **EXP1** CT advice (once delivered in 3 months (Smeets et al)) **EXP2** CT advice (3 times delivered in 9 months (De Vries et al))	Yes	SQUASH	Action moments/wk % compliant to PA guideline (moderate intensity PA for at least 30 min/day in at least 5 days/wk)	**MT** Significant effect on PA of EXP1 compared to C ES: 0.12 **LT** Significant effect on PA and % compliance to PA guideline of EXP2 compared to C ES: 0.15 ES: 0.14
Smeets, 2008 [79] *715*	NL	Participants [487] (18-65 yrs) recruited from the general population	**C** No intervention **EXP1** CT advice	Yes	SQUASH	Total PA (MET min/wk) Transport related PA (MET min/wk) Leisure-time related PA (MET min/wk) Sports related PA (MET min/wk)	**MT** Significant effect on transport related PA and total PA among motivated participants ES: 0.48 ES: 0.49
Spittaels, 2007 [78] *705*	BEL	Participants [434] (20-55 yrs) recruited through parents and staff of primary / secondary schools	**C** No intervention **EXP1** CT advice **EXP2** CT advice + repeated feedback	**Yes**	IPAQ	Total MVPA (min/wk) Transportation PA (min/wk) Household PA (min/wk) Leisure-time PA (min/wk) Job-related PA (min/wk) Weekday sitting time (min/day) Weekend sitting time (min/day)	**MT** Significant effect on transportation PA, leisure-time PA and weekday sitting time in EXP1 and EXP2 compared to C <u>EXP2 compared to C</u> ES (transportation PA): 0.21 ES (leisure-time PA): 0.52 ES (weekday sitting time): 1.58 <u>EXP1 compared to C</u> ES (transportation PA): 0.18 ES (leisure-time PA): 0.40 ES (weekday sitting time): 1.62

First author(s)[1] *reference number(s)*	Country	Study population [N]	Intervention modes[2]	Validated question-naire	Outcome measurement instruments	Outcome measurement units	Results[3] and Effect Size[4] at short- (ST), medium- (MT) or long-term (LT)[5]
A. PHYSICAL ACTIVITY (cont)							
Spittaels, 2007 [71] *720*	BEL	Participants [526] (25-55 yrs) recruited from worksites	**C**[1] Generic HE **EXP1**[2] CT advice **EXP2**[3] CT advice + stage-of-change based emails	**Yes**	IPAQ Accelerometer	Total PA (min/wk) MVPA (min/wk) 30 min of PA on most days (%)	**MT** No significant effects in EXP1 or EXP2 compared to C
Sternfeld, 2009 [42] *45*	USA	Participants [787] recruited from administration offices of a large healthcare organization	**C** No intervention **EXP1** CT advice	Yes	PAQ adapted from Cross-Cultural Activity Patterns Questionnaire	Total PA (MET-min/wk) MPA (min/wk) VPA (min/wk) Walking (min/wk) Sedentary behavior (min/wk)	**ST** Significant effect on MPA, VPA, walking and sedentary behavior **MT** Significant effect on MPA, walking and sedentary behavior **ST** Significant effect on MPA, VPA, walking and sedentary behavior among those who chose the PA path of the intervention ES: N/A
Van Keulen, 2011 [80] *2038*	NL	Participants [1629] (45-70) recruited from general practices	**C1** No intervention **C2** Coaching **C3** C2 + EXP1 **EXP1** TC advice	Yes	28-item modified Community Health Activities Model Program for Seniors	PA (hours/wk)	**MT** Significant effect of EXP1 compared to C1 ES: 0.20 **LT** (~11 months) Significant effect of EXP1 compared to C1 and C3 ES (EXP1-C1): 0.32 ES (EXP1-C3) : 0.15 **LT** (~18 months) No significant effects
Van Stralen, 2009 [23] *1212* Van Stralen, 2011 [24] *2039*	NL	Participants [1971] (>50 yrs) recruited from Regional Municipal Health Counsils	**C** No intervention **EXP1** CT advice (psychosocial) **EXP2** CT advice (psychosocial + environmental)	Yes	1-item from SQUASH	Self-rated PA (total weekly days of MPA) Self-rated compliance with PA guidelines (% of participants that show compliance with guidelines)	**MT** (3 months) Significant effect on self-rated PA in EXP1 and EXP2 compared to C; ES: 0.20; ES: 0.20 **MT** (3 months) Significant effect on PA initiation among insufficiently active participants in EXP1 and EXP2 compared to C ES: 0.26 ; ES: 0.21 **MT** (6 months) Significant effect on self-rated PA in EXP1 and EXP2 compared to C ; ES: 0.30; ES: 0.35 **MT** (6 months) Significant effect on PA initiation among insufficiently active participants in EXP1 and EXP2 compared to C ES: 0.32 ; ES: 0.27 **MT** (6 months) Significant effect on PA maintenance among sufficiently active participants in EXP 1 and EXP 2 compared to C ES: 0.33 ES: 0.34**LT** (12 months) Significant effect on self-rated PA in EXP1 and EXP2 compared to CES: 0.18 (for both EXP1 and EXP2)

First author(s)[1] *reference number(s)*	Country	Study population [N]	Intervention modes[2]	Validated question-naire	Outcome measurement instruments	Outcome measurement units	Results[3] and Effect Size[4] at short- (ST), medium- (MT) or long-term (LT)[5]
A. PHYSICAL ACTIVITY (cont)							
Walker, 2009 [25] *53* Walker, 2010 [26] *2040*	USA	Women [225] (50-69) recruited from the general population	**C** Generic HE **EXP1** CT advice	Yes	Modified 7-day PAR 1 mile walk test Modified sit-and-reach test Repeated timed chair stands	MVPA (min/day) Kilocalories expended per kilogram/day Time engaged in strengthening and stretching exercise (min/wk) Aerobic fitness (VO2max in ml/kg/min) Lower body muscular strength (timed chair stands in sec)	**MT** Significant effect on lower body muscular strength ES: -0.36 **LT** (12 months) Significant effect on lower body muscular strength ES: -0.41 **LT** (18 months) Significant effect on lower body muscular strength ES: -0.51
Wanner, 2009 [77] *551*	Switzerland	Participants [1531] recruited from the general population	**C** Generic HE **EXP1** CT advice	?	4-item derived from official PA monitoring in Swiss population Accelerometer	MPA/VPA (min/wk)	**ST/LT** No significant effect on MPA and VPA.
Werkman, 2010 [63] *13*	NL	Recent retirees [415] (55-65) recruited from pre-retirement workshops	**C** Generic HE **EXP1** CT advice	Yes	Dutch version of the PA Scale for the Elderly (PASE)[72]	Daily routine PA (min/wk) Recreation/sports PA (min/wk) Σ household activities (0-6) PASE-score (0-400)	**LT** No significant effect (12- and 24-months) on daily routine PA, recreation/sports PA, Σ household activities (0-6) and PASE-score
Winett, 2007 [40] *120*	USA	Participants [1071] recruited from churches	**C** No intervention **EXP1** CT advice **EXP2** CT advice + church support	?	Pedometer	Daily step counts	**LT (7 and 16 months)** Significant effect on PA in EXP2 compared to C ES (7 months): 0.23 ES (16 months): 0.27
B. FAT CONSUMPTION							
Blair Irvine, 2004 [85] *1018*	USA	Participants [517] recruited from a large hospital	**C** No intervention **EXP1** CT advice	Yes	21-item Diet Habits Questionnaire	Fat eating habits/behavior score	**ST** Significant effects on fat eating habits/behavior ES (1-month): -0.49 ES (2-months): -0.18
Dutton, 2008 [37] *95*	USA	Sedentary women [280] recruited from the general population	**C** Generic HE **EXP1** Self-help booklet **EXP2** CT advice	Yes	National Cancer Institute Screeners	Fat intake (en%)	**MT/LT** No significant effects on fat intake
Elder, 2005 [45] *1653* Elder, 2006 [46] *1598*	USA	Latinas [357] recruited from the general population	**C** Generic HE **EXP1** CT advice **EXP2** CT advice + Promotoras	Yes	Nutrition data system: 24 h dietary recall interview	% calories from fat Total and saturated fat intake (g)	**ST** Significant effects on total and saturated fat intake in EXP2 compared to EXP1 **LT** No sustained significant effects

First author(s)[1] *reference number(s)*	Country	Study population [N]	Intervention modes[2]	Validated question-naire	Outcome measurement instruments	Outcome measurement units	Results[3] and Effect Size[4] at short- (ST), medium- (MT) or long-term (LT)[5]
B. FAT CONSUMPTION (cont)							
Fries, 2005 [84] *469*	USA	Participants [754] (18-72) recruited from physician practices	**C** No intervention **EXP1** CT advice	?	Fat and fiber behavior-related questionnaire	Score from 0-3	**ST** Significant effect on dietary fat behavior ES: -0.41 **MT** Significant effect on dietary fat behavior ES: -0.29 **LT** Significant effect on dietary fat behavior ES: -0.23
Gans, 2009 [88] *261*	USA	Participants [1841] with low income, recruited from waiting rooms of public health clinics	**C** Generic HE **EXP1** CT advice (at once) **EXP2** CT advice (in 4 installments) **EXP3** EXP2 with retailoring	Yes	Adapted Food Habits Questionnaire (FHQ)	Fat intake (FHQ-score: low score=high prevalence fat-lowering behavior, thus lower fat intake)	**MT** Significant effect on fat intake in EXP2 and EXP3 compared to C ES (EXP2-C): -0.31 ES (EXP3-C): -0.31
Jacobs, 2004 [68] *884*	USA	Women [511] (50-64) recruited from nutrition and PA program (WISEWOMAN)	**C** Generic HE **EXP1** CT advice	Yes	54-item Dietary risk assessment	Score from 54-item scale: 0-108 not very atherogenic (0) to very atherogenic diet (108)	**LT** No significant effect on saturated fat and cholesterol intake
Kroeze, 2008 [86] *320*	NL	Participants [442] (18-65) recruited from companies and general population	**C** Generic HE **EXP1** CT advice (interactive CD-ROM) **EXP2** CT advice (print)	Yes	104-item FFQ	Total fat intake (g/day, en%) Saturated fat intake (g/day, %en)	**ST** Significant effects on total fat and saturated fat intake in EXP1 compared to C ES (total fat): -0.31 ES (saturated fat): -0.22 **ST** Significant effects on total fat intake among risk consumers in EXP1 compared to C ES: -0.41 **ST** Significant effects on total fat in EXP2 compared to C ES: -0.23 **ST** Significant effects on total fat and saturated fat intake among risk consumers in EXP2 compared to C ES (total fat): -0.49 ES (saturated fat): -0.42 **MT** Significant effect on total fat and saturated fat intake among risk consumers in EXP2 compared to C ES (total fat): -0.53 ES (saturated fat): -0.54

First author(s)[1] *reference number(s)*	Country	Study population [N]	Intervention modes[2]	Validated question-naire	Outcome measurement instruments	Outcome measurement units	Results[3] and Effect Size[4] at short- (ST), medium- (MT) or long-term (LT)[5]
B. FAT CONSUMPTION (cont)							
Kroeze, 2008 [87] *346*	NL	Participants [574] (18-65) recruited from large companies and the general population	**C** Generic HE **EXP1** CT advice (personal) **EXP2** CT advice (personal–normative) **EXP3** CT advice (personal–normative–action)	Yes	104-item FFQ 1-item	Total fat intake (g/day) Saturated fat intake (g/day) Self-rated fat intake (awareness) (-2 to +2)	**ST** Significant effect on awareness of fat intake in EXP1 and EXP3 compared to C ES (EXP1): 0.30 ES (EXP3): 0.41 **ST** Significant effect on fat intake and saturated fat intake in EXP3 compared to C ES (fat intake): -0.52 ES (saturated fat intake): -0.46 **MT** Significant effect on fat intake in EXP1, EXP2 and EXP3 compared to C ES (EXP1): 0.34 ES (EXP2): 0.55 ES (EXP3): 0.53 **MT** Significant effect on saturated fat intake in EXP3 compared to C ES: -0.51 **MT** Significant effect on fat and saturated fat intake among underestimators in EXP3 compared to C ES (fat intake): -0.64 ES (saturated fat intake): -0.63
Ni Mhurchu, 2010 [60] *219*	NWZ	Participants [1104] recruited from rom a selection of customers registred to use the Shop 'N Go System and in-store and community-based recruitment.	**C** No intervention **EXP1** CT advice **EXP2** CT advice + discount **EXP3** Discount	?	Electronic scanner (Shop 'N Go system)	% of energy from saturated fats in purchases	**MT** No significant effect on saturated fat purchases
Oenema, 2008 [76] *86*	NL	Participants [2159] (> 30) recruited from online research panel	**C** No intervention **EXP1** CT advice	Yes	35-item FFQ 1-item	Saturated fat intake (fat points/day from 0-80) Self-rated intake (scale from −2 to +2)	**ST** Significant effect on saturated fat intake ES: -0.16 **ST** Significant effect on saturated fat intake in at-risk group (those who did not comply with the recommended level of saturated fat intake at baseline) ES: -0.23

First author(s)[1] *reference number(s)*	Country	Study population [N]	Intervention modes[2]	Validated question-naire	Outcome measurement instruments	Outcome measurement units	Results[3] and Effect Size[4] at short- (ST), medium- (MT) or long-term (LT)[5]
B. FAT CONSUMPTION (cont)							
Prochaska, 2005 [32] *458* Prochaska, 2004 [31] *486*	USA	Sedentary primary care patients [5407] at risk for at least one of the target behaviors recruited from primary care practices (Prochaska, 2005-458). Parents of teenagers [2460] at risk for at least one of the target behaviors recruited from schools (Prochaska, 2005-486)	**C** No intervention **EXP1** CT advice	Yes	22-item Dietary Behavior Questionnaire	Score on subscales: Avoidance Substitution Modification	<u>Among sedentary primary care patients</u> **LT (12 months)** Significant effects on avoidance, modification and substitution ES (avoidance) :0.24 ES (modification) :0.18 ES (substitution) :0.22 **LT (24 months)** Significant effects on avoidance ES (avoidance) :0.27 ES (substitution) :0.20 <u>Among parents of teenagers</u> **LT (12 months)** Significant effects on avoidance and substitution ES (avoidance): 0.16 ES (substitution): 0.19 **LT (24 months)** Significant effects on avoidance and substitution ES (avoidance): 0.18 ES (substitution): 0.23
Smeets, 2007 [39] *126* De Vries, 2008 [38] *72*	NL	Participants [2827] (18-65) recruited from companies and the general population	**C** Generic HE **EXP1** CT advice (once delivered in 3 months (Smeets, 2007l)) **EXP2** CT advice (3 times delivered in 9 months (De Vries, 2008))	Yes	FFQ	Fat intake (g) Saturated fat intake (g) % compliant to guidelines for saturated fat intake	**MT** Significant effect on fat intake in EXP1 compared to C ES: -0.12 **LT** Significant effect on % compliant to guideline on saturated fat intake in EXP2 compared to C ES: -0.18
Sternfeld, 2009 [42] *45*	USA	Participants [787] recruited from administration offices of a large healthcare organization	**C** No intervention **EXP1** CT advice	Yes	Diet questionnaire based on Block Food Questionnaire	Saturated fats (g/day) Trans fats (g/day)	**ST** Significant effect on saturated and trans fat intake **ST** Significant effect on saturated and trans fat intake among those who chose the fats/sugar path of the intervention **MT** Significant effect on saturated and trans fat intake ES: N/A

First author(s)[1] *reference number(s)*	Country	Study population [N]	Intervention modes[2]	Validated question-naire	Outcome measurement instruments	Outcome measurement units	Results[3] and Effect Size[4] at short- (ST), medium- (MT) or long-term (LT)[5]
B. FAT CONSUMPTION (cont)							
De Bourdeaudhuij, 2007 [33] *380*	BEL	Participants [539] recruited from companies	**C** No intervention **EXP1** CT advice on PA and fat intake sequentially delivery **EXP2** CT advice on PA and fat intake simultaneously delivered **EXP3** CT advice only on fat intake	Yes	48-item FFQ	Total fat intake (g/day) Energy from fat (%) Fat intake (seperate food groups) (g/day)	**MT** Significant effect on energy from fat and total fat intake in EXP1 compared to C1 and C2 EXP1 compared to C1 ES (energy from fat): -0.37 ES (total fat intake): -0.32 EXP1 compared to C2 ES (energy from fat): -0.13 ES (total fat intake): 0.09 **MT** Significant difference in energy from fat between C1 and C2 ES: -0.24 **MT** Significant effect on energy from fat and total fat intake among participants who meet/do not meet fat intake recommendations in EXP1 compared to C1 and C2 ES: N/A
Walker, 2009 [25] *53* Walker, 2010 [26] *2040*	USA	Women [225] (50-69) recruited from the general population	**C** Generic HE **EXP1** CT advice	Yes	Web-based Block98 FFQ	% calories from fat % calories from saturated fat	**LT (6 months)** Significant effect on % calories from saturated fat ES: -0.30 **LT (12 months)** Significant effect on % calories from saturated fat ES: - 0.49 **LT (18 months)** Significant effect on % calories from saturated fat ES: -0.56
Werkman, 2010 [63] *13*	NL	Recent retirees [415] (55-65) recruited from pre-retirement workshops	**C** Generic HE **EXP1** CT advice	Yes	Semi quantitative FFQ	Fat intake (en%)	**LT** No significant effects on fat intake
Winett, 2007 [40] *120*	USA	Participants [1071] recruited from churches	**C** No intervention **EXP1** CT advice **EXP2** CT advice + church support	Yes	Block98 FFQ Food shopping receipts	% kcal from fat	**LT** No significant effects on fat intake
Alexander, 2010 [90] *222*	USA	Participants [2540] (21-65) recruited from health plans	**C** Generic HE **EXP1** CT advice **EXP2** CT advice + personal counseling	Yes	16-item FFQ by National Cancer Institute 2-item	Fruit and vegetables intake (servings in past month) Fruit and vegetables intake (servings on a typical day)	**LT** Significant effect on fruit and vegetables intake in the past month in EXP2 compared to C ES: 0.10 **LT** Significant effect on fruit and vegetables intake on a typical day in EXP1 and EXP2 compared to C ES (EXP1): 0.08 ES (EXP2): 0.13

First author(s)[1] *reference number(s)*	Country	Study population [N]	Intervention modes[2]	Validated questionnaire	Outcome measurement instruments	Outcome measurement units	Results[3] and Effect Size[4] at short- (ST), medium- (MT) or long-term (LT)[5]
C. FRUIT AND VEGETABLE CONSUMPTION							
Blair Irvine, 2004 [77] *1018*	USA	Participants [517] recruited from a large hospital	**C** No intervention **EXP1** CT advice	Yes	5-A-Day Screener	Fruit and vegetables consumption score	**ST** Significant effects on fruit and vegetables consumption ES (1-month): 0.21 ES (2-months): 0.04
Dutton, 2008 [85] *95*	USA	Sedentary women [280] recruited from the general population	**C** Generic HE **EXP1** Self-help booklet **EXP2** CT advice	Yes	National Cancer Institute Screeners	Fruit and vegetables intake (daily servings)	**MT/LT** No significant effects on fruit and vegetables intake
Gans, 2009 [88] *261*	USA	Participants [1841] with low income, recruited from waiting rooms of public health clinics	**C** Generic HE **EXP1** CT advice (at once) **EXP2** CT advice (in 4 installments) **EXP3** EXP2 with retailoring	?	7-item NCI fruit and vegetables screener assessment tool	Fruit and vegetables intake (servings/day)	**MT** Significant effect on fruit and vegetables intake in EXP1 and EXP2 compared to C and EXP3 ES (EXP1-C): 0.18 ES (EXP1-EXP3): 0.20 ES (EXP2-C): 0.12 ES (EXP2-EXP3): 0.14 **LT** Significant effect on fruit and vegetables intake in EXP2 compared to C ES: 0.17
Heimendinger, 2005 [91] *1629*	USA	Participants [3402] (18+) recruited through Cancer Information Service offices (callers)	**C** Generic HE (1 booklet) **EXP1** CT advice (1 booklet) **EXP2** CT advice (4 booklets) **EXP3** CT advice (4 booklets + retailoring)	Yes	1-item 7-item FFQ	Fruit and vegetables intake (daily servings)	**LT** Significant effect on fruit and vegetables intake in EXP2 and EXP3 compared to C ES: N/A
Kreuter, 2005 [89] *457*	USA	Lower-income African-American women [1227] (18-65) from 10 urban public health centers.	**C** No intervention **EXP1** CT advice tailored on behavioural constructs **EXP2** CT advice tailored on cultural factors **EXP3** EXP1 + EXP2	Yes	13-item FFQ	Fruit and vegetables intake (servings/day)	**MT** No significant effects on fruit and vegetables intake **LT** Significant effect on fruit and vegetables intake in EXP3 compared to other groups **LT** Significant effect among lower motivated women on fruit and vegetables intake in EXP3 compared to other groups ES: N/A

First author(s)[1] *reference number(s)*	Country	Study population [N]	Intervention modes[2]	Validated questionnaire	Outcome measurement instruments	Outcome measurement units	Results[3] and Effect Size[4] at short- (ST), medium- (MT) or long-term (LT)[5]
C. FRUIT AND VEGETABLE CONSUMPTION (cont)							
Nitzke, 2007 [35] *352* Do, 2008 [34] *291*	USA	Participants [2024] (18-24) recruited from non-college venues	**C** No intervention **EXP1** CT advice	Yes	5 A Day Screener 2-item 26-item FFQ	Fruit and vegetables intake (servings) Perceived daily intake Variety in fruit and vegetables intake (number of different items consumed at least once a month, regardless of amount)	**MT** Significant effects on fruit and fruit and vegetables intake and perceived vegetables intake ES (fruit intake): 0.12 ES (fruit and vegetables intake): 0.14 ES (perceived vegetables intake): 0.08 **LT** Significant effects on fruit and fruit and vegetables intake and perceived intake of vegetables and fruit and vegetables ES (fruit intake): 0.15 ES (fruit and vegetables intake): 0.13 ES (perceived vegetables intake): 0.11 ES (perceived intake fruit and vegetables): 0.12 **LT** Significant effects on variety in fruit and vegetables consumption, consumption of seasonal fruits, juices and high beta-carotene vegetables ES (variety fruit) >1.00 ES (variety vegetables) >1.00 ES (seasonal fruits consumption) >1.00 ES (juices consumption) >1.00 ES (high beta-carotene vegetables consumption)>1.00
Prochaska, 2005 [32] *458* Prochaska, 2004 [31] *486*	USA	Sedentary primary care patients [5407] at risk for at least one of the target behaviors recruited from primary care practices Parents of teenagers [2460] at risk for at least one of the target behaviors recruited from schools	**C** No intervention **EXP1** CT advice	Yes	22-item Dietary Behavior Questionnaire	Score on subscale fruit and vegetables	**LT** No significant effect on fruit and vegetables in both study samples

First author(s)[1] *reference number(s)*	Country	Study population [N]	Intervention modes[2]	Validated question-naire	Outcome measurement instruments	Outcome measurement units	Results[3] and Effect Size[4] at short- (ST), medium- (MT) or long-term (LT)[5]
C. FRUIT AND VEGETABLE CONSUMPTION (cont)							
Smeets, 2007 [39] *126* De Vries, 2008 [38] *72*	NL	Participants [2827] (18-65) recruited from companies and the general population	**C** Generic HE **EXP1** CT advice (once delivered in 3 months (Smeets et al)) **EXP2** CT advice (3 times delivered in 9 months (De Vries et al))	Yes	FFQ	Fruit intake (pieces/day) Vegetables intake (g/day) % compliant to guidelines for fruit intake (at least 2 pieces of fruit for 7 days/week) Vegetables intake % compliant to guidelines for vegetables intake (at least 200 g of vegetables/day for 7 days/week)	**MT** Significant effect on fruit intake among participants who did not meet recommendations for any behavior in EXP1 compared to C ES: 0.30 **MT** Significant effect on vegetables intake in EXP1 compared to C ES: 0.10 **LT** Significant effect on fruit intake and % compliant to fruit guidelines in EXP2 compared to C ES: 0.35 ES: 0.24 **LT** Significant effect on vegetable intake and % compliant to vegetables guidelines in EXP2 compared to C ES: 0.32 ES: 0.08
Sternfeld, 2009 [42] *45*	USA	Participants [787] recruited from administration offices of a large healthcare organization	**C** No intervention **EXP1** CT advice	Yes	Diet questionnaire based on Block Food Questionnaire	Fruit and vegetables intake (cup-equivalents/day)	**ST** Significant effect on fruit and vegetables intake **ST** Significant effect on fruit and vegetables intake among those who chose the fruit and vegetables path of the intervention **MT** Significant effect on fruit and vegetables intake ES: N/A

First author(s)[1] *reference number(s)*	Country	Study population [N]	Intervention modes[2]	Validated questionnaire	Outcome measurement instruments	Outcome measurement units	Results[3] and Effect Size[4] at short- (ST), medium- (MT) or long-term (LT)[5]
C. FRUIT AND VEGETABLE CONSUMPTION (cont)							
Van Keulen, 2011 [80] *2038*	NL	Participants [1629] (45-70) recruited from general practices	**C1** No intervention **C2** Coaching **C3** C2 + EXP1 **EXP1** TC advice	Yes	16-item short questionnaire	Fruit intake (servings/day) Vegetables (g/day)	**MT** Significant effect on fruit intake of EXP1 compared to C1 and C3 ES (EXP1-C1): 0.19 ES (EXP1-C3): 0.18 **MT** Significant effect on vegetables intake of EXP1 compared to C1 and C3 ES (EXP1-C1): 0.10 ES (EXP1-C3): 0.12 **LT** (~11 months) Significant effect on fruit intake of EXP1 compared to C1 ES: 0.32 **LT** (~11 months) Significant effect on vegetables intake of EXP1 compared to C1, C2 and C3 ES (EXP1-C1): 0.33 ES (EXP1-C2): 0.24 ES (EXP1-C3): 0.19 **LT** (~18 months) Significant effect on fruit intake of EXP1 compared to C1, C2 and C3 ES (EXP1-C1): 0.35 ES (EXP1-C2): 0.22 ES (EXP1-C3): 0.24 **LT** (~18 months) Significant effect on vegetables intake of EXP1 compared to C1 ES: 0.27
Walker, 2009 [25] 53 Walker, 2010 [26] 2040	USA	Women [225] (50-69) recruited from the general population	**C Generic HE** **EXP1 CT advice**	Yes	Web-based Block98 FFQ	Fruit and vegetables intake (daily servings)	**LT** (6 months) Significant effect on fruit and vegetables intake ES: 0.22 **LT** (12 months) Significant effect on fruit and vegetables intake ES: 0.41 **LT** (18 months) Significant effect on fruit and vegetables intake ES: 0.40
Werkman, 2010 [63] *13*	NL	Recent retirees [415] (55-65) recruited from pre-retirement workshops	**C** Generic HE **EXP1** CT advice	Yes	Semi quantitative FFQ	Fruit and vegetables intake (g/MJ)	**LT** No significant effect on fruit and vegetables intake

First author(s)[1] *reference number(s)*	Country	Study population [N]	Intervention modes[2]	Validated questionnaire	Outcome measurement instruments	Outcome measurement units	Results[3] and Effect Size[4] at short- (ST), medium- (MT) or long-term (LT)[5]
C. FRUIT AND VEGETABLE CONSUMPTION (cont)							
Winett, 2007 [40] *120*	USA	Participants [1071] recruited from churches	**C** No intervention **EXP1** CT advice **EXP2** CT advice + church support	Yes	Block98 FFQ Food shopping receipts	Fruit and vegetables intake (g/1000kcal)	**LT (7 months)** Significant effect on fruit and vegetables intake in EXP1 compared to C ES: 0.44 Significant effect on fruit and vegetables intake in EXP2 compared to C ES: 0.57 **LT (16 months)** Significant effect on fruit and vegetables intake in EXP1 compared to C ES: 0.12 Significant effect on fruit and vegetables intake in EXP2 compared to C ES: 0.32
D. OTHER DIETARY TOPICS							
Adachi, 2007 [30] *154* Tanaka, 2010 [29] *369*	JAP	Overweight Japanese women [205] recruited from the general population (Adachi, 2007) Overweight Japanese men [51] recruited from the general population (Tanaka, 2010)	**C1** Self-help booklet **C2** C + self-monitoring of weight and walking **EXP1** CT advice **EXP2**[6] CT advice + self- monitoring of weight and walking	?	Weight parameters	BMI (kg/m^2)	**ST** Significant effect on BMI in EXP1 & EXP2 compared to C1 & C2 among overweigh Japanese *women* BMI ES EXP1-C1: -0.60 ES EXP1-C2: -0.48 ES EXP2-C1: -0.77 ES EXP2-C2: -0.66 **ST** Significant effect on BMI in EXP2 compared to C1 among overweigh Japanese *men* BMI ES EXP2-C1: -0.69 **MT** Significant effect on BMI in EXP2 compared to C1 & C2 among overweight Japanese *women* BMI ES EXP2-C1: -0.70 ES EXP2-C2: -0.58 **LT** Significant effect on BMI in EXP2 compared to C1 & C2 among overweight Japanese *women* BMI ES EXP2-C1: -0.59 ES EXP2-C2: -0.55 **LT** No significant effect on BMI in EXP2 compared to C1among overweigh Japanese *men*

First author(s)[1] *reference number(s)*	Country	Study population [N]	Intervention modes[2]	Validated question-naire	Outcome measurement instruments	Outcome measurement units	Results[3] and Effect Size[4] at short- (ST), medium- (MT) or long-term (LT)[5]
D. OTHER DIETARY TOPICS (cont)							
Elder, 2005 [45] *1653* Elder, 2006 [46] *1598*	USA	Latinas [357] recruited from the general population	**C** Generic HE **EXP1** CT advice **EXP2** CT advice + promotoras	Yes	Nutrition data system (NDS): 24 h dietary recall interview	Total energy intake (kcal) Total carbohydrates intake (g)	**ST/LT** No significant effects
Fries, 2005 [84] *469*	USA	Participants [754] (18-72) recruited from physician practices	**C** No intervention **EXP1** CT advice	?	Fat and fiber behavior-related questionnaire	Score from 0-3	**ST** Significant effect on fiber behavior ES: -0.35 **MT** Significant effect on fiber behavior ES: -0.24
Haapala 2009 [62] *271*	FIN	Overweight participants [125] (25-44) from the general population	**C** Generic HE **EXP1** CT advice		Weight parameters	Body weight (kg) % Weight loss Waist circumference	**LT** Significant effect on weight loss and waist circumference ES (weight loss): -0.14 ES (waist circumference): -0.18
Kroeze, 2008 [86] *320*	NL	Participants [442] (18-65) recruited from companies and general population	**C** Generic HE **EXP1** CT advice (CD-ROM) **EXP2** CT advice (print)	Yes	104-item FFQ	Energy intake (MJ/day)	**ST** Significant effects on energy intake in EXP1 and EXP2 compared to C ES: -0.28 ES: -0.38 **ST** Significant effects on energy intake among risk consumers in EXP1 and EXP2 compared to C ES: -0.50 ES: -0.66 **MT** Significant effects on energy intake among risk consumers in EXP1 and EXP2 compared to C ES: -0.68 ES: -0.44 **MT** Significant effects on energy intake in EXP2 compared to C ES: -0.26
Poddar, 2010 [84] *312*	USA	College students [294] recruited from a land grant, research-intensive university	**C** No intervention **EXP1** CT advice	?	7 day food records	Average daily dairy servings	**MT** No significant effect
Prochaska, 2008 [92] *654*	USA	Participants [1400] at risk for at least one risk behavior (exercise, stress, BMI > 25 kg/m^2 and smoking) recruited from a major medical university	**C** Health Risk Assesment **EXP1** C + coaching **EXP2** C + TTM-based feedback	Yes	Self-report	% above/below BMI = 25 kg/m^2	**MT** No significant effect on BMI

First author(s)[1] *reference number(s)*	Country	Study population [N]	Intervention modes[2]	Validated question-naire	Outcome measurement instruments	Outcome measurement units	Results[3] and Effect Size[4] at short- (ST), medium- (MT) or long-term (LT)[5]
D. OTHER DIETARY TOPICS (cont)							
Rothert, 2006 [44] *161*	USA	Overweight and obese (BMI = 27 - 40 kg/m^2) participants [2862] recruited from health care delivery system	**C** Generic HE **EXP1** CT advice	?	Self-report	% of baseline weight lost	**MT/LT** Significant effect on % of baseline weight lost ES > 1.00
Sternfeld, 2009 [42] *45*	USA	Participants [787] recruited from administration offices of a large healthcare organization	**C** No intervention **EXP1** CT advice	Yes	Diet questionnaire based on Block Food Questionnaire	Added sugars (g/day)	**ST/MT** No significant effects on added sugars
Walker, 2009 [25] *53*	USA	Women [225] (50-69) recruited from the general population	**C** Generic HE **EXP1** CT advice	Yes	Web-based Block98 FFQ Bioelectrical impedance analysis Weight parameters	Whole-grain intake (daily servings) % Body fat BMI (kg/m^2)	**LT** No significant effects
Werkman, 2010 [63] *13*	NL	Recent retirees [415] (55-65) recruited from pre-retirement workshops	**C** Generic HE **EXP1** CT advice	Yes	Weight parameters Semi quantitative FFQ	Waist circumference (cm), BMI (kg/m^2) Energy intake (MJ/day)	**LT** Significant effect on waist circumference among men with low education
Winett, 2007 [40] *120* Fiber intakeWeight	USA	Participants [1071] recruited from churches	**C** No intervention **EXP1** CT advice **EXP2** CT advice + church support	Yes	Block98 FFQ Food shopping receipts Weight parameters	Fiber intake (g/1000kcal) Weight (lb)	**LT (7 months)** Significant effect on fruit and vegetables intake in EXP1 compared to C *ES:* 0.35 Significant effect on fruit and vegetables intake in EXP2 compared to C *ES:* 0.44 Significant effect on weight in EXP2 compared to C *ES: 0.21* **LT (16 months)** Significant effect on fruit and vegetables intake in EXP1 compared to C *ES:* 0.20 Significant effect on fruit and vegetables intake in EXP2 compared to C *ES:* 0.28

C=Control condition; EXP1=experimental condition 1; EXP2=experimental condition 2; EXP3=experimental condition 3; ES=effect size; [125]=125 participants; (50-69)=50 to 69 years old; JAP=Japan; USA=United States of America; UK=United Kingdom; NL=The Netherlands; BEL=Belgium; NWZ=New Zealand; [1]Some publications reported on the characteristics and effects of the same intervention, and are therefore clustered in one cell; [2] No intervention equals no info in the 2006-review, generic HE equals generic info in the 2006-review; [3]Significant effect = effect that reached statistical significance (p<0.05); [4]Effect sizes were calculated when mean and SD were available at posttest and a significant effect in favour of tailoring had been found. ES is interpreted according to Cohen's guidelines[73] based on an application in Dolan et al[74]; cut-off values of 0.2-0.5 = small, 0.5-0.8 = moderate and >0.8 = large effects; [5]Short-term (ST): < 3 months; medium-term (MT): 3-6 months; long-term (LT): > 6 months; [6]In the study of Tanaka et al 2010, only EXP2 versus the self-help booklet was tested.

Table 2: Study characteristics and effects of studies from the original (<2004) and updated review (>2004) compared

	Dietary behavior		**Physical activity**	
	Before 2004 N[1] = 26	**After 2004 N[1] = 34**	**Before 2004 N[1] = 10**	**After 2004 N[1] = 29**
	Reference number[2] N (%)	**Reference number N (%)**	**Reference number[2] N (%)**	**Reference number N (%)**
Comparison of computer-tailored intervention with a no intervention control group	35-39-43-47-53-54-56-33-42-46-50-51-52-55-60 34-44-48 **18 (69%)**	45-86-120-380-219-352-291-457-458-486-469-1018-312 - 2038 **14 (41%)**	33-34-35-38 **4 (40%)**	45-86-120-380-599-691-705-715-1212-2039-2038 **11 (38%)**
Comparison of computer-tailored intervention with a generic HE control group[5]	30-41-56-40-42-45-55-31-32-54 **10 (38%)**	13-53-2040-95-72-126-161-222-261-271-320- 346-884-1629-1653-1598 **16 (47%)**	28-29-30-32-37-38 **6 (60%)**	13-53-2040-72-126-488-529-550-551-679-690-720-724-768-884-176 **16 (55%)**
Objective measurements of effect indicators	39-50-51-52 **4 (15%)**	13-53-2040-120-219 **5 (15%)**	**0 (0%)**	53-120-154-369-550-551-679-690-691-720-768 **11 (38%)**
Inclusion of long-term (>= 6 months) follow up	32-33-36-43-46 **7 (27%)**	13-53-2040-72-95-120-154-369-161-222-261-271-291-352-457-458-486-469-884-1598-1653-1629-2038 **23 (68%)**	28-32-33-34-36-37 **6 (60%)**	13-72-120-154-369-550-551-679-690-724-95-884-2039-2038 **14 (48%)**
Significant effects of computer-tailored interventions found	30-35-39-41-43-47-49-53-56 **9 (35%)**	45-86-72-126-161-380-222-261-271-291-352-320-346-457-469-1018-1629-2038 **28 (82%)**	29-35 **2 (20%)**	45-53-2040-72-126-86-120-380-654-599-679-691-705-715-768-1212-2039-176-2038 **19 (66%)**
Printed intervention materials	30-31-32-33-34-40-41-42-43-44-45- 46-48-49-50-53-54-56 **18 (69%)**	53-72-95-126-154-219-261-346-352-457-458-486-884-1629-1653-1598 **15 (44%)**	28-29-30-31-32-33-34-37-38 **9 (90%)**	72-126-154-369-679-715-724-884-1212-2039 **10 (34%)**
Electronic intervention materials	35-36-39-44-47-51-52-55-60 **9 (35%)**	13-45-86-120-161-222-271-320-380-469-471-569-1018-1677 **14 (41%)**	35-36 **2 (20%)**	13-45-53-86-120-161-488-529-550-551-599-654-768-690-691-705-720-2040 **18 (62%)**

[1]N = number of studies; [2]Reference numbers are from the original review.[3] Reference numbers from the review update can be found in Table 1; [3]All studies; [4]Within one study both significant and non-significant results were found for either different subgroups or different outcome measures related to the target behavior; [5]In some studies a no-intervention and generic health education (=HE) control groups were both included

Appendix 1: Intervention characteristics

1st author(s) *reference number(s)*[1]	Target behavior(s)	Theories	Tools	Tailoring variables	Feedback frequency	Additional strategies/notes
A: PHYSICAL ACTIVITY						
Adachi, 2007 *154* Tanaka, 2010 *369*	Exercise	Behavioral therapy	Print	Personal characteristics Physical activity Readiness to change behaviors Weight history Weight rebound experience Primary purpose of weight control Target weight Body image	2	Intervention primary focuses on weight control and secondary on exercise and dietary habits Booklet of behavioural weight control
Caroll, 2010 *488*	Physical activity		Email reports	Physical activity Stage of change Processes of change Self-efficacy Barriers Benefits	4	
Dunton, 2008 *599*	Physical activity	TTM HBM	On screen	Physical activity Stage of change Barriers Motivators	1	10 weekly newsletters supporting the tailored advice & encouraging further learning
Hageman, 2005 *768*	Physical activity	HPM	On screen newsletters	Physical activity Benefits Barriers Self-efficacy Goals	3	
Hurling, 2007 *691*	Physical Activity	Social comparison ELM Goal setting Decisional Balance Theory	On screen	Physical activity Barriers Solutions Goal setting	1	Email and/or telephone reminders Online schedule to plan weekly exercise sessions Message board
Jacobs, 2004 *884*	Physical activity	SCT TTM RPT	Print/telephone	Behavioral goals Stage of change Knowledge Social Support High risk situations for relapse Benefits Barriers	8	Intervention also focuses on dietary intake
Marcus, 2007 *679*	Physical activity	TTM SCT	Telephone/print	Physical activity Stage of change Processes of change Decisional balance	14	Stage-targeted booklets Tip sheets
Marcus, 2007 *690*	Physical activity	TTM SCT	On screen/print	Physical activity Stage of change Processes of change Decisional balance	16	Educational materials and tips

1st author(s) *reference number(s)*[1]	Target behavior(s)	Theories	Tools	Tailoring variables	Feedback frequency	Additional strategies/notes
A: PHYSICAL ACTIVITY (cont)						
Napolitano, 2006 *724* Dutton, 2008 *95*[2]	Physical activity	TTM SCT	Print	Stage of change Processes of change Self-efficacy Decisional balance	4	
Oenema, 2008 *86*	Physical activity	PAPM	On screen and/or print	(Perceived) Physical activity Awareness Stage of change Attitude Self-efficacy Implementation intentions Demographics	At least 1 (more visits possible)	Intervention also focuses on dietary intake and smoking
Pekmezi, 2009 *529*	Physical activity	TTM SCT	Print	Stage of change Processes of change Self-efficacy Motivational readiness	6	PA logs with tip sheets
Prochaska, 2008 *654*	Exercise	TTM	On screen	Stage of change Self-efficacy Processes of change Benefits Barriers	3 (recommended)	Intervention also focuses on smoking, stress dietary intake
Quintiliani, 2010 *176*	Physical activity	TTM HBM Social learning theory	On screen	Physical activity Stage of change Perceived barriers	1	
Rothert, 2006 *161*	Physical activity		On screen	Physical activity Demographics Experiences on weight loss Personal/family health history Attitude Barriers Social support Goals Expectations Preferences Self-efficacy	4	Intervention primary focuses on weight control Encouraging email messages from buddy
Slootmaker, 2009 *550*	Physical activity		On screen	Physical activity Preferences Barriers	1 (more visits optional)	
Smeets, 2007 *126* De Vries, 2008 *72*	Physical activity	I-CHANGE	Print	Physical activity Stage of change Awareness Motivation Attitude Self-efficacy	1-3	Intervention also focuses on smoking and fruit and vegetables and fat intake Smeets at al evaluated the first computer-tailored letter at short-term, De Vries et al evaluated the effects of three letters with an action planning component randomly applied in 3th letter

1st author(s) *reference number(s)*[1]	Target behavior(s)	Theories	Tools	Tailoring variables	Feedback frequency	Additional strategies/notes
A: PHYSICAL ACTIVITY (cont)						
Smeets, 2008 *715*	Physical activity	I-CHANGE model	Print	Physical activity Stage of change Social support Preferences Benefits Barriers	1	
Spittaels, 2007 *705*	Physical Activity	TPB TTM	On screen	Physical activity Social support Intention Stage of change Knowledge Self-efficacy Attitude Barriers Benefits	1/2	Non-tailored emails with invitation to revisit website
Spittaels, 2007 *720*	Physical Activity	TPB TTM	On screen	Physical activity Stages of change Social support Intention knowledge Attitude Self-efficacy Barriers Benefits	1	Stage of change targeted email tip sheets
Sternfeld, 2009 *45*	Physical activity		Email reports	Physical activity Stage of change Self-efficacy Individual lifestyle constraints Physical activity preferences	12	Intervention also focuses on saturated and trans fats intake, fruit and vegetables intake Personal homepage: tips on how to achieve goals Weekly health note Simulation tools Progress tracking tool Review of barriers Discussion board Links to additional resources Reminder messages
Van Keulen, 2011 *2038*	Physical activity	I-Change model Control Theory	Print	Physical activity Awareness Demographics Stage of change Attitude Self-efficacy Expectations Action plans	4	

1st author(s) *reference number(s)*[1]	Target behavior(s)	Theories	Tools	Tailoring variables	Feedback frequency	Additional strategies/notes
A: PHYSICAL ACTIVITY (cont)						
Van Stralen, 2009 *1212* Van Stralen, 2011 *2039*	Physical activity	I-CHANGE model TTM HPA PAPM SRT SDT	Print	Basic tailored intervention: *Letter 1:* (self-estimated) Physical activity Stage of change Age Gender Attitude Self-efficacy Benefits Social support *Letter 2:* Attitude Self-efficacy Possibilities Social support *Letter 3:* Changes in physical activity and determinants Intervention Plus Additional: location	3	Access to forum and e-buddy system (Intervention Plus)
Walker, 2009 *53* Walker, 2010 *2040*	Physical activity	HPM	Email newsletter	Benefits Barriers Self-efficacy Habits Family Support	18	Instructional videotapes
Wanner, 2009 *551*	Physical activity	TTM	On screen	Physical activity Stage of change Decisional balance Processes of change Self-efficacy Attitude Knowledge	1 (3 invitations for re-visit)	Strength and stretching exercise sheets Organizational and motivational download forms
Werkman, 2010 *13*	Physical activity	Intervention mapping protocol	CD-ROM/print	CD-ROM I (module 2) BMI BMI-related health consequences Energy-balance behavior CD-ROM II (module 3) Physical activity Letter (module 5) Physical activity	3	Intervention (5 modules) also focuses on fat, fruit and vegetables intake and weight loss Encouraging/informative newsletters
Winett, 2007 *120*	Physical activity		On screen	Daily step counts Goal attainment Strategies Preferred reasons for using intervention (health/weight loss)	12	Intervention also focuses on fruit and vegetables intake, fat intake, fiber intake and weight loss Church-based supports

1st author(s) *reference number(s)*[1]	Target behavior(s)	Theories	Tools	Tailoring variables	Feedback frequency	Additional strategies/notes
B. DIET						
Adachi, 2007 *154* Tanaka, 2010 *369*	Dietary habits	Behavioral therapy	Print	Personal characteristics Readiness to change behavior Weight history Weight rebound experience Primary purpose of weight control Target weight Body image Eating habits	2	Intervention primary focuses on weight control and secondary on exercise and dietary habits Booklet of behavioural weight control
Alexander, 2010 *222*	Fruit and vegetables intake	SCT TTM HBM	On screen	Needs Dietary preferences, Interests	4	Intervention also included optional short video/audio files of behavioral strategies and/or recipe preperations
Blair Irvine, 2004 *1018*	Fat intake, Fruit and vegetables intake	TTM TRA SCT HCT	On screen	Stage of change Attitude Intentions Self-efficacy Demographics Eating habits Environmental factors	1 (more visits optional)	Intervention also includes interactive multimedia combining audio, video, graphics and printout
Elder, 2005 *1653* Elder, 2006 *1598*	Calories from fat, Fiber intake, Energy intake, Total and saturated fat intake, Carbohydrates intake	Lay Health Advisor Model	Print	BMI Top 10 meals prepared at home Readiness to change Points of influence for change	12	Intervention also includes 12 weekly home visits and activity inserts in newsletters
Fries, 2005 *469*	Fat behavior, Fiber behavior	SCT TTM SMM	Email report	Fat behavior Fiber behavior	1	Counselling phone call and self-help booklets
Gans 2009 *261*	Fat intake, Fruit and vegetables intake	TTM SCT	Print	Fruit and vegetables intake, Fat-related behavior Demographics Self-efficacy Barriers Interests	1- 4	Intervention also includes motivational DVD
Haapala,2009 *271*	Weight loss		On screen (mobile phone text messages)	Weight Daily energy requirement	on demand	
Heimendinger , 2005 *1629*	Fruit and vegetables intake	TTM HBM SCT	Print	Fruit and vegetables intake Stage of change Outcome expectations Barriers Benefits Skills Environmental factors	1/2	

1st author(s) *reference number(s)*[1]	Target behavior(s)	Theories	Tools	Tailoring variables	Feedback frequency	Additional strategies/notes
B. DIET (cont)						
Jacobs, 2004 *884*	Saturated fat intake, Cholesterol intake	SCT TTM RPT	Print/telephone	Behavioral goals Stage of change Knowledge Social Support High risk situations for relapse Benefits Barriers	8	
Kreuter, 2005 *457*	Fruit and vegetable intake		Print magazines	Demographics EXP1 Fruit and vegetables intake Knowledge Beliefs Perceived Barriers Stage of readiness Self-efficacy Exposure to and preference for different fruit and vegetables Having received a recommendation Interest in eating more fruit and vegetables Perceived importance Environmental factors EXP2 Religiosity Collectivism Racial pride Time orientation	6	Intervention also included promotion of mammography use (participants aged 40-65)
Kroeze, 2008 *320*	Fat intake	PAPM TPB	On screen/print	Perception of own fat intake (high-low) Attitude Self-efficacy Readiness to change Environmental factors Demographics	1	
Kroeze, 2008 *346*	Fat intake	PAPM TPB	Print	EXP1 + EXP2 Fat intake EXP3 Fat intake Self-efficacy Intention to change Attitude	1	
Mhurchu, 2010 *219*	Saturated fat purchases		Print	Usual food purchases	6	
Nitzke, 2007 *352* Do, 2008 *291*	Fruit and vegetable intake	TTM	Print	Fruit and vegetables intake Decisional balance Stage of change Processes Self-efficacy	6	Magazines 2 boostercalls at 4 wks and 4 months post-baseline

1st author(s) *reference number(s)*[1]	Target behavior(s)	Theories	Tools	Tailoring variables	Feedback frequency	Additional strategies/notes
B. DIET (cont)						
Oenema, 2008 *86*	Saturated fat intake	PAPM	On screen and/or print	(perceived) Intake of saturated fats Awareness Stage of change Attitude Self-efficacy Implementation intentions Demographics	at least 1 (more visits possible)	Intervention also focuses on PA and smoking
Poddar, 2010 *312*	Dairy intake	SCT	On screen	Dairy intake	23	
Prochaska, 2005 *458* Prochaska, 2004 *486*	Fat intake, Fruit and vegetables intake		Print	Stage of change Readiness to change Decisional balance Change processes Self-efficacy	3	Intervention also focuses on smoking, skin cancer prevention regular mammography use Integrated multiple risk behavior stage-matched self-help manual
Rothert, 2006 *161*	Dietary behavior		On screen	Dietary behavior Demographics Experiences on weight loss Personal/family health history Attitude Barriers Social support Goals Expectations Preferences Self-efficacy	4	Intervention primary focuses on weight control Encouraging email messages from buddy
Smeets, 2007 *126* De Vries, 2008 *72*	Fat intake, Fruit and vegetables intake	I-CHANGE	Print	Fruit and vegetables intake Fat intake Awareness Motivation Stage of change Attitude Self-efficacy	1-3	Intervention also focuses on smoking and PA Smeets at al evaluated the first computer-tailored letter at short-term, De Vries et al evaluated the effects of three letters with an action planning component randomly applied in 3th letter
Sternfeld, 2009 *45*	Saturated and trans fat intake, Fruit & vegetables intake, Added sugars		Email reports	Dietary intake Stage of change Self-efficacy Individual lifestyle constraints	12	Intervention also focuses on PA Personal homepage: tips on how to achieve goals Weekly health note Simulation tools Progress tracking tool Review of barriers Discussion board Links to additional resources Reminder messages

1st author(s) *reference number(s)*[1]	Target behavior(s)	Theories	Tools	Tailoring variables	Feedback frequency	Additional strategies/notes
B. DIET (cont)						
Van Keulen, 2011 *2038*	Fruit and vegetables intake	I-Change model Control Theory	Print	Fruit/vegetables intake Awareness Demographics Stage of change Attitude Self-efficacy Expectations Action plans	4	
de Bourdeaudhuij, 2007 *380*	Fat intake	TPB TTM	On screen and/or print	Fat intake Intentions Attitude Self-efficacy Social support Knowledge Benefits Barriers Demographics	1/2	
Walker, 2009 *53* Walker, 2010 *2040*	Fat intake, Fruit and vegetables intake	HPM	Print	Benefits Barriers Self-efficacy Habits Family Support	18	Instructional videotapes Action planning
Werkman, 2010 *13*	Fat intake, Fruit and vegetables intake	Intervention mapping protocol	CD-ROM/print	<u>CD-ROM I (module 2)</u> BMI BMI-related health consequences Energy-balance behavior <u>CD-ROM II (module 3)</u> Fibre consumption Portion sizes of energy dense foods Fat consumption <u>Letter (module 5)</u> Body weight Dietary intake	3	Intervention (5 modules) also focuses on PA and weight loss. Modules 1 and 4 are not tailored Encouraging/informative newsletters
Winett, 2007 *120*	Fat intake, Fruit and vegetables intake		On screen	Nutrition Goal attainment Strategies Preferred reasons for using intervention (health/weight loss)	12	Intervention also focuses on fruit and vegetables intake, fat intake, fiber intake and weight loss Church-based supports

TPB = Theory of Planned Behavior; TTM = Transtheoretical Model; HBM = Health Belief Model; SCT = Social Cognitive Theory; ELM = Elaboration Likelihood Model; HPM = Health Promotion Model; PAPM = Precaution Adoption Process Model; SRT = Self-regulation Theory; SDT = Self-determination theory; RPT = Relapse Prevention Theory; [1]Some publications reported on the same intervention, and are therefore clustered in one cell; [2]Dutton, 2008 examined the effects of an intervention aimed at physical activity on dietary intake.

CHAPTER 3

A tailored lifestyle intervention to reduce the cardiovascular disease risk of individuals with Familial Hypercholesterolemia (FH): design of the PRO-FIT randomised controlled trial

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Background

Because of a high cardiovascular disease (CVD) risk in people with Familial Hypercholesterolemia (FH), early prevention of cardiovascular disease is important for health gain and cost reduction. This project focuses on the development and evaluation of an innovative intervention aiming to reduce CVD risk by promoting a healthy lifestyle among people with FH.

Methods

This project is designed as a randomised controlled trial in which individuals with FH will be assigned randomly to a control or intervention group. In the intervention group (n = 200), participants will receive a personalized intervention which is a combination of web-based tailored lifestyle advice and personal counselling by a lifestyle coach. The control group (n = 200) will receive care as usual. Primary outcomes are biological indicators of CVD risk: systolic blood pressure, glucose, BMI, waist circumference and lipids (triglycerides, total, LDL and HDL cholesterol). Secondary outcomes are: 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). Measurement will take place at baseline, and at 3 and 12 months after randomisation. Additionally, a throughout process-evaluation will be conducted to assess and monitor intervention implementation during the trial.

Discussion

Results of the PRO-FIT project will provide information about the effects and implementation of a healthy lifestyle intervention for individuals with FH. Our experiences with this intervention will be indicative about the suitability, feasibility and benefits of this approach for future interventions in other high-risk groups, such as Familial Combined Hypercholesterolemia (FCH) and diabetes.

INTRODUCTION

Familial hypercholesterolemia (FH) is an autosomal dominant disorder of the lipoprotein metabolism. Due to a defect of the low density lipoprotein (LDL) receptor gene, plasma concentrations of LDL cholesterol (LDL-C) are elevated. [1] In the Netherlands, approximately one in 300 people is affected with the heterozygous type of FH. [2] In 2003, the Ministry of Health, Welfare, and Sports introduced a national cascade screening program to detect people with FH. The screening program is run by the Foundation for Tracing Hereditary Hypercholesterolemia (StOEH) and through this program, some tens of thousands of people in the Netherlands have already been and are made aware that they have FH. [3]

Elevated serum LDL-C and therefore also FH is associated with an elevated risk of premature cardiovascular disease (CVD) [4], which is the disease with the highest burden in disability adjusted life years (DALYs) in the Netherlands. [5] If elevated LDL-C is not diagnosed and treated, the cumulative risk of developing coronary artery disease (CAD) by the age of 60 years is over 60% for men, and over 30% for women. [6] This increased risk does not appear to make people with FH more worrisome. [7] They seem to underestimate their CVD risk [8] and perceive it similar to those in whom no mutation was found. [7]

A substantial number of LDL-C mutation carriers are identified through the national screening program. However, a large variety in phenotypic expressions among FH carriers has been found. [9] Environmental factors, lifestyle factors in particular, appear to play an important role in modulating the course of this disorder. [10,11] Until now, research has mainly been focussed on the effectiveness of pharmaceutical therapy, whereas achieving improvement by lifestyle change has hardly been investigated. Large primary and secondary prevention trials with statins have clearly demonstrated the benefit of reducing LDL-C in subjects with high LDL-C. [12,13] Statin therapy is the cornerstone of dyslipidemic management for people with FH, but significant CVD risk persists despite effective LDL-C lowering statin treatment. [14] Two main strategies are of importance to further reduce CVD risk among FH patients: 1) Improvement of adherence to statin therapy, and 2) Improvement of CVD-risk-related lifestyle. Large proportions of individuals with FH receive lipid-lowering statin therapy and still do not achieve LDL-C target levels as stated by the guidelines of the National Cholesterol Education Program (NCEP). [15] Even though compliance to medication seems high, still 12% of the people with FH never started, and 6.4% discontinued their medication after identification of FH. [16] Additional activities to promote treatment (adherence) have the potential to be effective in reducing CVD risk in these groups.

A healthy lifestyle is an aspect of the treatment of FH with many benefits beyond LDL-C-lowering drugs. [17] Results of primary prevention trials in high-risk persons and secondary prevention trials in CVD patients both show that substantial reductions in the CVD risk can be obtained through lifestyle changes. [18] For example, the INTERHEART study showed that eating fruit and vegetables daily, being physically active regularly and avoiding smoking were effective in reducing the risk of a myocardial infarction by 80%. [19]

Altogether, these findings indicate that more comprehensive treatment of dyslipidemia is needed among FH patients to establish treatment goals. Raising awareness of the actual CVD risk, lifestyle improvement and improving compliance to statin therapy are promising strategies in reducing CVD risk among people with FH. There is a lack of evidence-based interventions that incorporate this comprehensive approach in the Netherlands as well as elsewhere. Our experiences with this intervention will be indicative about the suitability, feasibility and benefits of this approach for future interventions in other high-risk groups, such as Familial Combined Hypercholesterolemia (FCH) and diabetes.

The PRO-FIT project aims to develop such a comprehensive tailored lifestyle intervention and to evaluate this intervention in a randomized controlled trial, supported by a process and cost evaluation. In this article, we aim to outline the intervention and research design of the PRO-FIT project. PRO-FIT stands for promoting a healthy lifestyle in people with FH through an individually tailored lifestyle intervention.

METHODS

Methods/Design

Development of the intervention

The PRO-FIT intervention was developed in a stepwise fashion, informed by a comprehensive theoretical framework and supported by an external advisory group. The advisory group brought together experts on behavioural change, computer tailored health education, and on FH and cardiovascular diseases. Their feedback and input was used to develop the intervention, and will be used during the intervention trial.

Theoretical framework

The intervention of the PRO-FIT project was developed according to the integrated model for

exploring motivational and behavioural change, the I-Change model (2.0). [20] The core of the I-Change model is the Attitude-Social Influence-Self-efficacy (ASE) model which is comparable to the Theory of Planned Behaviour. [21], but incorporates modelling and social support as social influences besides subjective norms. The I-Change model combines the ASE model with insight from stages of change models. [24,25] and action planning models [26,27] to provide a comprehensive framework to study and facilitate behaviour change processes. It assumes that the behavioural change process can be distinguished in three phases: 1) awareness, 2) motivation and 3) action. For each phase, specific change determinants have been proposed.

In the 'pre-motivational' awareness phase, people need to become aware of their risk behaviour. Important factors to proceed through this phase according to I-Change are knowledge, risk perceptions, and cues that prompt people to become aware. In the motivational phase, people need to become motivated to change their behaviour. Important factors in this phase according to the I-Change model are attitudes, social support and self-efficacy expectations. Proceeding through the motivational phase results in positive intention to change one's behaviour. In the action phase people need to translate intentions into actual behaviour change. In this phase several preparatory actions to facilitate behaviour change need to be planned and executed. People should convert their more global goal intentions into specific implementation intentions or action plans, with relevant strategies that will enable them to attain their goal.

For a detailed overview of the I-Change model, see figure 1.

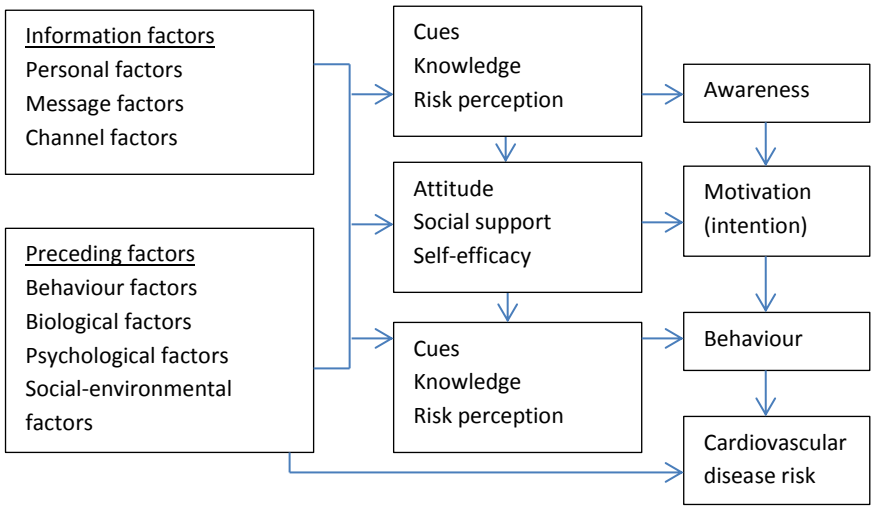

Figure 1: I-Change model 2.0. An integrated model for exploring motivational and behavioural change, used as theoretical framework during the development of the PRO-FIT intervention.

Strategies

During the development of the PRO-FIT intervention, we aimed to focus on the earlier-mentioned factors of behavioural change identified in the I-Change model. A more detailed description of these factors, the strategies that will be employed, as well as the intervention components are outlined in table 1.

Table 1: Strategies to influence factors of behavioural change

Factors of behavioural change	**Strategy**
Awareness factors knowledge, risk perception and cues to action	Educating participants on their current CVD risk factors, with regard to their size and changeability (**risk communication**). Thereafter, translating this to behavioural change in their personal situation. Raising awareness by providing personal and normative behavioural feedback following **motivational interviewing** techniques.
Predisposing factors genetic predisposition, current lifestyle, personal characteristics and information factors.	**Tailoring** the communication of CVD risk factors and lifestyle counseling to the genetically predisposed risk of the participants and their personal characteristics (age, gender, members of the household) and their current lifestyle behaviour. A **multi-channel approach** is chosen, thereby offering the intervention by internet, face-to-face and by telephone.
Motivational factors attitude, social influence and self-efficacy	Giving personal feedback to participant's self-reported attitude and self-efficacy and by involving the social environment of the participant in making action plans.
Ability factors,	Stimulating participants to make action plans and discussing how to overcome possible barriers in behavioural change, thereby following **motivational interviewing** techniques.

Risk communication

To raise awareness, participants will be presented with CVD risk information. Due to the predispositional character of the risk and its high dependency on medication use and current lifestyle behaviour, it is not possible to present participants with a valid, accurate personal numeral risk. Rather, participants will be presented with: 1) feedback on CVD risk behaviours to educate them about the contribution of these CVD risk factors to their overall CVD risk, 2) information on the changeability of these factors, and 3) cues about how these risk behaviours may be changed. The risk factors, their changeability and the cues to action will be presented to the participants on a personal webpage.

Computer tailoring

Earlier research has shown that computer-tailored education is an innovative and promising method to motivate people to change their physical activity and dietary behaviours, and it has shown better effects than generic health education. [23] The fact that computer-tailored health education provides people with personalized feedback and advice is probably the main determinant of its effectiveness. [24]

In this project, online tailored advice is focused on saturated fat intake, fruit and vegetables intake, physical activity, smoking behaviour and compliance to statin therapy. Online advice on saturated fat intake, physical activity and smoking behaviour is based on existing tailored information modules of the 'Healthy Life Check' (in Dutch: 'Gezondlevencheck') of the Netherlands Heart Foundation. This web-based computer-tailored lifestyle intervention was evaluated by Oenema et al [25] and reduced saturated fat intake and increased physical activity. Computer-tailoring is focused on personal performance level (current lifestyle behaviour), awareness of their own performance, as well as personal motivation to change, outcome expectations, attitude and self-efficacy. Since CVD risk reduction can be achieved by daily fruit and vegetable intake as well [19], online tailored advice modules on fruit and vegetables are added to the online tailored advice, mainly based on existing modules of the Live Healthy Coach (in Dutch: Leefgezondcoach) of the Dutch Diabetes Federation, developed at the Erasmus University Medical Center in Rotterdam, the Netherlands. Personalized feedback on compliance to statin therapy will be given through an existing tailored information module, tailoring on knowledge and personal beliefs about (the effect of) statin therapy, potential side effects of the prescribed drug and current compliance. This module was developed at the Rijksuniversiteit Groningen, the Netherlands. Additionally, a short-term plan and potential barriers to achieve this plan can be formulated in the online system. These tailored advice modules are integrated into one online PRO-FIT*advice environment, a website that participants can visit using their personal account.

For the PRO-FIT computer-tailored intervention we have taken the main limitations into account identified in the main systematic review of effectiveness of computer-tailoring in the behavioural nutrition and physical activity field. [23] More specific, PRO-FIT combines web-based education with interpersonal counselling, and thereby combines repeated exposure to the intervention with individualization of messages and a social component.

Motivational interviewing

Motivational interviewing (MI) was chosen as a technique to counsel the participants towards the desired behavioural change. MI was developed by Miller and Rollnick [26] and is a useful intervention strategy in behaviour change interventions. [27] MI is directive, but client-centred and its main goal is to facilitate the client in identifying and mobilizing his or her intrinsic values and goals related to the targeted behavioural changes. Meta-analyses indicate that MI can be effective in facilitating health behavioural changes across a range of domains. [28,29] The five main principles of MI are: 1) showing empathy, 2) avoiding discussion, 3) rolling with resistance, 4) supporting self-efficacy, and 5) raising awareness of a dissonance between actual behaviour and behavioural goals. The main interviewing strategies of MI are: asking open-ended questions, showing empathy, reflecting on the client, confirming and summarizing. [26] In this project, brief MI will be performed by a personal coach, a health professional trained in MI. MI will be done once face-to-face at the participants' home and five times by telephone. The main principles of MI will be used to develop interview protocols. For telephone counselling, an adjusted version of the telephone interview protocol of the Healthy Body Healthy Spirit trial will be used. [30,31]

The PRO-FIT intervention

The intervention consists of a personalized health counselling intervention. This is a combination of tailored web-based advice (*PRO-FIT*advice*) and face-to-face counselling complemented with telephone booster sessions (*PRO-FIT*coach*).

The goal of the intervention is to: 1) improve awareness of the cardiovascular disease risk through an increase of specific knowledge, cues to action and change in risk perception, 2) improve motivation with respect to healthy behaviour through an increase of specific knowledge and a change in attitude, self-efficacy and social influences, 3) adopt and maintain a healthier lifestyle, with regard to physical activity, saturated fat intake, fruit and vegetables intake, smoking and compliance to statin therapy, and 4) lower the level of LDL-C and other biological CVD risk indicators and thereby a reduction of the CVD risk.

Risk communication

Participants of the intervention group will receive a web link that directs them to the project website, where they can go through a number of web pages providing them with information about their CVD risk profile. After going through these web pages, they can log on to the tailored lifestyle advice (PRO-FIT*advice) with their personal username and password that are given in the email.

Computer tailoring

*PRO-FIT*advice* contains six advice modules on physical activity, fruit intake, vegetables intake, saturated fat intake, smoking and compliance to statin therapy. Participants can choose what modules to go through and in what order, but they will be advised and encouraged to complete all relevant modules (e.g. the module 'smoking' only if the participant is a smoker). For each module, participants first complete an online questionnaire that enables assessment of current behaviour and the relevant psychosocial correlates suggested by the I-Change model. After completion, the PRO-FIT*advice software will analyse the answers and create personalized feedback and behaviour change advice, provided on the computer screen. More specifically, feedback on current behaviour in accordance with national recommendations will be provided and, if the behaviour is not according to recommendations, suggestions will be given on how to make relevant behaviour changes. The participants will be encouraged to make a concrete action plan, i.e. to specify when, where and how they will make the changes as well as what preparatory actions are necessary.

Motivational interviewing

Two weeks after sending their personal PRO-FIT*advice username and password, participants will be visited at home by their lifestyle coach. The participant and the coach will further establish the level of the participant's knowledge about FH and cardiovascular risk factors, and risk perception in a personal counselling session assisted by the information from the risk communication web pages. Furthermore, the coach will have access to the participant's personal PRO-FIT*advice account and the advice will be discussed, ambivalence and barriers related to the recommended behaviour changes will be explored based on MI.

During the 12 months of follow-up one to five counsellor-initiated booster telephone sessions will be performed. The goal of these calls is twofold: to encourage the participant's current behavioural changes and to provide further brief motivational interviewing to encourage the planned behavioural changes. The number of telephone sessions will be based on the participant's action plans and their need for additional counselling. The calls will be scheduled with the participant and will be documented in the form of a personal calendar that is send to the participant with a small booklet in which all topics to be addressed during the counselling session will be listed.

Face-to-face counselling and telephone booster sessions will be performed by two trained lifestyle coaches. They received a special 3-day training programme on motivational interviewing

techniques. For training purpose, during a pilot study, 20 pilot counselling sessions were scored by the coaches according to the Motivational Interviewing Skills Code (MISC) [32] and the Motivational Interviewing Treatment Integrity Code (MITI). [33] According to these scores, and the experiences of the participants and the trainees, the quality of counselling was discussed and potential points of improvement were brought up. Each counselling session will be audio taped and both content and general characteristics will be documented into a database registration system. Both face-to-face and telephone counselling will be examined by two trained coders for fidelity to MI, using Motivational Interviewing Treatment Integrity (MITI 3.0) code. [34] To promote continued participation in the PRO-FIT trial, participants in both study groups will receive three incentives during the course of the trial.

Pilot study

A pilot study to test the feasibility of the intervention and measurement content and procedures of the PRO-FIT trial was conducted in November 2008. Twenty participants from the target population were recruited for this pilot following the same recruitment strategies as are intended for the trial. All 20 participants completed the measurement and intervention in a one month time frame. Participants were interviewed and surveyed about their appreciation and logistics of and experiences with the measurement and intervention. Based on the pilot, minor adjustments were made in the content and procedure of both the measurement and intervention.

Evaluation of the intervention

This PROFIT trial is designed as an RCT. Participants will be randomly assigned to either intervention or control group. In the intervention group, the participants will receive the comprehensive intervention as described above. Participants in the control group will receive usual care, which means that they will receive no intervention. Recruitment started in February 2009. Data collection continues until the summer of 2010.

The project design, procedures and informed consent form were approved by the Medical Ethics Committee of the VU University Medical Center (under registration number 2008/149), and all participants provide written informed consent.

Study population

Participants are individuals who were diagnosed with FH by StOEH from January 1st2007 to April 15th 2009. The invitation included an information brochure, a reply card, an informed consent letter and a reply envelope. Responders to the invitation are included in the project if they: 1) are

aged 18-70 years, 2) are sufficiently fluent in Dutch, 3) have given informed consent, 4) have a LDL-C level that is >75th percentile (corrected for age and gender), 5) live in a 150 km radius of Amsterdam, and 5) have access to the internet.

Sample size

Information is lacking on the Standard Deviation (SD) of the mean intra-individual change in LDL-C, the main CVD risk indicator, over one year period of follow-up in a population that has recently been notified of their positive FH status. Being conservative, we expect the change to be large (35%). With an alpha of 0.05, the mentioned numbers (200 participants in intervention and 200 in control group) and an expected drop-out of 20%, the power is 90% to statistically detect an intervention effect of 9%. A 10% reduction of LDL-C is associated with a 13% reduced risk of major coronary events. [35]

Randomisation

A stratified computerized randomisation procedure will be carried out using Microsoft© Office Access 2003 software. We will stratify participants according to cholesterol lowering medication use (yes/no), assuming that medication use implicates treatment by a general practitioner and/or medical specialist, who could have already given advice on lifestyle behaviour. In addition, we expect that a decrease in LDL-C because of the intervention is smaller if a participant already uses medication. After stratification, the randomisation procedure will be carried out.

If participants are members of the same household, cluster randomisation will be performed by clustering these participants and allocating them randomly to either the control or the intervention group. This will be done to prevent contamination of the intervention effect due to reciprocal communication about the intervention or control condition among participants. Stratification and randomization will be performed by an independent researcher, who is not involved in the intervention.

Participant flow

After the participant completed the reply card and signed the informed consent letter, baseline measurements will be performed and the baseline questionnaire will be sent out. Thereafter, 400 participants will be randomly assigned to either the intervention (n = 200) or control group (n = 200). Participants are followed for 12 months. For a detailed flow chart, see figure 2.

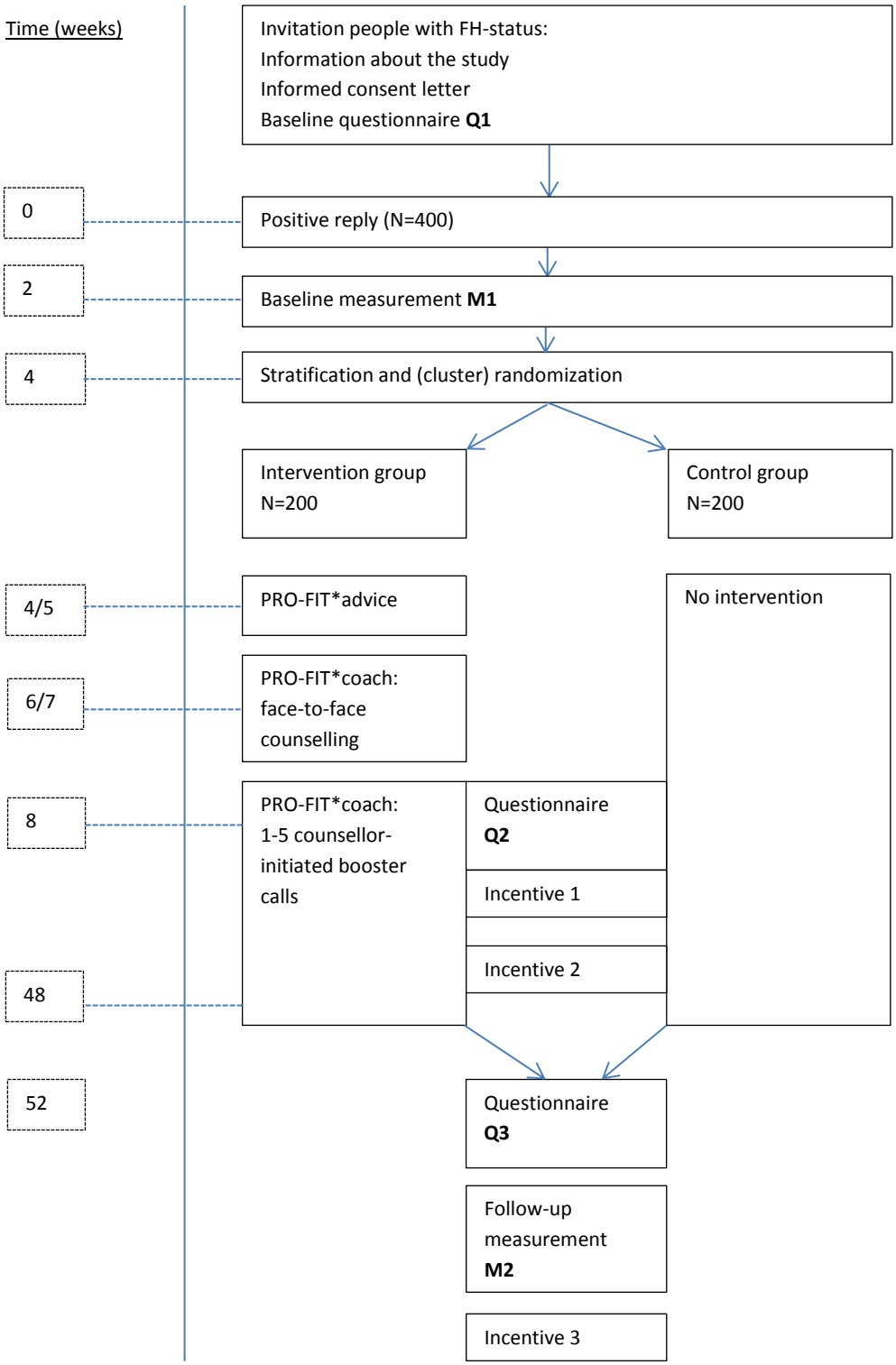

Figure 2: Participant flow. A detailed participant flow chart of the PRO-FIT project.

Measurements

Biological CVD risk indicators

LDL-C, HDL-C and total cholesterol, triglycerides and glucose will be measured with fasting finger stick samples analyzed on a Cholestech LDX desktop analyzer (Cholestech, Hayward, USA). This portable analyzer is capable of providing a lipid profile (LDL-C-, HDL-C and TC, TC/HDL ratio and triglycerides) and glucose in approximately 5 minutes, using a lipid profile and glucose test cassette. The reproducibility and precision of lipids measurement by the LDX analyzer are within the guidelines of the NCEP. [36,37] The Cholestech LDX analyzer has been validated for point-of-care lipid measurements in clinical practice. [38] Blood pressure (in mmHg) is measured twice with a fully automated blood pressure monitor. The right arm is placed on a table and a cuff is placed on the right upper arm. Participants with a blood pressure of 140/90 mmHg or higher will be advised to visit their general practitioner. The mean value of the two measurements will be computed.

BMI and waist circumference

Height (in cm) will be measured on bare feet with a portable device with a wide measuring slide and a heel plate. Calibrated scales will be used to determine body weight (in kg) while participants wear light clothing only (e.g. underwear). Both weight and height will be measured twice, and the mean value of the two measurements will be computed and used to calculate BMI. Waist circumference (in cm) will be measured twice with a measurement tape to the nearest 0.1 cm, at the midpoint between the lower border of the ribs and the upper border of the pelvis. The mean value of the two measurements will be computed.

All measurements will be performed by a trained research assistant at the beginning of participation (M1 in figure 2) and after 12 months (M2 in figure 2).

Questionnaires

Lifestyle behaviours

The level of physical activity will be measured by the Short QUestionnaire to ASsess Health-enhancing physical activity (SQUASH), which has been found to be fairly reliable (overall correlation: 0.58) and reasonably valid. [39] The focus regarding dietary intake is on saturated fat, fruit and vegetable intake, and will be measured by the short Dutch questionnaire on total and saturated fat intake [40,41] and on fruit and vegetable intake. [42] These questionnaires have been validated as related to seven day dietary records (47-49). For the fruit and vegetable questionnaire also biomarker validity was established. [43] Smoking behaviour will be assessed by a self-reported measure, asking participants if they are a current smoker, an ex-smoker, or a never smoker, how

many years they smoke(d) and how many cigarettes or other tobacco products they smoke(d) a day. [44]

Self-reported compliance to statin therapy

The five-item Medication Adherence Report Scale (MARS-5) will be used to measure self-reported compliance to statin therapy, which was found to have good reliability and validity. [45] In addition, pharmacy records will be used to study the persistence of medication use (period from first prescription to discontinuation) and refill compliance (percentage of prescribed medication that was actually obtained at the pharmacy). Permission to consult pharmacy records will be asked in the informed consent form.

Intention

Intention to change will be assessed with a self-report measure, asking participants:*Do you plan to change behaviour X*. The behaviour and the change was specified according to recommendations (e.g. raise the level of physical activity to >30 minutes a day) on a 5-point Likert scale ranging from *certainly yes* to *certainly no*. Additionally the participants will be asked how certain they were about acting upon their intention and *How sure are you of this?* (*absolutely sure* to *absolutely not sure*).

Risk perception

Leventhal's self-regulation model of illness cognition (SRM) provides a useful framework for considering and assessing the role of risk perception in response to communicating CVD risk to people with FH. [46] According to this model, a health threat activates a self-regulatory process where initially a coherent, common-sense understanding of the problem is developed. The cognitive illness-risk representations that are formed can be translated to the five core constructs of the SRM: identity, causal beliefs, timeline, consequences and control. [47] Questions on risk perception were developed from the literature and partly based on the brief Illness Perception Questionnaire (IPQ), the revised IPQ (IPQ-R)[48,49] and questionnaire of Claassen et al. [50] The constructs of the IPQ and IPQ-R are mainly based on the five elements of the SRM. Participants will be asked if they actually know about their CVD risk and if they know how to reduce this risk, on a 5-point Likert scale ranging from *I totally disagree* to *I totally agree*. Emotional representation of CVD risk will be assessed questioning *When I think of my CVD risk, I feel...* on a 7-point Likert scale ranging from *not anxious at all* to *very anxious* and *not worried at all* to *very worried*. The perceived CVD risk will be assessed questioning the comparative risk (*Of 100 men/women of my age, I think that approximately .... people will develop a CVD within the next 10 years*), the verbal perceived risk (*How likely is your*

chance of getting a CVD within the next 10 years?) and verbal comparative risk (*According to you, what is your chance of developing a CVD within the next 10 years, compared to an average men/women of your age without FH?*) both on a 7-point Likert scale ranging from *very unlikely* to *very likely*. Additionally, we will assess perceived CVD risk from a personal point of view, questioning *For your own feeling, how big is your chance of developing a CVD within the next 10 years?*' on a 7-point Likert scale ranging from *very small* to *very big*. Finally, participants will be asked to score whether twenty possible causal beliefs (e.g. *I expect chance or bad luck as a potential cause for CVD*) for CVD were applicable to their situation. Furthermore, participants will rank what they thought were the three most important causes.

Psychosocial factors

Attitude, self-efficacy and social influence will be measured on a 5-point Likert scale ranging from (attitude) *very bad* to *very good*, (self-efficacy) *very difficult* to *very easy* and (social influence of partner, relatives, children, friends and/or experts) from *I totally agree* to *I totally do not agree*. Whether (a relative) having FH, (a relative) having CVD, an elevated CVD risk and/or death of a relative through CVD were cues to change lifestyle behaviour, will be measured on a 5-point Likert scale ranging from *I totally agree* to *I totally do not agree*. The psychosocial factors mentioned above will be measured with regard to all lifestyle behaviours, as well as to compliance to statin therapy. In addition, preference for autonomy will be measured with one item, asking *In general, when it comes to my health, I would rather have an expert tell me what I should do* on a 5-point Likert scale ranging from *I totally agree* to*I totally do not agree*. Response efficacy will be measured on a similar scale, assessing whether the participant believes statin treatment and lifestyle improvement are effective in reducing CVD risk.

Electronic questionnaires will be sent to the participants at the beginning of participation (Q1 in figure 2) and after 12 months (Q3). Additionally, risk perception will be measured after 3 months (Q2 in figure 2), and preference for autonomy will be measured after 12 months (Q3).

Statistical analysis

Multiple linear and logistic regression analysis techniques will be performed. Potential confounders and effect modifiers (i.e. gender and age) will be checked. Data will be analysed according to the intention-to-treat principle.

Process evaluation

A thorough systematic approach is chosen to monitor and document the implementation of the

intervention during the trial. By using the RE-AIM framework, the translatability and public health impact of our project will be repeatedly evaluated by examining our work in light of the following five dimensions: 1) reach among the target population; 2) efficacy of the intervention; 3) adoption by intermediaries; 4) implementation - consistency of delivery of intervention; 5) maintenance of intervention effects in individuals and populations over time. [51] Consequently, a structured process evaluation plan is developed according to Saunders. [52] A systematic approach is chosen to assess the implementation of the intervention, including recommended elements like fidelity, dose (delivered and received), reach, recruitment and context. Process evaluation questions are formulated on each element and accompany the questionnaire at 3 months (Q2) and at follow up (Q3).

Economic evaluation

Economic evaluation consists of an analysis of differences in intervention development and implementation between the intervention and control group. The incremental costs of the intervention group compared to the control group will be divided by the incremental effect for the percentage improvement in LDL-C. The 95%-CI for these ratios is calculated using bootstrapping methods and they will be graphically presented on a cost-effectiveness plane. Utilities for the cost-utility analysis will be based on the EuroQol questionnaire[53], accompanying the questionnaire at baseline (Q1), at 3 months (Q2) and at follow-up (Q3).

DISCUSSION

In this article, we aim to outline the design of the PRO-FIT project, which is a RCT on the (cost-) effectiveness of a tailored lifestyle intervention to reduce the CVD risk of individuals with FH. The intervention is theory-driven and works systematically, aiming at a reduction of CVD risk through improvement of lifestyle behaviours and medication adherence.

Anticipated strengths of the approach include: it starts with aiming at accurate awareness of CVD risk, then giving evidence-based tailored feedback on lifestyle and finally, personally motivating people to move towards a healthy lifestyle. The social interaction during the face-to-face coaching session complements the single weakness of the individualized web-based approach, and thereby making this combination a promising one. Former research has shown that similar lifestyle interventions can effectively improve lifestyle behaviour. [18]

Limitations of this project are: the study population is characterized by diversity and similarity at the

same time. Both aspects can cause contamination of effects. Diversity is mainly due to the expected inter-participant differences at baseline, regarding biological CVD risk indicators, lifestyle behaviour, and use and type of medication. Similarity is caused by the familial nature of FH, resulting in a population with a high level of mutual communication. Both stratifying our sample on use of medication, and randomizing them in household clusters are methods to minimize potential contamination. However, these limitations should be considered during data analysis.

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CHAPTER 4

The efficacy of a tailored lifestyle intervention on multiple lifestyle behaviours in people with Familial Hypercholesterolemia

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Objective

To evaluate the efficacy of an individualised tailored lifestyle intervention on physical activity, dietary intake, smoking and compliance to statin therapy in people with Familial Hypercholesterolemia (FH).

Methods

Adults with FH (n=340) were randomly assigned to a usual care control group or an intervention group. The intervention consisted of web-based tailored lifestyle advice and face-to-face counselling. Physical activity, fat, fruit and vegetable intake, smoking and compliance to statin therapy were self-reported at baseline and after 12 months. Regression analyses were conducted to examine between-group differences. Intervention reach, dose and fidelity were assessed.

Results

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). In the intervention group, 95% received a log on account, of which 49% logged on and completed one module. Nearly all participants received face-to-face counselling and on average, 4.2 telephone booster calls. Intervention fidelity was low.

Conclusions

Individually tailored feedback is not superior to usual care regarding changes in multiple lifestyle behaviours in people with FH.

Practice implications

A higher received dose of computer-tailored interventions should be achieved by uplifting the website and reducing the burden of screening questionnaires. Counsellor training should be more extensive.

INTRODUCTION

Familial hypercholesterolemia (FH) is an autosomal dominant disorder of the lipoprotein metabolism. Due to a defect of the low density lipoprotein (LDL) receptor gene, plasma concentrations of LDL cholesterol (LDL-C) are elevated. [28] In most Western countries, approximately one in 500 people is affected with FH. [19] Elevated serum LDL-C and therefore FH is associated with an elevated risk of premature cardiovascular disease (CVD) [1], which is the disease with the highest burden in disability adjusted life years in the Netherlands. [56] If elevated LDL-C is not diagnosed and treated, the cumulative risk of developing coronary artery disease by the age of 60 years is over 60% for men, and over 30% for women. [64]

Yet, research has mainly been focused on the effectiveness of pharmaceutical therapy, whereas achieving (additional) improvement by lifestyle change has hardly been investigated in people with FH. Large primary and secondary prevention trials with statins have clearly demonstrated the benefit of reducing LDL-C in subjects with high LDL-C [4,29]. Also, Versmissen and colleagues showed an overall risk reduction in a large cohort (n=2146) of people with FH that used statins. [60] However, lifestyle factors also appear to play an important role in moderating the course of FH. [3,23] The EUROASPIRE III survey, conducted in 2006-2007 in 22 European countries, showed a high prevalence of unhealthy lifestyles among CVD patients treated by cardiologists, and moreover, use of medication was often inadequate to achieve treatment goals. [31] Overall, two main strategies are of importance to optimally reduce CVD risk among people with FH: 1) improvement of compliance to statin therapy, and 2) improvement of CVD-risk-related lifestyle.

A healthy lifestyle is mentioned as an aspect of the treatment of FH with many benefits beyond LDL-C-lowering drugs. [12] In the most recent European guidelines on cardiovascular disease prevention [20], lifestyle modification is recommended for individuals at high risk for CVD. Results of primary prevention trials in high-risk persons and secondary prevention trials in CVD patients both show that substantial reductions in the CVD risk can be obtained through lifestyle changes. [5,35] For example, the INTERHEART study showed that eating fruit and vegetables daily, being physically active regularly and avoiding smoking were effective in reducing the risk of a myocardial infarction by 80%. [65] A short-lifestyle counselling intervention in England showed sustained improvements regarding dietary intake, regular exercise and cigarettes smoked per day at 12 months. [17] Particularly, interpersonal and tailored interventions matching an individual's specific needs and preferences have shown promising results within a range of lifestyle behaviours. [24,43]

There is a lack of evidence-based interventions that incorporate a comprehensive approach to optimise treatment goals of people with FH in the Netherlands, as well as elsewhere. We assume that lifestyle improvements can positively change biological CVD risk indicators, and that this would eventually lead to a reduction of the CVD risk. The PRO-FIT project focuses on the development and evaluation of an innovative intervention aiming at reducing CVD risk by promoting a healthy lifestyle among people with FH. In this paper, our research question is whether this intervention has an effect on physical activity, dietary saturated fat, fruit and vegetable intake, smoking and compliance to statin therapy.

METHODS

Design and participants

A randomised controlled trial was conducted with measurements at baseline and at 12 months post-baseline. Participants diagnosed with FH through DNA analyses from January 1st 2007 to April 15th 2009, aged from 18 to 70 years and with a LDL-level > 75th percentile (age and gender specific) were recruited from the national cascade screening program of the Foundation for the Identification of Persons with Inherited Hypercholesterolemia (StOEH). [2] Access to internet, sufficient fluency in Dutch and residency < 150 km radius from Amsterdam were additional eligibility criteria. Invitation brochures were send to 986 people during six months and resulted in 340 participants 34%), of whom 336 (99%) completed the baseline questionnaire, and 318 (94%) completed the baseline and follow-up questionnaire. Details on recruitment and participant flow can be found in figure 1.

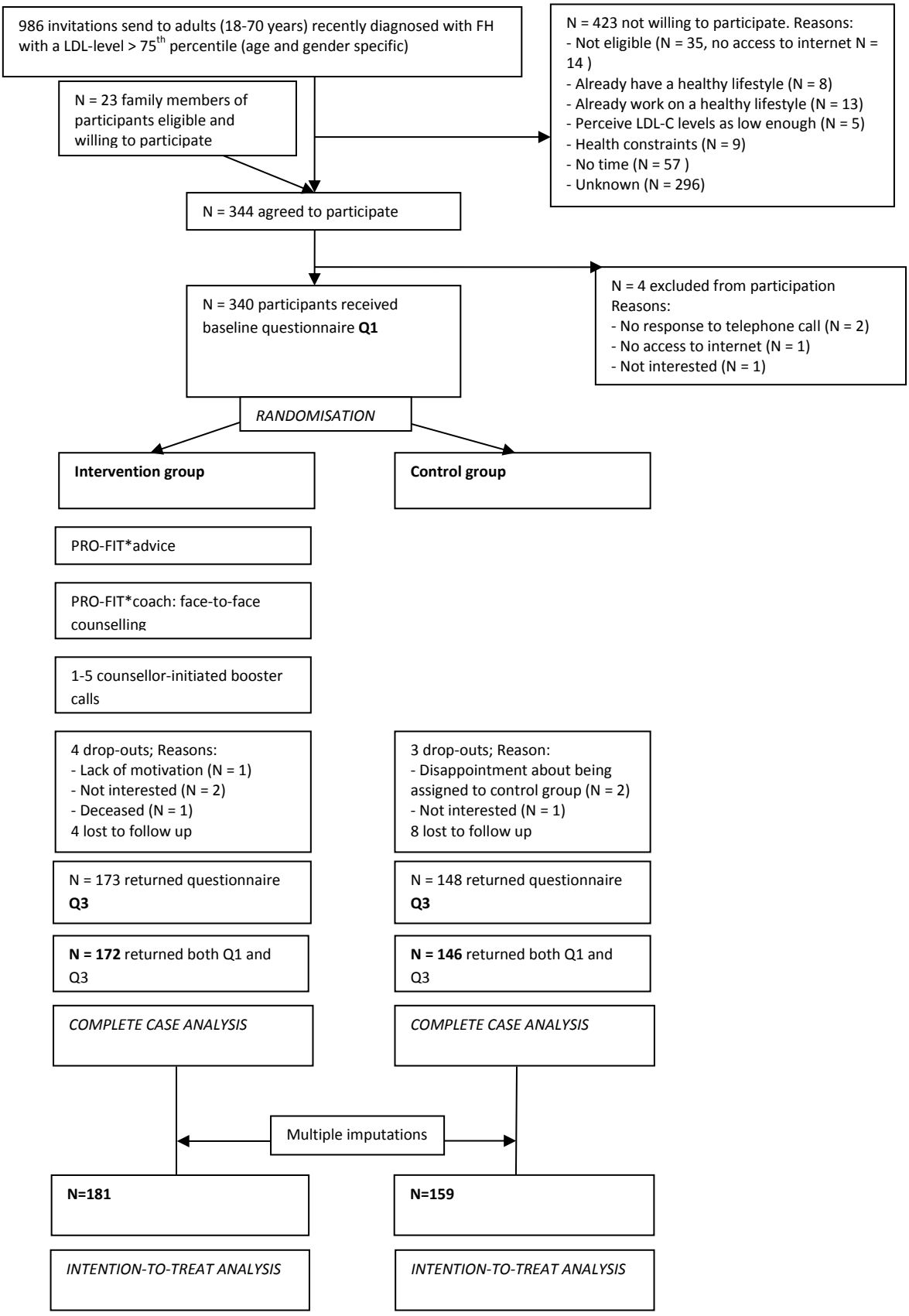

Figure 1: Recruitment, participant and retention flow

The content of this paper was guided by the recommendations for reporting randomised controlled trials of the CONSORT (Consolidated Standards of Reporting Trials) statement. [51] The PRO-FIT project was approved by the Medical Ethics Committee of the VU University Medical Centre and all participants gave written informed consent.

Procedure

After the participant had confirmed to participate and had signed the informed consent form, the baseline questionnaire was sent out. Thereafter, the concealed randomisation procedure was carried out. Participants were randomly assigned to either the usual care control group (n=159) or the intervention group (n=181) through a stratified computerised randomisation procedure using Microsoft© Office Access 2003 software. At first, participants were stratified according to cholesterol lowering medication use, assuming that medication use implicates treatment by a general practitioner and/or medical specialist, who could have already given lifestyle advice. In addition, we expected that a decrease in LDL-C – the primary outcome of this project - because of the intervention is smaller if a participant already uses medication. Family members of the same household were clustered and subsequently randomised as a cluster to prevent contamination of the intervention effect due to spill over of communication about the intervention among participants.

Theoretical framework

The intervention of the PRO-FIT project was developed according to the integrated model for exploring motivational and behavioural change, the I-Change model (2.0). [8,16] Briefly, it assumes that the behavioural change process can be distinguished in three phases: awareness, motivation and action/behaviour. Hypothetically, due to gained knowledge and awareness of one's CVD risk, a participant will become motivated to change lifestyle behaviour(s), and subsequently, implementation intentions and action plans will be formed to actually achieve (maintenance of) behavioural change. In addition, it is assumed that this will eventually lead to a reduction in CVD risk (see figure 2).

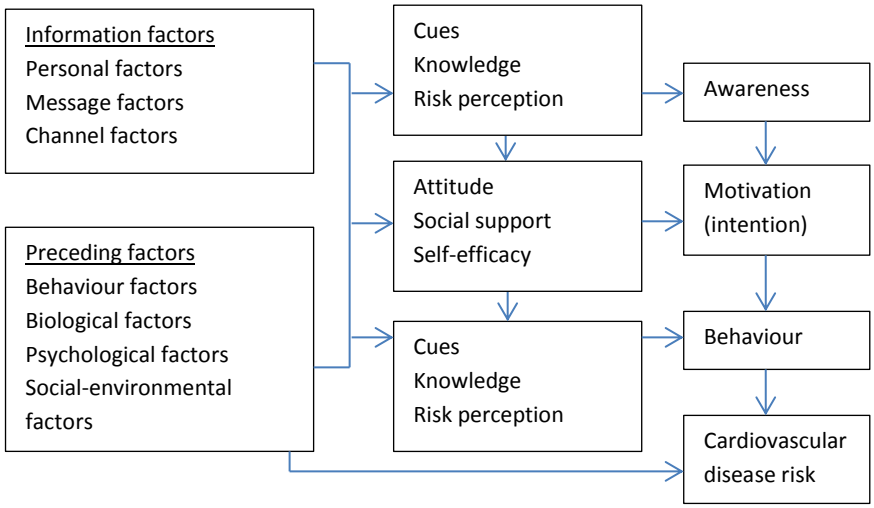

Figure 2: The I-Change model 2.0

Intervention

The intervention consisted of a combination of tailored web-based advice (*PRO-FIT*advice*) and face-to-face counselling complemented with telephone booster sessions (*PRO-FIT*coach)*. The goal was to: 1) improve awareness of the cardiovascular disease risk through an increase of specific knowledge, cues to action and change in risk perception, 2) improve motivation with respect to healthy behaviour through an increase of specific knowledge and a change in attitude, self-efficacy and social influences, 3) adopt and maintain a healthier lifestyle, with regard to physical activity, saturated fat intake, fruit and vegetables intake, smoking and compliance to statin therapy, and 4) lower the level of LDL-C and other biological CVD risk indicators and thereby reducing the CVD risk.

The intervention has been described in detail elsewhere. [8] Briefly, participants were encouraged to visit a weblink referring to the project website, where generic CVD risk information was presented, containing feedback on CVD risk behaviours, their contribution to overall CVD risk, and cues on how to change behaviours. Thereafter, participants could log on to a personal account, consisting of six tailored advice modules on smoking, physical activity, saturated fat intake, fruit intake, vegetables intake and compliance to statin therapy. The module on compliance to statin therapy was developed at the Rijksuniversiteit Groningen, the Netherlands. The other modules were based on existing tailored information modules of the 'Healthy Life Check' (in Dutch: 'Gezondlevencheck') of the Netherlands Heart Foundation. [44] The modules on fruit and vegetables were mainly based on existing modules of the Live Healthy Coach (in Dutch: Leefgezondcoach) of the Dutch Diabetes Federation, developed at the Erasmus University Medical Centre in Rotterdam, the Netherlands.

On-screen personalised feedback was tailored to personal performance level (current lifestyle behaviour), awareness of one's own performance, as well as personal motivation to change,

outcome expectations, attitude and self-efficacy. Personalised feedback to compliance to statin therapy was tailored on knowledge and personal beliefs about (the effect of) statin therapy, potential side effects of the prescribed drug and current compliance.

Subsequently, the participant and the personal coach further established the level of the participant's knowledge/awareness about FH and CVD risk factors. Furthermore, the assessment(s) and advice(s) within the participant's personal *PRO-FIT*advice* account were discussed and ambivalence and barriers related to the recommended behaviour changes were explored based on Motivational Interviewing (MI) techniques. [49] Further, an additional one to five counsellor-initiated booster telephone sessions were performed to further encourage the participant's behavioural changes. The two personal coaches had lifestyle coaching and nursing/ teaching backgrounds and had received an additional 3-day MI workshop, incorporating both introductive lessons and practical training sessions with professional actors.

The control group received care as usual.

Measurements

Lifestyle related outcomes

The level of physical activity in minutes of moderate to vigorous physical activity performed per week, as well as whether participants either did meet or did not meet the physical activity guideline of 30 minutes of moderate- to vigorous physical activity on at least 5 days a week [30], was measured by the Short QUestionnaire to ASsess Health-enhancing physical activity (SQUASH), which has been found to be fairly reliable and reasonably valid. [63]

Saturated fat, fruit and vegetables intake were measured by the short Dutch questionnaire on total and saturated fat intake and on fruit and vegetable intake, that have been validated as related to seven day dietary records. [57, 58] For the fruit and vegetable questionnaire also biomarker validity has been established. [6] From this questionnaire, a score for saturated fat intake, ranging from 0 (lowest) to 80 (highest) fat points was computed, as well as servings of fruit and grams of vegetables per day. One fat point equals 2 gram of saturated fat. Subsequently, it was assessed whether a participant met the Dutch recommendations for daily saturated fat intake, being ≤28 gram/day for men and ≤22 gram/day for women, as well as for daily fruit intake (2 servings/day) and daily vegetable intake (200 gram/day). [18,61] Smoking behaviour was assessed by a self-reported measure, asking participants if they were a current smoker, an ex-smoker, or a never smoker, how many years they had smoked and how many cigarettes or other tobacco products they smoke or had

smoked a day. [39]

The five-item Medication Adherence Report Scale (MARS-5) was used to measure self-reported compliance to statin therapy, which was found to have good reliability and validity. [25] Scores on five items were combined to a total score ranging from 5 (lowest) to 25 (highest). The items referred to whether participants always (1) / never (5) forget or stop their medication, decide to miss out a dose, take less than instructed or alter the dose of their medication without consulting a medical doctor and/or pharmacist. Based on former research, low compliance is suggested if one or more doses are missing, thereby assuming an overestimation of the actual compliance. [21, 54] As a consequence, participants with a score of 25 were categorised as compliant to statin therapy, others (score<25) as non-compliant.

Other outcomes

Intention to change was assessed with a self-report measure, asking participants whether they plan to change behaviour X on a 5-point Likert scale (certainly yes (1) to certainly no (5)) and how sure they are of this (absolutely sure (1) to absolutely not sure(5)). Both scores were averaged and participants were categorised into motivated (average score≤ 2) or unmotivated (average score> 2) to change behaviour for each specific behaviour. [14]

Both height (in cm) and body weight (in kg) were measured twice on calibrated scales. Body Mass Index (BMI) was calculated from the average scores. LDL-C was measured with fasting finger stick samples analysed on a Cholestech LDX desktop analyser (Cholestech, Hayward, USA). The reproducibility and precision of lipids measurement by the LDX analyser are within the guidelines of the NCEP. [26,45] The Cholestech LDX analyser has been validated for point-of-care lipid measurements in clinical practice. [11]

A process evaluation was carried out, taking into account the process elements reach, dose (delivered and received) and fidelity. The research methods of this evaluation, as well as the results and discussion are extensively described in chapter 6. In short, reach (the number of people with FH that took part in the project, as well as how representative the participants in the intervention group were for the study population and non-participants) was assessed by consulting the StOEH client database, as well as the PRO-FIT client database. The dose of all delivered elements of the intervention was assessed by logs that were kept by the coaches and the project database. Dose received, i.e. the way participants used PRO-FIT*advice (% of participants that logged on, number of modules finished), was assessed by means of log on rates and website use data. Whether face-to-face counselling sessions were implemented as planned according to MI guidelines (i.e. MI fidelity)

was assessed by two MI experts, following the Motivational Interviewing Treatment Integrity code (MITI 3.1.1.). [38]

Statistical analyses

Potential baseline differences were checked between intervention and control group, regarding gender, age, education, BMI, medication use, LDL-C and whether participants met the recommendations on the different lifestyle behaviours at baseline. In addition, differences between dropouts and non-dropouts regarding the above-mentioned baseline characteristics were tested with linear and logistic regression analyses. If baseline differences were found, the variable concerned was included in further analyses. Effect modification of the above-mentioned variables and intention to change was checked and confirmed if the p-value of the interaction term was <0.05.

Primary, a complete case analysis was conducted at the participant level, restricted to those who filled in questionnaires at both baseline and follow-up. These numbers vary for different outcome measures. Subsequently, an intention-to-treat analysis was conducted, involving all participants who were randomly assigned (n=340). Missing data on physical activity, dietary saturated fat, fruit and vegetable intake, smoking and compliance to statin therapy were imputed using multiple imputations. Five different datasets were created in SPSS (version 18.0) using Fully Conditional Specification and Predictive Mean Matching procedures. All available data on the above-mentioned lifestyle outcomes, as well as on group allocation, gender, age, education, BMI, medication use and LDL-C were included in the imputation model. Thereafter the multiple datasets were analysed as described below, using SPSS (version 18.0). Pooled estimates were computed following the rules as described by Rubin. [50] As no major differences were found, only the results of the complete case analysis are presented.

In order to investigate whether this intervention had had an effect on physical activity, dietary saturated fat, fruit and vegetable intake, smoking and compliance to statin therapy, regression analyses were conducted. Linear regression analyses were conducted for group differences on the continuous outcome measures (saturated fat intake, fruit and vegetables intake, physical activity, compliance to statin therapy). Binary logistic regression analyses were conducted to test for group differences for smoking. The post-test scores were regressed on study group and baseline measure of the outcome variable.

RESULTS

Baseline characteristics of participants

In Figure 1 the recruitment, participant and retention flow is presented. As can be seen from Table 1, the participants were equally distributed with regard to gender. Overall, a mainly middle-aged, medium to highly educated, fairly overweight sample participated in the project. The majority had an elevated LDL-C and used cholesterol-lowering medication. Baseline differences between control and intervention group were found for BMI (beta=-1.10; CI -2.17- -0.04). As a consequence, this variable was included in the regression analyses. No differences were found between dropouts and participants regarding the baseline characteristics.

Table 1: Baseline characteristics of the control and intervention group

	Control group	**Intervention group**
Gender (% female; N)	56.3; N=159	57.1; N=181
Age (years, mean ± SD; N)	45.9 (13.0); N=159	44.7 (12.9); N=181
Education (%; N)		
low	3.6	3.1
medium	62.8	58.2
high	33.6; N=137	38.7; n=163
BMI (kg/m^2, mean ± SD; N)	**27.1 (5.3); N=159**	**26.0 (4.7); N=181**
Medication use (% yes; N)	69.6; N=159	68.8; N=181
LDL-C (mmol/l, mean ± SD; N)	3.7 (1.2); N=130	3.7 (1.3); N=146

N=sample size; SD=standard deviation; BMI=body mass index; Significant differences between control and intervention group (P<0.05) are printed in bold font.

Effects on physical activity

No significant between-group differences were found regarding physical activity. As can be seen from Table 2, after 12 months, the control and intervention group performed more minutes of moderate to vigorous physical activity per week. The majority of both groups was compliant to the Dutch guideline of physical activity at baseline (both 78%) and after 12 months (both 80%).

Effects on saturated fat and fruit and vegetable intake

After 12 months, the control and intervention group consumed less fat points compared to baseline values. No significant between-group effect was found. Gender appeared to be a significant effect modifier (p=0.03). Post-hoc analysis showed a significant decreased fat consumption specifically among women in the intervention group compared to the control group after 12 months (see Table

2). In general, after 12 months, 13% more participants in the intervention group met the recommendations for fat intake, compared to 1% more in the control group.

No significant between-group differences were found regarding fruit intake. A minimal change was seen in the amount of servings of fruit per day consumed by both control and intervention group after 12 months (see Table 2). In both control and intervention group, the percentage of participants meeting the recommendations for fruit intake slightly increased (+2% and 7%).
No significant between-group differences were found regarding vegetables intake. More grams of vegetables per day were consumed in both control and intervention group after 12 months (see Table 2). After 12 months, 12% more participants in the control group met the recommendations for vegetable intake, as opposed to 4% more participants in the intervention group.

Effects on smoking behavior

No significant between-group effect was found on smoking behaviour. A decrease in the overall percentage of smokers was seen in both control and intervention group after 12 months (see Table 2). Changes in smoking behaviour were similar in both groups. The majority (control group: 80%; intervention group: 85%) continued not-smoking, and 13% (control group) and 10% (intervention group) continued to be a smoker. Respectively 7% (control group) and 5% (intervention group) quitted smoking in the past year, and 1% in both groups started smoking.

Effects on compliance to statin therapy

No significant between-group effect was found on compliance to statin therapy. Of the participants who used cholesterol lowering medication at baseline, 44% of the participants in the control group was categorised as compliant at baseline, associated with a score of 25 on the MARS-5 questionnaire, compared to 38% in the intervention group. After 12 months, an increase in compliance was seen in both the control group and the intervention group.

Table 2: Lifestyle behaviours at baseline and follow-up and intervention effects from linear or logistic regression analyses[1]

	Control group Mean (SD);N	**Intervention group Mean (SD);N**	**Beta**	**95% CI**
MVPA[2] (min/wk)				
Baseline	363.1 (3.5); N=146	422.0 (3.1); N=171	1.11[3]	-0.12-0.33
12 months	428.0 (3.7); N=146	501.0 (3.3); N=171		
Difference	+64.9	+79.0		
Saturated fat intake (fat points/day)				
Baseline	14.3 (4.9) N=146	15.4 (4.8) N=171	-0.61	-1.35-0.14
12 months	13.7 (4.6) N=146	14.0 (5.0) N=171		
Difference	-0.6	-1.4		
Fruit intake (servings/day)				
Baseline	1.4 (1.1); N=145	1.5 (1.3); N=169		
12 months	1.4 (1.1); N=145	1.6 (1.1); N=169	0.05	-0.12-0.22
Difference	+0.0	+0.1		
Vegetables intake (grams/day)				
Baseline	151.2 (77.8); N=144	162.1 (75.8); N=169		-9.78-16.29
12 months	163.4 (77.2); N=146	171.5 (76.6); N=169	3.26	
Difference	+12.2	+9.4		
Smokers (%)				
Baseline	15.2; N=145	18.3; N=171	OR=1.15	0.39-3.33
12 months	10.2; N=146	13.5; N-171		
Difference	-5	-4.8		
Compliant to statin therapy (%)[4]				
Baseline	44.4; N=99	38.1; N=118	OR=0.99	0.51-1.94
12 months	51.4; N=105	44.5; N=119		
Difference	+7.0	+6.4		
Post-hoc analyses				
Saturated fat intake (fat points/day) **in men**				
Baseline	16.3 (5.3); N=63	16.7 (4.9); N=73	-0.06	-1.30-1.16
12 months	15.2 (4.5); N=63	15.5 (5.2); N=73		
Difference	-1.1	-1.2		
Saturated fat intake (fat points/day) **in women**				
Baseline	12.8 (3.9); N=82	14.4 (4.5); N=98		
12 months	12.6 (4.4); N=83	12.8 (4.6); N=98	**-1.03**	**-1.98- -0.08**
Difference	-0.2	-1.6		

[1]Differences between control and intervention group after 12 months are tested through linear of logistic regression analyses, controlled for baseline values and baseline BMI. N=sample size; SD=standard deviation; β / OR=beta or Odds ratio as effect indicators from linear or logistic regression analyses; 95% CI=95% confidence interval as effect indicator from linear or logistic regression analyses; Significant differences between control and intervention group (P<0.05) printed in bold font.[2]MVPA=Physical activity with moderate to vigorous intensity; means are geometric means; [3] Log-linear regression was conducted; [4]Assessed with the MARS-5 questionnaire, a score=25 is defined as compliant, <=24 is defined as noncompliant. Since no major differences were found between intention-to-treat analysis and complete case analysis, only the results of the complete case analysis are presented.

Process

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.

DISCUSSION AND CONCLUSION

Discussion

In this paper, we aimed to investigate the efficacy of an individualised lifestyle intervention on physical activity, dietary intake, smoking and compliance to statin therapy among people with FH. After 12 months, improvements were seen in both control and intervention group in physical activity, saturated fat intake, fruit and vegetable intake, smoking and compliance to statin therapy. Although most changes were more pronounced among participants in the intervention group, the between-group differences were small and not significant. Post-hoc analyses showed a significant decrease in the intervention group in saturated fat intake among women.

This lack of effects is in contrast with the latest evidence in the field of computer-tailored promotion of healthy lifestyle behaviours; recent reviews and meta-analyses indicate that such tailored interventions are likely to be effective. [13,22,32,34,37,40,41,43,49,53] However, evidence on the effects of such and other lifestyle interventions in a FH population is scarce. In a review on dietary interventions in a FH population, Shafiq and colleagues emphasise the need for large, parallel randomised controlled trials, since no reliable conclusions could be drawn from the included studies. [52] Until now, no indisputable effects have been published so far.

It may be that the intervention reach and true exposure (dose received) was insufficient to initiate behaviour changes. The content of the intervention was largely based on earlier tailored interventions, that were effective on behaviour changes, and our process evaluation indicates that participants were sufficiently exposed to the intervention. However, the results also indicate that only half of the participants logged on at the *PRO-FIT*advice* website and completed at least one of the advice modules, and that face-to-face counselling sessions were delivered with low MI fidelity. Mixed evidence has been published on computer-tailored interventions addressing more than one lifestyle behaviour. In their latest review, Sweet and colleagues concluded that single health behaviour interventions are more effective at changing specific health behaviours than multiple-behaviour interventions. [55] Further, it appears from literature that multiple-behaviour interventions may be burdensome for some individuals, and advices may be too long. [42,46,47] Regarding the low MI fidelity, it has often been reported that skills required for effective MI may take longer to develop than the 3-day MI workshop in our project. [7,36] Probably, the provided MI workshop was not sufficient and more thorough monitoring and supervision of counselling skills during the intervention should have been built in.

The lack of large improvements in both control and intervention group, might be caused by the relatively healthy lifestyle of our population. Results showed that the majority of the people with FH in this project already met the recommendations on physical activity and smoking behaviour at baseline (physical activity: 78%; non-smokers: 81-85%). On this point, the FH population obviously differed from the general Dutch population, as survey data show that only 53% of the Dutch general population is sufficiently physically active and 73% of all Dutch adults are non-smokers. [30,66] Though, there was much room for improvement with regard to saturated fat and fruit and vegetable consumption. Only 49-57% of our study population met the Dutch recommendations on saturated fat consumption, and only one third on fruit and vegetable consumption.

The baseline self-reported compliance to statin therapy in our project (38-44%) is comparable to those reported in the literature. Our results showed no significant intervention effect. According to recent reviews, the effects of compliance-improving interventions are small. [21,33] About 50% of the interventions proved to be efficacious, and effects on treatment outcomes (e.g. LDL-C) were often absent. So far, little is known about the determinants of compliance. [21] Julius and colleagues recommended assessing patients' motivation to take prescribed medications, and to identify and address potential barriers to compliance. [27]

Strengths and limitations

To our knowledge, the PRO-FIT intervention is the first to evaluate the effects of an innovative lifestyle intervention on multiple lifestyle behaviours among people with FH. The intervention is innovative in combining three communication channels: the individualised web-based approach added by the social interaction of the face-to-face and telephone coaching sessions. So far, few studies have evaluated the effects of an intervention that had combined web-based computer-tailored lifestyle education *and* motivational interviewing techniques on multiple lifestyles. [10,48,59] Thereby, the step-wise approach of raising awareness first, then giving tailored feedback and thereafter motivating people towards behavioural change, is thoroughly described and based on a firm theoretical framework. [8,15] Moreover, from the process measures reach and dose it can be said that the implementation of the intervention was feasible. Confidence in the validity of our findings is increased by the randomised study design and absence of differential attrition.

This project also had limitations. Behaviour is multi-dimensional and complex to measure by self-report. The use of inappropriate or crude measures has serious implications and could likely have led to misleading results, for instance an underestimation of effect sizes. Although fairly reliable and valid questionnaires were used, the choice of a (self-report) measure often remains a compromise between the research aim, accuracy level and feasibility. [62]

Despite randomization of 4 clusters of family members living in the same household, communication among family members of control and intervention group was unavoidable. The Dutch screening program works cascade-wise; once a person is diagnosed (the index patient), pedigrees are consulted to trace other potentially FH positive family members. In a relative small country such as the Netherlands, families appeared to be wide-spread and overlapping each other, making it rather challenging to prevent communication, which therefore should be taken into account when interpreting the results.

Conclusion

In conclusion, this project suggests that in general individually tailored feedback is not superior to generic feedback regarding changes in multiple lifestyle behaviours in people with FH. Women aged 18-40 years in the intervention group consumed significantly less saturated fats, and compliance to statin therapy significantly improved among unmotivated medication users in the intervention group. These results should be carefully interpreted, due to post-hoc analyses of relatively small subgroups. Research is needed to gain more insight in the characteristics of this specific high-risk population, for instance risk perceptions and determinants of behaviour, such as self-efficacy, attitude, motivation and social influence. The effects of the small lifestyle changes on CVD risk remains (and is due) to be

investigated.

Practice implications

In practice, it is crucial to achieve an optimal received dose of a computer-tailored intervention, by e.g. reducing the burden of filling in (screening) questionnaires to a minimum in order to keep participants motivated, e.g. by creating a joint questionnaire, for both evaluative and tailoring purposes. Thereby, it is known that incorporating iterative feedback and interactive website components are positively associated with exposure to web-based interventions. [9] Further, MI training of counsellors should be more extensive, incorporating more thorough monitoring and supervision of counselling skills.

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CHAPTER 5

No significant improvement of cardiovascular disease risk indicators by a lifestyle intervention in people with Familial Hypercholesterolemia compared to usual care: results of a randomised controlled trial

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Background

People with Familial Hypercholesterolemia (FH) may benefit from lifestyle changes supporting their primary treatment of dyslipidaemia. This project evaluated the efficacy of an individualised tailored lifestyle intervention on lipids (low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), total cholesterol (TC) and triglycerides), systolic blood pressure, glucose, body mass index (BMI) and waist circumference in people with FH.

Methods

Adults with FH (n = 340), recruited from a Dutch cascade screening program, were randomly assigned to either a control group or an intervention group. The personalised intervention consisted of web-based tailored lifestyle advice and personal counselling. The control group received care as usual. Lipids, systolic blood pressure, glucose, BMI, and waist circumference were measured at baseline and after 12 months. Regression analyses were conducted to examine differences between both groups.

Results

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.

Conclusions

This project suggests that an individually tailored lifestyle intervention did not have an additional effect in improving CVD risk indicators among people with FH. The cumulative effect of many small improvements in all indicators on long term CVD risk remains to be assessed in future studies.

INTRODUCTION

Familial hypercholesterolemia (FH) is an autosomal dominant disorder of the lipoprotein metabolism. Due to a defect of the low density lipoprotein (LDL) receptor gene, plasma concentrations of LDL cholesterol (LDL-C) are elevated . [1] In the Netherlands, approximately one in 500 people is affected with the heterozygous type of FH. [2] Elevated serum LDL-C and therefore FH is associated with an elevated risk of premature cardiovascular disease (CVD) [3], which is the disease with the highest burden in disability adjusted life years in the Netherlands. [4] If elevated LDL-C is not diagnosed and treated, the cumulative risk of developing coronary artery disease (CAD) by the age of 60 years is over 60% for men, and over 30% for women. [5]Large primary and secondary prevention trials with statins have clearly demonstrated the benefit of reducing LDL-C in subjects with high LDL-C. [6,7] Also, Versmissen and colleagues showed an overall risk reduction in a large cohort (n = 2146) of people with FH that used statins. [8] Still, significant CVD risk persists despite effective LDL-C lowering statin treatment. [9]

Apparently, lifestyle factors can play an important role in moderating the course of this disorder [10,11], as is underlined by the EUROASPIRE III survey, conducted in 2006–2007 in 22 European countries. This survey showed a high prevalence of unhealthy lifestyles among CVD patients treated by cardiologists, and moreover, that use of medication was often inadequate to achieve treatment goals. [12] Results of primary prevention trials in high-risk persons and secondary prevention trials in CVD patients both show that substantial reductions in the CVD risk can be obtained through lifestyle changes. [13,14] For example, the INTERHEART study showed that eating fruit and vegetables daily, being physically active regularly and avoiding smoking were effective in reducing the risk of a myocardial infarction by 80%. [15] Estimates from a study by Hopkins suggested that a cholesterol-lowering diet could reduce LDL-C levels by up to 21% in people with heterogeneous FH. [16] Clearly, a healthy lifestyle is an aspect of the treatment of FH with benefits beyond LDL-C-lowering drugs. [17] FH treatment should not merely focus on LDL-C, but also on a larger spectrum of risk factors. [18] We therefore assumed that raised awareness of the actual CVD risk, improved lifestyle behaviours and improved compliance to statin therapy is a promising strategy in reducing CVD risk in people with FH.

In the PRO-FIT project, we developed an individually tailored lifestyle intervention aimed at a CVD risk reduction in individuals with FH. At first, we investigated the efficacy of the intervention on smoking, physical activity, dietary intake and compliance to statin therapy (see chapter 4). In this paper, we report the efficacy on biological CVD risk indicators: lipids (LDL-C, HDL-C, TC and triglycerides), systolic blood pressure, glucose, body mass index (BMI) and waist circumference.

METHODS

Design and participants

A randomised controlled trial was conducted with measurements at baseline and at 12 months post-baseline. Participants diagnosed with FH from January 1st 2007 to April 15th 2009, aged from 18 to 70 years and with a LDL-C level > 75th percentile (age and gender specific) were recruited from the national cascade screening programme of the Foundation for the Identification of Persons with Inherited Hypercholesterolemia (StOEH). Access to internet, sufficient fluency in Dutch and residency <150 km radius from Amsterdam were additional eligibility criteria.

Details on the participant flow can be found in Figure 1. The content of this paper was guided by the recommendations for reporting randomised controlled trials of the CONSORT (Consolidated Standards of Reporting Trials) statement. [19] The ethical principles of the Helsinki Declaration were followed and the PRO-FIT project was approved by the Medical Ethics Committee of the VU University Medical Centre. All participants gave written informed consent.

Invitation brochures were send to 986 people, of whom 321 (32%) responded and agreed to participate. An additional 23 participants were recruited through brochures that were distributed among family members of participants, meeting the same eligibility criteria. The recruitment period lasted 6 months and resulted in 340 participants. Three hundred and fifteen participants (93%) attended the baseline and follow-up measurements. Missing data on lipids (LDL-C, HDL-C, TC and triglycerides), systolic blood pressure, glucose, BMI and waist circumference were imputed using multiple imputations, allowing an intention-to-treat analysis based on 340 participants

Procedure

Participants were randomly assigned to either the no-intervention control group (n = 159) or the intervention group (n = 181) through a stratified computerised randomisation procedure using Microsoft© Office Access 2003 software. Randomisation was concealed. At first, participants were stratified according to cholesterol lowering medication use (yes/no), assuming that medication use implicates treatment by a general practitioner and/or medical specialist, who could have already given advice on lifestyle behaviour. In addition, we expected that a decrease in LDL-C because of the intervention would be smaller if a participant already used medication. Family members of the same household were clustered and subsequently randomised as a cluster to prevent contamination of the intervention effect due to spill over of communication about the intervention among family

members.

Theoretical framework

The intervention of the PRO-FIT project was developed according to the integrated model for exploring motivational and behavioural change, the I-Change model (2.0). [20,21] Briefly, it assumes that the behavioural change process can be distinguished in three phases: 1) awareness, 2) motivation and 3) action. Hypothetically, due to gained knowledge and awareness of one's CVD risk, a participant will become motivated to change lifestyle behaviour(s), and subsequently, implementation intentions and action plans will be formed to actually achieve (maintenance of) behavioural change. In addition, it is assumed that this will eventually lead to a reduction in CVD risk. The assumed pathway is illustrated in the I- Change model (2.0) in Figure 2.

Hypothetically, due to gained knowledge and awareness of one's CVD risk, a participant will become motivated to change lifestyle behaviour(s), and subsequently, implementation intentions and action plans will be formed to actually achieve (maintenance of) behavioural change. In addition, it is assumed that this will eventually lead to a reduction in CVD risk

Intervention

The intervention consisted of a personalised health counselling intervention; a combination of computer-generated tailored web-based advice (PRO-FIT*advice) and face-to-face counselling complemented with telephone booster sessions (PRO-FIT*coach). The goal was to: 1) improve awareness of the cardiovascular disease risk through an increase of specific knowledge, cues to action and change in risk perception, 2) improve motivation with respect to healthy behaviour through an increase of specific knowledge and a change in attitude, self- efficacy and social influences, 3) adopt and maintain a healthier lifestyle, with regard to physical activity, saturated fat intake, fruit and vegetables intake, smoking and compliance to statin therapy, and 4) lower the level of LDL-C and other biological CVD risk indicators and thereby reducing the CVD risk.

The intervention has been described in detail elsewhere. [21] Briefly, participants were encouraged to visit a web link referring to the project website, where generic online CVD risk information was presented, containing feedback on CVD risk behaviours and their contribution to overall CVD risk, as well as information on the changeability of these behaviours and cues on how to change behaviours. Thereafter, participants could log on to a personal PRO-FIT*advice account, consisting of six tailored advice modules on smoking, physical activity, saturated fat intake, fruit intake, vegetables intake and compliance to statin therapy. On-screen computer-generated personalised feedback was tailored to

personal performance level (current lifestyle behaviour), awareness of one's own performance, as well as personal motivation to change, outcome expectations, attitude and self-efficacy. Personalised feedback on compliance to statin therapy was tailored to knowledge and personal beliefs about (the effect of) statin therapy, potential side effects of the prescribed drug and current compliance.

Subsequently, a month later, the participant and the personal coach further established the level of the participant's knowledge/awareness about FH and cardiovascular risk factors. Furthermore, the assessment(s) and advice(s) within the participant's personal PRO- FIT*advice account were discussed and ambivalence and barriers related to the recommended behaviour changes were explored based on Motivational Interviewing (MI) techniques. [22] Further, one to five counsellor-initiated booster telephone sessions were performed during a period of 9 months to encourage the participant's behavioural changes and to provide further brief motivational interviewing to encourage the planned behavioural changes.

The control group received care as usual.

Measurements

In this project, lipids (LDL-C, HDL-C, TC and triglycerides), systolic blood pressure, glucose, BMI and waist circumference were defined as CVD risk indicators, also known as classical CVD risk factors, as reported by the Adult Treatment Panel (ATP) III of the NCEP, that formulated an evidence-based set of guidelines of cholesterol management for the general population. [23] These classical risk factors also contribute to the CVD risk in people with FH. [24]

All CVD risk indicators were measured at the participants' homes. LDL-C, HDL-C and TC, triglycerides and glucose were measured with fasting finger stick samples analysed on a Cholestech LDX desktop analyser (Cholestech, Hayward, USA). This portable analyser is capable of providing a lipid profile and glucose in approximately 5 minutes. The reproducibility and precision of lipids measurement by the LDX analyser are within the guidelines of the NCEP. [25,26] The Cholestech LDX analyser has been validated for point- of-care lipid measurements in clinical practice. [27] Systolic and diastolic blood pressure (in mmHg) was measured twice with a fully automated blood pressure monitor (type: Omron M5-I). The mean value of the two measurements was computed.

Body height (in cm) was measured on bare feet with a portable device with a wide measuring slide and a heel plate. Calibrated scales were used to determine body weight (in kg) while participants wore light clothing only (e.g. underwear). Both body weight and height were measured twice, and the mean value of the two measurements was used to calculate BMI. Waist circumference (in cm)

was measured twice with a measurement tape to the nearest 0.10 cm, at the midpoint between the lower border of the ribs and the upper border of the pelvis. The mean value of the two measurements was computed.

A process evaluation was carried out, taking into account the process elements reach, dose (delivered and received) and fidelity. [28] In short, reach (the number of people included in the project, as well as their representativeness for the study population and non-participants) was assessed by consulting the StOEH/PRO-FIT client database. The dose of all delivered elements of the intervention was assessed by logs that were kept by the coaches and the project database. Dose received, i.e. the way participants used PRO-FIT*advice (% of participants that logged on, number of modules finished), was assessed by means of log on rates and website use data. Whether face-to-face counseling sessions were implemented as planned according to Motivational Interviewing (MI) guidelines (fidelity) was assessed by two MI experts, following the MI Treatment Integrity code 3.1.1. [29] For this assessment, a random sample of 20 audio taped counselling sessions (10 sessions of each lifestyle coach; approximately 10% of all sessions) was drawn. A verbatim transcript [30] of each drawn session was evaluated and resulted in two scores: a global score, capturing an overall impression of the conversation on a 5-point Likert scale on the following 5 dimensions: Evocation, Collaboration, Autonomy/Support, Direction and Empathy. In addition, specific behaviours of the lifestyle coach, such as the number of open/closed questions and simple/complex reflections (reflective statements made by the counsellor in response to participant, without/with additional meaning or emphasis to what the participant has said) were counted. Counselling sessions were considered MI if the average of global scores was ≥ 3.5, reflection to question ratio was in favour of reflection, >50% of the questions were open questions, >40% of the reflections were complex reflections and >90% of all utterances was MI-adherent. [29]

Statistical analyses

Potential baseline differences were checked between intervention and control group, regarding gender, age, education, BMI, medication use and LDL-C. In case of baseline differences between intervention and control group, the concerned covariate was included in the analyses. In addition, differences between dropouts and participants regarding the above- mentioned baseline characteristics were tested by linear regression analyses.

Primary, a complete case analysis was conducted at the participant level, restricted to those who attended baseline and follow-up measurements. These numbers vary for different outcome measures. Subsequently, an intention-to-treat analysis was conducted, involving all participants who were randomly assigned (n = 340). Missing data on lipids (LDL-C, HDL-C, TC and triglycerides), systolic

blood pressure, glucose, BMI and waist circumference were imputed using multiple imputations. Five different datasets were created in SPSS (version 18.0) using Fully Conditional Specification and Predictive Mean Matching procedures. All available data on the above-mentioned outcomes, as well as on group allocation, gender, age, education, BMI, medication use and LDL-C were included in the imputation model. Thereafter the multiple datasets were analysed as described below, using SPSS (version 18.0). Pooled estimates were computed following the rules as described by Rubin. [31] As no major differences were found, only the results of the complete case analysis are presented.

In order to investigate whether this intervention had an effect on lipids (LDL-C, HDL-C, TC and triglycerides), systolic blood pressure, glucose, BMI and waist circumference, linear regression analyses were conducted to detect between group differences after 12 months (two-sided; significance level 0.05). The post-test scores were regressed on study group and baseline measure of the outcome variable.

RESULTS

Baseline characteristics of participants

In Figure 1 the recruitment, participant and retention flow is presented. As can be seen from Table 1, the participants were equally distributed with regard to gender. Overall, a mainly middle aged, medium to highly educated, fairly overweight and the majority has an elevated LDL-C and used cholesterol-lowering medication. Baseline differences between the control and intervention group were found for BMI (beta = −1.10; CI −2.17- -0.04). As a consequence, this variable was included in the regression analyses as a potential confounder. No differences were found between dropouts and participants regarding the baseline characteristics.

Table 1: Baseline characteristics of the control and intervention group

	Control group	**Intervention group**
Gender (% female; N)	56.3; N=159	57.1; N=181
Age (years, mean ± SD; N)	45.9 (13.0); N=159	44.7 (12.9); N=181
Education (%; N)		
Low/medium/high	3.6/62.8/33.6; N=137	3.1/58.2/38.7; N=163
BMI (kg/m^2, mean ± SD; N)	**27.1 (5.3); N=159**	**26.0 (4.7); N=181**
Medication use (% yes; N)	69.6; N=159	68.8; N=181
LDL-C (mmol/l, mean ± SD; N)	3.7 (1.2); N=130	3.7 (1.3); N=146

N=sample size; SD=standard deviation; BMI=body mass index; Significant differences between control and intervention group (P<0.05) are printed in bold font.

Effect on biological risk indicators

After 12 months, LDL-C had decreased in both the intervention and control group (see Table 2). No significant between-group difference was found, as well as for HDL-C, TC, triglycerides, systolic blood pressure, glucose, BMI and waist circumference. Both groups showed no major changes in HDL and a slight decrease of TC and glucose. A minor increase of triglycerides was seen in the intervention group, in contrast to a decrease in the control group. In the control group, no change in BMI was observed after 12 months, compared to a decrease in the intervention group. Waist circumference did not change in the control group and decreased in the intervention group.

Table 2: Biological CVD risk indicators at baseline and follow-up and intervention effects from linear regression analyses, based on a complete-case analysis[*]

	Control group	**Intervention group**	**Beta**	**95% CI**
LDL-C (mmol/l, mean ± SD)	N=105	N=128		
Baseline	3.7 (1.2)	3.6 (1.3)		
12 months	3.6 (1.2)	3.5 (1.1)	-0.20	-0.40-0.03
Difference	-0.1	-0.1		
HDL-C (mmol/l, mean ± SD)	N=143	N=169		
Baseline	1.2 (0.4)	1.2 (0.4)		
12 months	1.2 (0.4)	1.2 (0.4)	0.02	-0.04-0.08
Difference	0	0		
TC (mmol/l, mean ± SD)	N=146	N=169		
Baseline	5.2 (1.2)	5.3 (1.4)		
12 months	5.1 (1.2)	5.2 (1.2)	-0.04	-0.25-0.18
Difference	-0.1	-0.1		
Triglycerides (mmol/l, mean ± SD)	N=110	N=128		
Baseline	1.3 (0.7)	1.2 (0.6)		
12 months	1.2 (0.6)	1.3 (0.7)	0.08	-0.08-0.23
Difference	-0.1	+0.1		
Systolic blood pressure (mmHg, mean ± SD)	N=143	N=169		
Baseline	126.3 (15.7)	123.0 (14.4)		
12 months	125.2 (14.4)	123.0 (14.1)	0.003	-2.28-2.28
Difference	-1.1	0		
Glucose (mmol/l, mean ± SD)	N=145	N=169		
Baseline	4.9 (1.0)	4.9 (0.8)		
12 months	4.8 (0.8)	4.7 (0.7)	-0.06	-0.19-0.07
Difference	-0.1	-0.2		
BMI (kg/m^2, mean ± SD)	N=147	N=167		
Baseline	27.1 (5.4)	25.9 (4.5)		
12 months	27.1 (5.2)	25.8 (4.4)	-0.18	-0.43-0.07
Difference	0	-0.1		
Waist circumference (cm, mean ± SD)	N=146	N=165		
Baseline	89.9 (14.5)	86.4 (11.9)		
12 months	89.9 (14.3)	86.1 (11.5)	-0.54	-1.45-0.40
Difference	0	-0.3		

[*] *Differences between control and intervention group after 12 months are tested through linear regression analyses, controlled for baseline values and baseline BMI. Beta = unstandardised regression coefficient; N=sample size; SD=standard deviation; 95% CI=95% confidence interval as effect indicator from linear regression analyses; Means presented are from unadjusted analyses; Significant differences between control and intervention group (P<0.05) printed in bold font. Only the results of the complete case analysis are presented, since no major differences were found between intention-to-treat analysis and complete case analysis.*

Process

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) in the StOEH client database 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 counseling session and on average, 4.2 telephone booster calls were delivered. None of the face-to-face sessions were implemented according to MI guidelines.

DISCUSSION

In this paper, the efficacy of an individually tailored lifestyle intervention on lipids (LDL-C, HDL-C, TC and triglycerides), systolic blood pressure, glucose, BMI and waist circumference in people with FH was investigated. After 12 months, LDL-C levels had decreased in both the intervention and control group. This difference between intervention and control group was not statistically significant. Furthermore, the LDL-C concentrations in both groups did not result in reaching the recommended treatment target concentration of ≤2.5 mmol/l for most participants. [32] Based on a comparable population, Huijgen and colleagues also concluded that only a minority of the medication users reaches LDL-C treatment targets within two years after screening. [33]

Overall, we also did not observe any significant intervention effects on HDL-C, TC, triglycerides, systolic blood pressure, glucose, BMI and waist circumference. However, it may be that the collective contribution of all these small improvements together is cumulative, and larger than the CVD risk reduction associated with a single risk indicator. But since to date, no CVD risk prediction tool is available for FH populations, it is impossible to have an accurate estimate of the CVD risk reduction from all the small improvements together. Such a CVD risk prediction tool would be beneficial for the interpretation of our results. Moreover, it would be possible to identify people with severely increased CVD risk. Several CVD risk estimates are available, such as the risk assessment tool that uses data from the Framingham Heart Study to estimate 10-year risk for hard coronary heart disease outcomes. [34] However, these tools are based on calculations in a non-FH reference population, and it is known that classical risk factors in a FH population do not necessarily play the same role with the same intensity. [24] Civeira proposed a risk assessment tool, dividing people with FH in three risk categories: low-moderate-high 10 year CVD mortality risk. [17] However, lipoprotein-A and carotid intima media thickness, defined as major risk factors by Civeira, were not assessed in this project.

Participants who were not on statin treatment had notably higher LDL-C and TC levels at baseline,

and according to post-hoc analyses, reductions in LDL-C and TC concentrations were most obvious among participants who used no statins (data not shown). Clearly, a reduction in lipids levels is most expected among this subsample, since more reduction of lipid levels can be achieved. However, due to the small subsample (n = 72), this finding should be interpreted with great caution.

We did not find any significant intervention effects on all targeted lifestyle behaviours in the PRO-FIT project (data not shown). We can not confirm nor reject whether small improvements of biological CVD indicators were caused by behavioural improvements. The lack of intervention effects on biological CVD risk indicators and lifestyle behaviours found in the PRO-FIT project are not in accordance with the latest evidence, as in a literature review, Blokstra et al. showed that multifactorial lifestyle interventions could have favorable effects among individuals with a high CVD risk: improvements in blood pressure (−2-4 mmHg), nutrition, physical activity and smoking (−25-40%) were found. [14] Studies on other high-risk populations also showed that biological changes can be achieved, though often small and not significant at a long term (> 6 months). [35,36] However, the above- mentioned studies did not include FH subjects. In a recent review of Shafiq (2011), no differences were reported between cholesterol-lowering diet in comparison with no intervention or other dietary interventions in people with FH. [37]

It may be that the intervention reach and dose received were insufficient to initiate behaviour changes and, subsequently, changes in CVD indicators. Our process evaluation indicates that participants were sufficiently exposed to the intervention. However, only half of the participants logged on at the PRO-FIT*advice website and completed at least one of the advice modules, and face-to-face counselling sessions were delivered with low MI fidelity.

More in-depth analysis showed weak and positive associations between dose and LDL-C change for all intervention components (data not shown). Due to the small sample of audio taped sessions (n = 20), the association between MI fidelity and efficacy could not be tested in this study, but previous studies showed that a better MI performance is associated with larger intervention effects. [22,38] Also, mixed evidence has been published on computer-tailored interventions addressing more than one lifestyle behaviour. It is possible that multiple- behaviour interventions may be burdensome for some individuals, and advices may be too long. [39-41] Overall, it is possible that the poor MI fidelity and dose of PRO-FIT*advice received contributed to the lack of efficacy. Probably, the provided MI workshop was not sufficient and more thorough monitoring and supervision of counselling skills during the intervention should have been built in, as it has often been reported that skills required for effective MI may take longer to develop than the 3-day MI workshop in our project. [42,43]

The strengths of this project include the randomised design, which avoided study contamination that could have resulted from individual changes of participants in both intervention and control group. To our knowledge, the PRO-FIT intervention is the first to evaluate the effects of a lifestyle intervention on multiple lifestyle behaviours and CVD risk indicators among people with FH. The RCT was conducted in a sample representative for the screened FH population in the Netherlands with a small dropout rate. However, the recruitment rate of our study was only 34% and contained a self-selected sample of mainly medium-educated participants with internet access and sufficient fluency in Dutch. Although no differences on age, gender and LDL-C levels were found between participants and non- participants, our sample could have been more motivated to change lifestyle behaviour, which might limit the generalisability of our findings. [44]

While various unhealthy lifestyle factors are related to the atherosclerotic process, it is the long-term exposure that leads to the clinical manifestations of cardiovascular events. [45] Vice versa, the effect of lifestyle improvements is likely to lead to CVD risk reduction only at the longer term. Inclusion of more long-term follow-up measurements in future RTCs on the efficacy of lifestyle interventions is to be recommended, since it would shed more light on possible effects on CVD risk and hard outcomes (e.g. CVD/death).

Altogether, it remains unclear how genetic and lifestyle factors interact in the FH population. FH is a monogenetic condition, though variations are found in mortality [46], suggesting that environmental factors play an important role as well. Whether the gene-environment interactions are synergistic or simply additive remains to be revealed. It would be informative to conduct a trial similar to the PRO-FIT project with the inclusion of a non-FH control group with elevated LDL-C levels. Despite the unknown interactions, the primary goal of treatment of people with FH should be considered as invariable: achieving optimal CVD risk reduction.

In conclusion, this project suggests that an individually tailored lifestyle intervention is not superior to usual care, regarding changes in LDL-C levels in people with FH. A small CVD risk reduction might result from the generally slight improvements of all the CVD risk indicators. However, in order to draw conclusions on impact of the cumulative effect of all these small improvements, and thus on the efficacy of lifestyle improvements in a FH population, more RCTs should be performed, including more long-term objective measurements (of e.g. carotid intima thickness and lipoprotein A) and long-term monitoring of CVD-related morbidity and mortality.

CONCLUSIONS

An individually tailored lifestyle intervention did not have an additional effect in reducing LDL-C levels among people with FH. The cumulative effect of many small improvements in all CVD risk factors on long term CVD risk remains to be assessed in future studies.

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CHAPTER 6

Is the process of delivery of an individually tailored lifestyle intervention associated with improvements in LDL cholesterol and multiple lifestyle behaviours in people with Familial Hypercholesterolemia?

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Background

More insight in the association between reach, dose and fidelity of intervention components and effects is needed. In the current study, we aimed to evaluate reach, dose and fidelity of an individually tailored lifestyle intervention in people with Familial Hypercholesterolemia (FH) and the association between intervention dose and changes in LDL-Cholesterol (LDL-C), and multiple lifestyle behaviours at 12-months follow-up.

Methods

Participants (n = 181) randomly allocated to the intervention group received the PRO-FIT intervention consisting of computer-tailored lifestyle advice (*PRO-FIT*advice*) and counselling (face-to-face and telephone booster calls) using Motivational Interviewing (MI). 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.

Results

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.

Conclusions

Implementation of the PRO-FIT intervention in practice appears feasible, particularly *PRO-FIT*advice*, since it can be relative easily implemented with a high dose delivered. However, only less than half of the intervention group received the complete intervention-package as intended. Strategies to let participants optimally engage in using web-based computer-tailored interventions like *PRO-FIT*advice* are needed. Further, more emphasis should be put on more extensive MI training and monitoring/supervision.

BACKGROUND

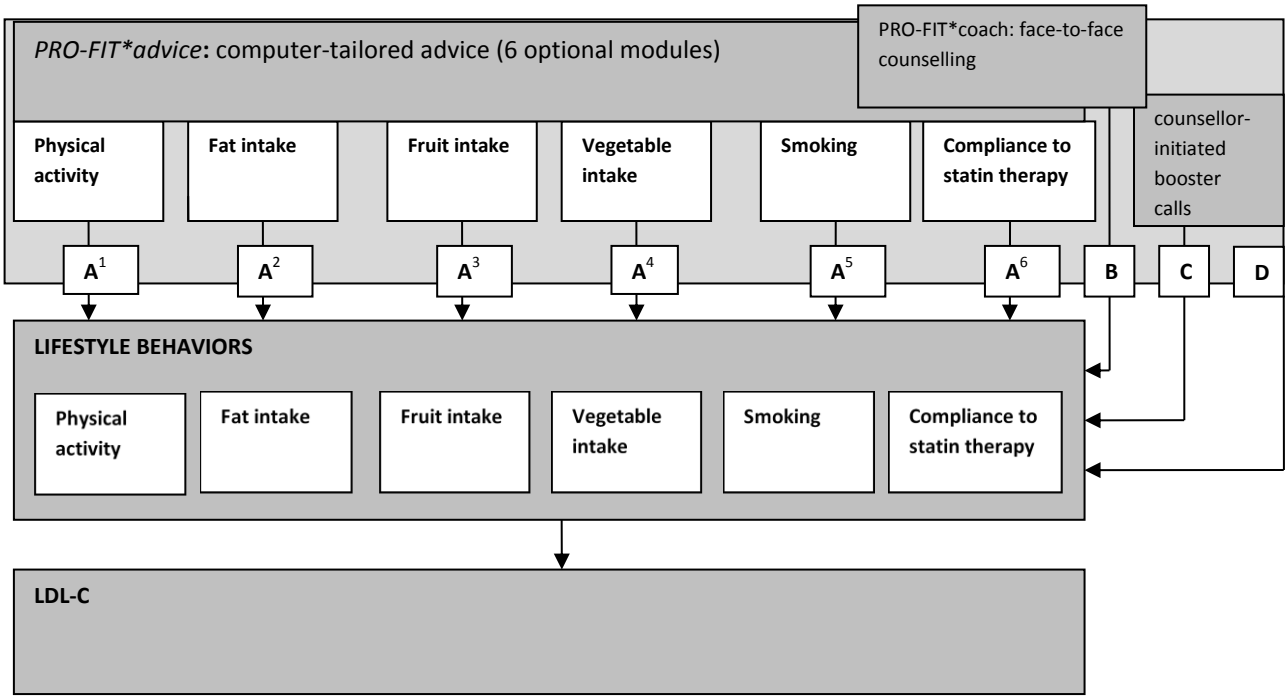
In public health research, much emphasis is put on the evaluation of interventions in randomised controlled trials (RCTs). Conducting a process evaluation is indispensable, since it helps to explore if the intervention was adopted and implemented as planned, and how and why the intervention worked or not. [1-4] Public health interventions often are complex interventions combining different potential active ingredients tailored and targeted to context. Complex interventions often prove efficacious in RCTs conducted in well-controlled circumstances, but less effective in practice. [5,6]

In 2009, we started the PRO-FIT project (PROmoting a healthy lifestyle in people with Familial Hypercholesterolemia (FH) through an Individually Tailored lifestyle intervention). [7] The purpose of the PRO-FIT project was to reduce cardiovascular disease (CVD) risk by promoting a healthy lifestyle in people with FH. The intervention aimed to reduce CVD risk by improving awareness of CVD risk, by improving one's motivation to obtain and maintain a healthier lifestyle (regarding physical activity, saturated fat intake, fruit intake, vegetables intake, smoking and compliance to statin therapy). Basically, the intervention was a combination of two components: I) computer-tailored lifestyle advice (called: *PRO-FIT*advice*), and II) counselling (face-to-face and telephone booster calls) using Motivational Interviewing (MI).

In the past years, both computer-tailored lifestyle advice and MI-guided counselling have been tested in RCTs for effects on changes in separate health behaviours. Print-delivered as well as on-line computer-tailored health advice has been shown to be efficacious in changing behaviours, even though effect sizes mostly are small. [8-12] Advantages of using the internet as the channel for tailored health advice is the opportunity to provide interactive, individualised interventions to large numbers of people that match each person's unique characteristics, circumstances, beliefs, motivation to change and behaviour. [13-15] Despite the evidence for efficacy of these interventions, earlier efficacy studies have indicated that the use of and exposure to the content of internet interventions may often not be optimal. [16,17] Especially for people of lower socio-economic positions [18] and older age [19], it may be less likely to save and re-read interactively delivered feedback, due to difficulties to read or process information from a computer screen. Apparently, once delivered, affecting the received dose and further use of the intervention is challenging. Knowledge about delivery, use and efficacy could help us to gain insight in efficacious components of web-based interventions. Counselling according to MI has been regarded as a potentially promising tool to encourage health behaviour change. [20-22] MI has been defined as a 'client-centred, directive method for enhancing intrinsic motivation to behaviour change by exploring and resolving

ambivalence'. [23] The therapeutic relationship is a partnership with respect of client autonomy and relies upon identifying and mobilising the client's intrinsic values and goals to stimulate behaviour change. [21] However, the impact of MI largely depends on the fidelity of intervention delivery. [24,25] Clearly, more insight in the association between reach, dose and fidelity of intervention components and efficacy is needed.

Earlier, we investigated the efficacy of the PRO-FIT intervention on multiple lifestyle behaviours (smoking, physical activity, fruit intake, vegetable intake, and compliance to statin therapy) [26] and on LDL-Cholesterol (LDL-C). [27] The aim of the present paper is twofold: first to evaluate the reach, dose (delivered and received) and fidelity of the PRO-FIT intervention, and second to investigate whether the dose of: A) *PRO-FIT*advice*, B) face-to-face counselling, C) telephone booster calls, and D) the complete intervention-package, was associated with change in lifestyle behaviour and LDL-C levels (further called: associations A-D) (Figure 1).



*A^{1-6} = Associations between the completion of PRO-FIT*advice modules and the related lifestyle behaviours*
*B = Association between counselling of the PRO-FIT*coach and the multiple lifestyle behaviours*
C = Association between the telephone booster calls and lifestyle behaviours
*D = A + B + C = Association between the complete intervention-package (at least one PRO-FIT*advice module, face-to-face counselling and at least one telephone booster call) and lifestyle behaviours*
MI = Motivational Interviewing; LDL-C = Low Density Lipoprotein Cholesterol

Figure 1: The PRO-FIT intervention and assumed efficacy pathways

METHODS

The PRO-FIT intervention

Participants of the PRO-FIT trial were recruited from the national cascade screening program of the Foundation for the Identification of Persons with Inherited Hypercholesterolemia (StOEH). Within this program, the StOEH actively approaches first and second degree relatives of index patients (that is, clinically diagnosed FH patients with a known mutation) about their potential risk by mail. A genetic field worker telephones and, if the family member agrees to participate, makes an appointment for testing at home. If the results of DNA analysis are positive, first and second degree relatives are approached and offered testing, and so on. No further counseling is given within the screening program. [28] Within the PRO-FIT project, individuals were invited who were diagnosed with FH by StOEH from January 1st 2007 to April 15th 2009, no longer than 2 years before the start of the project. Access to internet, sufficient fluency in Dutch, residency < 150 km radius from Amsterdam, age 18–70 and LDL-C > 75th percentile were eligibility criteria. People were invited by postal mail and telephoned in case of no response. When people decided to participate, the study procedure was explained by telephone. After randomised allocation to the intervention group, participants were encouraged to visit a weblink referring to the project website, on which they could log on to a personal *PRO-FIT*advice* account. This account gave access to six tailored advice modules on smoking, physical activity, saturated fat intake, fruit intake, vegetables intake and compliance to statin therapy. Each module required the completion of a screening questionnaire. Subsequently, on-screen personalised feedback was tailored to personal performance level (current lifestyle behaviour), awareness of one's own performance, as well as personal motivation to change, outcome expectations, attitude and self-efficacy. Personalised feedback to compliance to statin therapy was tailored to knowledge and personal beliefs about (the effect of) statin therapy, potential side effects of the prescribed drug and current compliance. After finishing a module, participants were encouraged to make action plans to change behaviour (except for the advice module on compliance to statin therapy).

Thereafter, in a face-to-face session, the participant and the personal coach together further established the level of the participant's knowledge/awareness about FH and cardiovascular risk factors, according to the assessment(s) and advice(s) within the participant's personal *PRO-FIT*advice* account. Ambivalence and barriers related to the recommended behaviour changes were explored in a face-to-face session based on MI techniques. Further, the participant was encouraged to plan five additional counsellor-initiated booster telephone calls, according to their need for additional counselling, intended to support the participant's behavioural changes and to provide

further brief MI to encourage the planned behavioural changes. The two personal coaches had lifestyle coaching and nursing/ teaching backgrounds and had received an additional 3-day MI workshop, incorporating both introductive lessons and practical training sessions with professional actors. A schematic overview of the intervention can be found in Figure 1, including the assumed efficacy pathways of the intervention (associations A-D). A more detailed description of the PRO-FIT intervention can be found elsewhere. [7] The ethical principles of the Helsinki Declaration were followed and the PRO-FIT project was approved by the Medical Ethics Committee of the VU University Medical Centre (reference number: NL23932.029.08). All participants gave written informed consent.

Theoretical framework

The RE-AIM evaluation framework conceptualised the evaluation of the translatability of an intervention and included reach, efficacy, adoption, implementation and maintenance. [29] Linnan and Steckler also included implementation among their key components of a process evaluation including context, reach, dose delivered, dose received, fidelity, implementation and recruitment. [3] Both authors agree on reach, implementation, including dose and fidelity as important factors for process evaluations. Generally, reach is defined as the number of people of the target population taking part in the project and their representativeness with regard to the target population. Dose is either defined as 'dose delivered', i.e. the number of components of the intervention delivered, or as 'dose received', i.e. the extent to which the participants used the components of the intervention as intended. Fidelity is defined as the extent to which the intervention was implemented as intended.

Guided by Saunders and colleagues, a process evaluation plan was developed in order to monitor and document the implementation of an intervention. [30] In this plan, the evaluated intervention was described in detail, including its specific strategies as well as what would be entailed in a complete and acceptable delivery of the intervention. Consequently, a list of potential process evaluation questions and measures was made and answered by using self-formulated methods (see Table 1).

Table 1: Process evaluation plan formulated according to Saunders et al. [30]

Process evaluation question	**Complete and acceptable delivery**	**Process measure**
How many people of the target population took part in the project? How representative is the intervention group for the study population? **(Reach)**	The intervention group is comparable to the study population.	Self-report, StOEH client database
To how many participants was a *PRO-FIT*advice* account provided? **(Dose delivered)**	A log on account was provided to all (100%) participants.	Coach logs/project database
To what extent did participants actively engage in using *PRO-FIT*advice* as intended, with regard to: logging on - the number of modules finished - action planning (**Dose received)**	All participants (100%) logged on and completed at least one of the modules of *PRO-FIT*advice*. Action planning was optional.	Website use data
How many participants received a visit from a personal lifestyle coach? **(Dose delivered)**	All (100%) participants received a visit from the lifestyle coach.	Coach logs/project database
To what extent was face-to-face counselling delivered as planned by MI guidelines? (**Fidelity)**	All (100%) face-to-face counselling sessions were delivered according to MI guidelines.	The Motivational Interviewing Treatment Integrity (MITI 3.1.1.) code
How many telephone booster sessions were provided? **(Dose delivered)**	1-5 telephone booster sessions were delivered.	Coach logs

Reach

In order to assess the number of people with FH that took part in the project, as well as how representative the participants in the intervention group were for the study population and non-participants (people who did not respond to the invitation to participate, or people who chose not to participate), the StOEH client database, as well as the PRO-FIT client database were consulted. Differences between participants and non-participants in main characteristics (age, gender, and LDL-

C levels) were explored.

Dose

The number of participants who had received a *PRO-FIT*advice* log on account, a face-to-face counselling session and subsequent telephone booster calls (dose delivered), was assessed by logs that were kept by the coaches and stored in the project database. We aimed at a 100% delivery of the intervention components and delivery of one to five telephone booster calls. The way participants used the *PRO-FIT*advice* log on account (dose received) was assessed by exploring participants' log on behaviour (% of participants that logged on), as well as participants' actions on the PRO-FIT* advice account (number of modules finished,% of participants that had made online action plans) by means of log on rates and website use data.

Fidelity

Whether face-to-face counselling sessions were implemented as planned according to MI guidelines (i.e. MI fidelity) was assessed by two MI experts, following the Motivational Interviewing Treatment Integrity code (MITI 3.1.1.). [31] The MI experts were attached to the Foundation Centre for Motivation and Change (Hilversum, the Netherlands), that works in cooperation with the International Motivational Interviewing Network of Trainers (Virginia, US; www.motivationalinterviewing.org), and were trained in coding fidelity using the MITI 3.1.1. For this assessment, a random sample of 20 audio taped counselling sessions (10 sessions of each lifestyle coach; approximately 10% of all sessions) was drawn. A verbatim transcript [32] of each drawn session was evaluated and resulted in two scores: a global score and behaviour counts. The global score captured an overall impression of the conversation on a 5-point Likert scale for the following 5 dimensions: Evocation, Collaboration, Autonomy/Support, Direction and Empathy. In addition, the behaviour counts capture specific behaviours of the lifestyle coach, such as the number of open/closed questions, simple/complex reflections, MI (non)adherent utterances and provision of information. We aimed for 100% of the counselling sessions to be provided according to MI. Counselling sessions were considered MI if the following conditions were met: average of global scores ≥ 3.5, reflection to question ratio is in favour of reflection, >50% open questions, >40% complex reflections and >90% MI-adherent utterances. The total scores were weighed for the number of counselling sessions conducted by each coach.

Change in lifestyle behaviours

The level of physical activity was measured by the Short QUestionnaire to ASsess Health-enhancing physical activity (SQUASH) and was expressed as minutes of moderate to vigorous physical activity

performed per week. [33] Saturated fat, fruit and vegetables intake were measured by the short Dutch questionnaire on total and saturated fat intake and on fruit and vegetable intake. From this questionnaire, a score for saturated fat intake, ranging from 0 (lowest) to 80 (highest) fat points was computed, as well as servings of fruit and grams of vegetables per day. [34-36] Smoking behaviour was assessed by a self-reported measure, resulting in a score of 0 (non-smoker) or 1 (smoker). [37] The five-item Medication Adherence Report Scale (MARS-5) was used to measure self-reported compliance to statin therapy. Scores on five items were combined to a total score ranging from 5 (lowest) to 25 (highest). Participants with a score of 25 were categorised as compliant to statin therapy, others (score < 25) as non-compliant. [38]

Change in LDL-C

At baseline and 12-month follow-up, the participants' LDL-C was assessed at the participant's home with fasting finger stick samples analysed on a Cholestech LDX desktop analyser (Cholestech, Hayward, USA). This portable analyser is capable of providing a lipid profile in approximately 5 minutes. The reproducibility and precision of lipids measurement using the LDX analyser are within the guidelines of the National Cholesterol Education Program (NCEP). [39,40] The Cholestech LDX analyser has been validated for point-of-care lipid measurements in clinical practice. [41]

Statistical analyses

Differences in age, gender, and LDL-C levels between participant and non-participant characteristics were checked with linear and logistic regression analyses for each variable separately. Associations between intervention dose and lifestyle behaviours and LDL-C (associations A-D) were explored with linear (for physical activity, fat/fruit and vegetables intake and LDL-C levels) and logistic (for smoking and compliance to statin therapy) regression analysis with the following independent variables: logged on at *PRO-FIT*advice* and advice module completed (yes/no) (association A), face-to-face counselling received (yes/no) (association B), number of telephone booster calls (association C), and the complete intervention-package (at least one *PRO-FIT*advice* module, face-to-face counselling and at least one telephone booster call) received (yes/no) (association D). The post-test scores of the dependent variables were regressed to the baseline measures. Effect parameters (regression coefficient (beta) or odd's ratio (OR)) either indicated a positive association if LDL-C/lifestyle behaviours improved when regressed to the intervention dose, or a negative association if vice versa. An association was considered as significant if $p < 0.05$.

RESULTS

Reach

During the six months of recruitment for the PRO-FIT project, nearly 6200 people in the Netherlands were screened by StOEH, of whom an averaged 35% actually did have FH. [42] Invitation brochures were send to 986 people who were screened by StOEH and who were positively diagnosed with FH. Of those, 340 (34%) responded and agreed to participate. This number included 23 family members of invited people who spontaneously responded and met the eligibility criteria. Reasons for not participating were mainly a lack of interest and time, and reporting to 'already have a healthy lifestyle'. The participants did not differ from the non-participants (those who did not respond to the invitation and those who refused to participate; N = 623) in age (beta:0.23; 95% CI:-1.85-2.31) and gender (OR:0.89; 95% CI:0.68-1.16), but did with regard to LDL-C levels (beta:-0.35; 95% CI:-0.63- -0.07) (see Table 1). The majority (57%) of the study sample was female, middle-aged (mean age = 45.3 years) , and had elevated (≥2.5 mmol/l) LDL-C levels. No significant baseline differences between intervention and control group were found. During the PRO-FIT project, five participants in the intervention group dropped out (i.e. their participation was discontinued with a given reason). Their reasons for discontinuation were no motivation (n = 1), no interest (n = 2), death (n = 1), and health constraints (n = 1).

Dose

An account to use the online *PRO-FIT*advice*, was provided to 172 (95%) of the 181 participants in the intervention group (see Table 2). The remaining 5% (9 participants) explicitly reported to have no interest in using *PRO-FIT*advice* and therefore, received no log on information. Subsequently, nearly all participants (99%) in the intervention group were visited by the lifestyle coach. Furthermore, on average of 4.2 telephone booster calls per respondent were conducted. The main reasons for not receiving subsequent booster calls was no perceived need for additional counselling because respondents regarded the lifestyle as healthy.

Table 2: Baseline characteristics of responders and non-responders and dose of the PRO-FIT intervention in the intervention group

	Intervention group	**Control group**	**Non-responders**
Gender (% female; N)	57.1; N = 181	56.3; N = 159	53.8; N = 623
Age (years, mean ± SD; N)	44.7 (12.9); N = 181	45.9 (13.0);N = 159	45.1 (15.8); N = 623
LDL-C (mmol/l, mean ± SD; N)	3.7 (1.3); N = 146	3.7 (1.2); N = 130	4.05 (1.33); N = 110
Participants that received a *PRO-FIT*advice* log on account	95% (172/181)		
Participants that logged on at *PRO-FIT*advice* and completed at least one module	49% (85/172)		
Participants that logged on at *PRO-FIT*advice* and completed the module on:			
Physical activity	41% (71/172)		
Fat intake	35% (60/172)		
Fruit intake	37% (64/172)		
Vegetable intake	34% (59/172)		
Smoking	14% (24/172)		
Compliance to statin therapy	26% (44/172)		
Participants that formulated an action plan at *PRO-FIT*advice* for at least 1 of the modules[1]	31% (53/172)		
Participants that received face-to-face counselling	99% (179/181)		
Telephone booster calls delivered (mean ± SD; N)	4.2 (1.3); N = 181		
Participants that logged on, finished at least 1 module, received face-to-face counselling and at least 1 telephone booster call (=complete intervention-package)	47% (85/181)		

N=sample size; SD = standard deviation; Significant differences in baseline characteristics between control and intervention group (P < 0.05) are printed in bold font; [1] Action planning was not possible in the advice module on compliance to statin therapy

Of the 172 participants in the intervention group who had received a log on account, 85 (49%) actually logged on to *PRO-FIT*advice*, and completed at least one of the six advice modules. The most popular module, based on completion rates, was physical activity (41%), followed by fruit intake (37%), fat intake (35%), vegetable intake (34%), smoking (14%) and compliance to statin therapy (26%). Nearly one third (31%) completed at least one module and made an action plan online. Although revisiting the website was not so explicitly encouraged, 7% did. The complete

intervention-package as intended, requiring log on at *PRO-FIT*advice*, the completion of at least one module, face-to-face counselling and at least one received telephone booster call, was delivered to 47% of the intervention group. The five drop-outs all received a log on account to *PRO-FIT*advice* and two of them logged on. Consequently, they all received face-to-face counselling and an average of 2 telephone booster calls.

Fidelity

Eighty-five percent of the face-to-face counselling sessions were performed by coach 1, and 15% by coach 2. In Table 3, the extent to which MI was applied during the face-to-face counselling sessions by the two coaches is shown. The global scores and behavioural counts indicate that none of the sessions was implemented according to MI guidelines. Significant differences in counselling performance between the two coaches were found for using (complex) reflections, the number of MI adherent statements, the reflection to question ratio, directiveness and showing empathy.

Table 3: MI fidelity within a sample of face-to-face counselling sessions (n = 20) according to the MITI scoring instrument

	Global scores[1] (recommended) (mean (SD))			**Behaviour counts[2] (recommended)**			
	Empathy (>3.5)	Spirit (>3.5)	Direction (>3.5)	RF:QU (in favour of RF) (mean (SD))	OQ (%) (>50%)	CR (%) (>40%)	MIA (%) (>90%)
Coach 1	**3.1 (0.9)**	2.7 (1.0)	**3.4 (0.7)**	**1.09 (0.35)**	21 (12)	**42 (21)**	**87 (9)**
Coach 2	**1.5 (0.7)**	2.2 (0.9)	**2.6 (1.1)**	**0.68 (0.30)**	19 (13)	**23 (14)**	**62 (17)**
Total[3] (100%)	2.9	2.7	3.3	1.03	21	39	83

[1] The global scores capture an overall impression of the conversation on a 5-point Likert scale for the following 5 dimensions: empathy, spirit (evocation, collaboration and autonomy) and direction; [2] Behaviour counts incorporate: RF:QU=ratio reflections to questions; OQ=percentage open questions; CR=percentage complex reflections; MIA=percentage motivational interviewing adherent; Spirit=combination of evocation, collaboration and autonomy; [3] Aggregated scores weighted for the number of counselling sessions conducted by each coach (coach 1: 85%, coach 2: 15%); Significant differences (p < 0.05) in scores between coaches are printed in bold

Associations between intervention dose and change in lifestyle behaviours and LDL-C levels

*Association A: the association between the dose of each PRO-FIT*advice module (A^{1-6}) and change of the related lifestyle behaviour and LDL-C.*

As was assumed in Figure 1, there were positive associations between the completion of each advice module and the related behaviour, except for vegetable intake, and logging on and completing at least one advice module was also positively associated with change in LDL-C (see Table 4) However, these associations were not statistically significant.

*Table 4: Association (regression coefficient beta/odd's ratio (OR) and 95% confidence interval (CI)) of dose of PRO-FIT*advice and counselling with post-test LDL-C and multiple lifestyle behaviours, adjusted for baseline levels of the dependent variable, in the intervention group (n = 181)*

	LDL-C (mmol/l)	**MVPA**[1] **(**minutes/wk)	**Fat intake** (fat points/day)	**Fruit intake** (servings/day)	**Vegetable intake** (grams/day)	**Smoking** (yes)	**Compliance to statin therapy** (yes)
	beta *95% CI*	beta *95% CI*	beta *95% CI*	beta *95% CI*	beta *95% CI*	OR *95% CI*	OR *95% CI*
Participants who had logged on at *PRO-FIT*advice* and completed at least one advice module	−0.18 *−0.45-0.09*						
Participants who had logged on at *PRO-FIT*advice* and completed the module on:							
Physical activity	−0.09 *−0.37-0.19*	0.16 *−0.14-0.45*					
Fat intake	−0.13 *−0.42-0.16*		−0.51 *−1.55-0.54*				
Fruit intake	−0.13 *−0.41-0.16*			0.19 *−0.05-0.43*			
Vegetable intake	−0.13 *−0.42-0.15*				−7.13 *−25.18-10.92*		
Smoking	−0.06 *−0.44-0.32*					0.11 *0.01-1.25*	
Compliance to statin therapy	−0.11 *−0.42-0.19*						1.09 *0.41-2.93*
Participants who had received face-to-face counselling	N/A[2]	N/A[2]	N/A[2]	N/A[2]	N/A[2]	N/A[2]	N/A[2]
Telephone booster calls delivered (mean, SD)	0.06 *−0.06-0.17*	−0.04 *−0.10-0.17*	0.26 *−0.16-0.68*	−0.03 *−0.13-0.07*	−4.66 *−11.94-2.63*	1.00 *0.61-1.64*	1.02 *0.69-1.51*

Participants who had logged on, finished at least 1 module[3], received face-to-face counselling and at least 1 telephone booster call (=complete intervention-package)	−0.18 *−0.45-0.09*	0.10 *−0.20-0.40*	−0.50 *−1.56-0.56*	0.16 *−0.08-0.40*	−6.87 *−25.09-11.36*	0.11 *0.01-1.25*	0.90 *0.33-2.44*

See next page for legend

[1] MVPA=moderate to vigorous physical activity. Due to skewed data, log-linear regression was conducted. Therefore, the beta should be interpreted as follows: a 1% increase of the independent variable is associated with a beta% increase in physical activity; [2] Due to minimal variation in dose delivered, no association between dose delivered and efficacy could be teste; [3] For LDL-C this means at least one module, for the lifestyle behaviours, this means the related advice module (e.g. for physical activity, the completion of the physical activity module); Significant associations between dose and efficacy (p < 0.05) are printed in bold. Effect parameters (beta regression coefficient or odd's ratio (OR)) either indicated a positive association if LDL-C/lifestyle behaviours improved when regressed to the process, or a negative association if vice versa

Association B: the association between the dose of face-to-face counselling and change of multiple lifestyle behaviours and LDL-C.

Due to the high percentage of participants who had received a face-to-face counselling session (99%), no associations with LDL-C and lifestyle behaviours could be tested.

Association C: the association between the dose of telephone booster calls and change of multiple lifestyle behaviours and LDL-C.

The number of telephone booster calls delivered appeared to be negatively associated with change in LDL-C and all lifestyle behaviours (see Table 4), but these associations were not statistically significant.

*Association D: the association of the dose of the complete intervention-package as intended (at least one PRO-FIT*advice module, face-to-face counselling and at least one telephone booster call) with change in multiple lifestyle behaviours and LDL-C.*

Participants who had received the complete intervention-package as intended showed improved LDL-C levels and all lifestyle behaviours, except for vegetable intake and compliance to statin therapy (see Table 4), but these associations were also not statistically significant.

DISCUSSION

The present paper describes the reach, dose (delivered and received) and fidelity of the PRO-FIT intervention, a combination of a web-based computer-tailored lifestyle advice (*PRO-FIT*advice*) and

(face-to-face and telephone) counselling guided by MI. The results indicate that a representative proportion of the intended study sample agreed to participate of whom only half logged on at the *PRO-FIT*advice* website and completed at least one of the advice modules. Almost all participants received face-to-face counselling, however with low MI fidelity, and the majority of the planned number of telephone booster calls was delivered.

Despite its representativeness, only 34% of the people with FH invited to participate in the PRO-FIT project took part in the study. This low participation rate, as well as the StOEH screening rate, has implications for the generalizability of the results, as the sample was self-selective. Participants are likely to be more motivated to change lifestyle behaviour and our study showed significanty higher LDL-C levels in non-participants compared to participants. This is disappointing, since people with elevated LDL-C levels are most in need for a lifestyle intervention. In addition, because of the low participation rate, a decreased (cost-) effectiveness is expected on a population level. [43,44] By conducting measurements and providing counseling sessions at the participant's home, we already tried to minimize the main burden and time investments of the participants. However, in future comparable trials, other proactive strategies to recruit high-risk participants are suggested, such as the incorporation of healthcare professionals (e.g. medical specialists or StOEH genetic field workers) during the recruitment phase, and the provision of incentives for participation.

Despite the high dose of the *PRO-FIT*advice* accounts delivered, the extent to which participants actively engaged in using the website as intended was disappointing. The power of web-based interventions is that they can be delivered at almost any time and anywhere, as suites the individual participant. [45] However, suboptimal exposure to web-based interventions has already been pointed out as a major concern in such health promotion studies. [14] Apparently, dose received is a less controllable process element as compared to dose delivered, which is under the control of the implementers. Robroek et al also evaluated the use of an internet-delivered behaviour change program for construction workers and found 43% of them visiting the website. [46] *PRO-FIT*advice* was based on the Dutch GezondLevenCheck, a quite comparable web-based tool which contains 5 (instead of 6) advice modules and is freely available to the general public and online registration before entering the advice modules is required. Comparable to *PRO-FIT*advice*, multiple visits to the GezondLevenCheck were possible and recommended, but not mandatory. Brouwer et al. reported a registration rate of 29% and found 91% of the registered users actually finishing at least one module. [47] This confirms that, despite the potential of *PRO-FIT*advice* (or web-based interventions in general) to be delivered at a high dose, achieving an acceptable dose received remains challenging and less controllable. The length of the screening questionnaires of the advice modules could have

inhibited participants from completing an advice module, particularly since they overlapped with the questionnaires for evaluative purposes. In future studies on computer-tailoring, the burden of filling in (screening) questionnaires should be brought to a minimum in order to keep participants motivated, e.g. by creating a joint questionnaire, for both evaluative and tailoring purposes. Thereby, it is known that incorporating iterative feedback and interactive website components are positively associated with exposure to web-based interventions. [14] The combination of *PRO-FIT*advice* and personal counselling could be more successful if counsellor support is also available at an interactive communication board/forum, whereon participants also can communicate with each other. Still, the consequences of the low dose received of *PRO-FIT*advice* remain to be questioned, as the complete PRO-FIT intervention also incorporated face-to-face and telephone booster calls. In other words, to what extent were the gaps with regard to (un)completed advice modules and (lack of) formulated action plans, filled in by the content of the face-to-face counselling sessions?

Regarding face-to-face counselling, the dose delivered again appeared to be high, since almost all participants were visited by their personal coach. However, none of the analysed face-to-face counselling sessions met the MITI thresholds. Other studies on MI counselling have also reported below-threshold scores. [48-51] The association between MI fidelity and efficacy could not be tested in this study, but previous studies showed that a better MI performance is associated with larger intervention effects. [21,52] It has often been reported that skills required for effective MI may take longer to develop than the 3-day MI workshop in our project. [53,54] Probably, the provided MI workshop was not sufficient and more thorough monitoring and supervision of counselling skills during the intervention should have been built in. Beyond meeting MI thresholds, the face-to-face counselling sessions were part of the complete PRO-FIT intervention, and also included the discussion of the given advice at *PRO-FIT*advice*, and/or the (re)making of action plans. Thus, despite being a useful supplement to *PRO-FIT*advice*, this could have worked at the expense of fidelity to MI. Strict separation between the intervention components was impossible and undesirable.

The significant difference between the two coaches in MI fidelity, is noteworthy. By providing a 3-day workshop and an intervention protocol to both coaches, we attempted to achieve comparable delivery of MI throughout the sessions. Nevertheless, despite all effort, differences in background, demographics and other personal characteristics (e.g. counselling style) were unavoidable, and undoubtedly must have affected counselling performance. The analysed sessions showed that the coach with a more extended and diverse counselling history performed poorer than the coach with a more limited (though lifestyle counselling-) background. Literature has also shown that it has advantages to train more inexperienced coaches, e.g. students. [55] Overall, we should keep in mind

that in a real-life setting, differences in the above-mentioned inter-coach characteristics are indispensable.

The secondary aim of this paper was to investigate whether the dose of: A) *PRO-FIT*advice*, B) face-to-face counselling, C) telephone booster calls, and D) the complete intervention-package, was associated with change in lifestyle behaviour and LDL-C levels. The delivery of the complete intervention-package as intended led to non-significant improvements in LDL-C and lifestyle behaviours. More particular, associations between the completion of the separate advice modules of *PRO-FIT*advice* and change in LDL-C and related lifestyle behaviours were positive, but non-significant. Other studies also showed weak or absent dose–response relationships regarding web-based lifestyle interventions. [56,57] Further, generally negative associations were found between the number of telephone booster calls and LDL-C and lifestyle behaviours, but these associations were also not statistically significant. Even if these negative associations are valid, this does not necessarily mean that the telephone booster sessions might have inhibited behavioural improvements. It may be that with fewer sessions performed, more improvements regarding lifestyle behaviours may already have been made and no further session were necessary, given that the participants were encouraged to plan the telephone sessions themselves according to their need for additional counselling.

This process evaluation has limitations. At first, the sample in this process evaluation (n = 181) might be too small to draw firm conclusions, since sample size calculations in the PRO-FIT project were based on the power to statistically detect an intervention effect. [7] Further, associations of process indicators with demographic (e.g. age), psychosocial (e.g. motivation) and behavioural (e.g. physical activity level) correlates, that could further clarify for whom the intervention works best, were not included in this process evaluation. Also, not all recommended process elements were incorporated in this process evaluation, e.g. maintenance. In general, to produce lasting effects, interventions will need to address successful intervention components/strategies that lead to sustained behavioural change. We cannot draw conclusions on the longer-term effects of the PRO-FIT intervention and the association with intervention dose. Further, the assessment of MI fidelity was limited to 20 counselling sessions, which was sufficient for determining MI quality, but made it unable to explore its association with efficacy.

Strengths of the present process evaluation include that a thorough, theory-based approach was conducted incorporating the most important process indicators. Data were mostly collected from objective sources, such as website data/coach logs. By linking these indicators to efficacy, we meet

the call for more insight in the association between the process of delivery of intervention components and efficacy, contributing to a more transparent evaluation of a public health intervention and being able to indicate facilitators and barriers in translating such an intervention into practice.

CONCLUSIONS

In conclusion, it would be feasible to implement the PRO-FIT intervention in practice, particularly *PRO-FIT*advice*, since it can be relative easily implemented with a high dose delivered. However, only less than half of the intervention group received the complete intervention-package as intended. Strategies to let participants optimally engage in using *PRO-FIT*advice* (and web-based computer-tailored interventions in general) are needed. Implementing MI in face-to-face lifestyle counselling sessions is challenging and emphasis should be put on more extensive MI training and monitoring. In order to conduct more efficacious intervention studies in the field of health promotion, we challenge fellow researchers to perform systematic process evaluations incorporating the exploration of the key process indicators reach, dose and fidelity, as well as its association with efficacy.

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CHAPTER 7

An economic evaluation alongside a randomised controlled trial evaluating an individually tailored lifestyle intervention compared with usual care in people with Familial Hypercholesterolemia

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Under review

Objective

To evaluate the cost-effectiveness and cost-utility an individually tailored lifestyle intervention compared to usual care in people with Familial Hypercholesterolemia (FH).

Method

In a randomized controlled trial, usual care was compared to a personalised lifestyle intervention in adults with FH (n=340). LDL cholesterol (LDL-C), quality of life and cost data were measured at baseline and after 12 months. Missing data were multiply imputed. 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.

Results

Non-significant decreases in LDL-C and QALYs were found of -0.14 (-0.34;0.07) and -0.002 (-0.02;0.01), respectively, 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). The ICERs were 1729 per 1 mmol/l LDL-C and 145,899 per QALY gained. Assumed that the small non-significant decrease in LDL-C can be attributed to the intervention, the probability of cost-effectiveness of the intervention compared to usual care was 91% per 1 mmol/l LDL-C reduction and 75% per QALY gained at a ceiling ratio of €20,000.

Conclusion

The intervention is not (cost-)effective in comparison with usual care.

INTRODUCTION

In the Netherlands, approximately one in every 500 people is affected with Familial Hypercholesterolemia (FH) [1], which is a genetic disorder of the lipoprotein metabolism, associated with elevated plasma concentrations of LDL-C. [2] Elevated serum LDL-C and FH are associated with an increased risk of early cardiovascular disease (CVD). [3] Since 1994, already 23,668 of the estimated 40,000 mutation carriers have been found and genetically diagnosed through the cascade screening program of the Dutch Foundation for Tracing Hereditary Hypercholesterolemia (in Dutch: StOEH). [4]

CVD is a major contributor to the global burden of disease, as it decreases quality of life and accounts for 20% of disability-adjusted life years (DALYs) lost in developed countries. [5] CVD also constitutes a large economic burden, as approximately 10% of the European health budget is spent on CVD. [6] Moreover, productivity losses due to premature death and illness of CVD patients of working age and costs due to informal care for people with CVD also contribute greatly to the societal economic burden (21% of the total costs of CVD). [6] Results of primary prevention trials in high-risk persons and secondary prevention trials in CVD patients show that substantial reductions in CVD risk can be achieved through lifestyle changes. [7, 8] Given the burden of CVD and the limited resources available for health care, information on the cost-effectiveness of available intervention strategies to reduce CVD risk is important. The aim of this study is to assess the cost-effectiveness and the cost-utility of an individually tailored lifestyle intervention compared with usual care in people with FH after 12 months from a health care perspective.

METHODS

Design of the study

An economic evaluation was conducted from a healthcare perspective alongside a Randomized Controlled Trial (RCT). Details on the design of the project and the intervention content have been published elsewhere. [9] The study design and informed consent procedure were approved by the Medical Ethics Committee of the VU University Medical Center and all participants provided written informed consent. The trial has been registered at dutchtrialregister.nl as NTR1899.

Study population and setting

Participants diagnosed with the heterozygous type of FH from January 1st 2007 to April 15th 2009, aged 18-70 years and with a LDL-C level >75th percentile (age and gender specific) were recruited

from the national cascade screening program of the StOEH. [11] Access to internet, sufficient fluency in Dutch and residency <150 km radius from Amsterdam were additional eligibility criteria. Participants were randomly assigned to either the control group (n=159) or the intervention group (n=181) through a stratified computerized blinded randomisation procedure using Microsoft© Office Access 2003 software. Participants were stratified according to cholesterol lowering medication use (yes/no), assuming that medication use implicates treatment by a general practitioner and/or medical specialist, who could have already given advice on lifestyle behavior. In addition, we expected that the potential decrease in LDL-C because of the intervention would be smaller if a participant already used medication. Family members from the same household were clustered and subsequently randomized as a cluster to prevent contamination due to spill over of communication about the intervention among family members.

Intervention and control

The intervention consisted of a combination of tailored web-based advice (*PRO-FIT**advice) and one face-to-face counselling session complemented with telephone booster sessions (*PRO-FIT**coach). [9] The goal of the intervention was to improve awareness of the CVD risk, by increasing knowledge about CVD risk based on current lifestyle behavior, cues to action and change in risk perception, and to lower LDL-C levels and adopt and maintain a healthier lifestyle, regarding physical activity, saturated fat intake, fruit and vegetables intake, smoking and compliance to statin therapy. [9]

Briefly, participants were encouraged to visit a web link referring to the project website, where generic CVD risk information was presented, containing information on CVD risk behaviors and their contribution to overall CVD risk, as well as information on the changeability of these behaviors and cues on how to change behaviors. Thereafter, participants could log on to a personal *PRO-FIT**advice account, consisting of six advice modules on smoking, physical activity, saturated fat intake, fruit intake, vegetables intake and compliance to statin therapy. On-screen personalized feedback was tailored to personal performance level (current lifestyle behavior), awareness of one's own performance, as well as personal motivation to change, outcome expectations, attitude and self-efficacy.

Subsequently, one face-to-face counselling session was provided to each participant by a lifestyle coach at the participants' home with a duration of 45 minutes. The assessment(s) and advice(s) within the participant's personal *PRO-FIT**advice account were discussed, and ambivalence and barriers related to the recommended behavior changes were explored using Motivational Interviewing (MI) techniques. [10] In the following 9 months, the lifestyle coach offered one to five

booster telephone sessions of 15 minutes per participant, to encourage the participant's behavioral changes and to provide further brief MI to encourage the planned behavioral changes.

The control group received care as usual, which means that they received no extra intervention besides the care they already received: at least one visit to the general practitioner and/or medical specialist a year and the use of cholesterol-lowering medication (approximately 70% of the participants).

Study measures

Clinical outcomes

LDL-C was measured at baseline and 12 months with fasting finger stick samples analysed on a Cholestech LDX desktop analyser (Cholestech, Hayward, USA). [9] For the cost-utility analysis, the EuroQol-5D (EQ-5D) was used to assess quality of life at baseline and at 12 months. [11] To estimate the utility of health states described by the participants, the Dutch tariff was used. [12] Quality adjusted life years (QALYs) were calculated by multiplying the utilities with the amount of time a participant spent in a particular health state. Transitions between health states were linearly interpolated.

Cost measures

Data were collected from a healthcare perspective, i.e. only healthcare-related costs were included in the economic evaluation. Prices were adjusted for the year 2010, the year in which most data were collected, using consumer price indices. [13]

Information on healthcare utilization and prescribed medication associated with FH and/or CVD was obtained through a 12-month retrospective questionnaire. Healthcare utilization consisted of costs of primary care (including general practitioner and therapist care) and secondary care (including medical specialist care and hospitalization associated with FH and/or CVD), and were valued with Dutch standard costs. [14] If these were not available, prices according to professional organizations were used. The costs of prescribed medication were calculated using prices charged by the Royal Dutch Society for Pharmacy. [15]

Intervention costs were estimated using a bottom-up micro-costing approach, i.e. detailed data were collected regarding the quantity of resources consumed per patient as well as their unit prices. Costing was based on the assumption that the intervention would be implemented for a 5-year period by an academic medical center. According to StOEH data, approximately 2700 people would

be eligible and willing to participate during this period. [4] Consequently, five lifestyle coaches would be needed for the coaching component of the intervention. Variable costs per participant depended on the number of counselling sessions received and were calculated using annual salaries of the lifestyle coaches with added taxes and benefits. Intervention costs additionally included costs of the development and implementation of materials, training and supervision of the lifestyle coaches, and the development and implementation of the PRO-FIT*advice web-environment.

Statistical analyses

Missing healthcare costs, QALY data and LDL-C levels were multiply imputed in SPSS 17 creating ten different data sets. [16-18] Data were imputed separately for the intervention and control group. The imputational model included important demographics and prognostic variables associated with the missing data: age, gender, LDL-C levels and body mass index (BMI) at baseline and follow-up, intervention costs, primary care (general practitioner and therapist) costs, secondary care (outpatient visits and hospital admission) costs and medication costs, and utilities at baseline and follow-up. Pooled estimates of effects and costs were estimated according to Rubin's rules. [19]

Main analyses were according to the intention to treat principle and based on the imputed data. Differences in baseline characteristics between the intervention and control group and between cases with missing data and cases with complete data were tested using linear and logistic regression analysis. The effects on clinical outcomes at 12 months were analysed using linear regression analyses, adjusted for baseline values. Mean cost differences between the intervention and control group were calculated for primary and secondary care, medication, and total costs. The Approximate Bootstrap Confidence (ABC) algorithm with 5000 bootstrap samples was used to estimate 95% confidence intervals surrounding the cost differences. [20] Incremental cost-effectiveness ratios (ICERs) were calculated by dividing the difference in total costs between the intervention and control group by the difference in clinical outcomes adjusted for baseline values. The ICER indicates the additional investments needed for the intervention group to gain one extra unit in health effect, i.e. 1 mmol/l LDL-C and 1 QALY, in comparison with usual care. The bootstrapped cost-effect pairs were graphically presented in a cost-effectiveness (CE) plane, to show the uncertainty around the ICER. Cost-effectiveness acceptability curves (CEACs) were also estimated. CEACs show the 'willingness to pay' for a unit of health effect extra (i.e. ceiling ratio) on the x-axis and the corresponding probability that the intervention is cost-effective at that ceiling ratio on the y-axis. All analyses were done in R (version 2.10.1). [21]

To assess the robustness of the results, three sensitivity analyses were performed. First, a cost-

effectiveness analysis (CEA) taking only complete cases into account was conducted (CEA2). Second, a CEA was performed using the actual costs of the PRO-FIT intervention within the PRO-FIT trial (including 340 participants, 2 lifestyle coaches, implemented in a one-year period) (CEA3). Third, a CEA was conducted in which the hospital admission costs were excluded from the total costs (CEA4).

RESULTS

Participant flow and baseline characteristics

Invitation letters were sent to 986 people, of whom 340 (34%) responded and participated in the trial. The participant flow is presented in Figure 1. A small proportion of participants decided to discontinue participation or was lost to follow-up in both the intervention (5%) and control group (8%), resulting in 318 participants completing the study. The number of participants with complete follow-up data ranged from 64% to 90%. Baseline characteristics are given in Table 1. A significant difference in baseline BMI between intervention and control group was found (mean difference=-1.10; 95% CI: -2.16 to -0.05) in the imputed and complete cases dataset. As a consequence, baseline BMI values were included in all analyses of cost-effectiveness regarding LDL-C and QALYs.

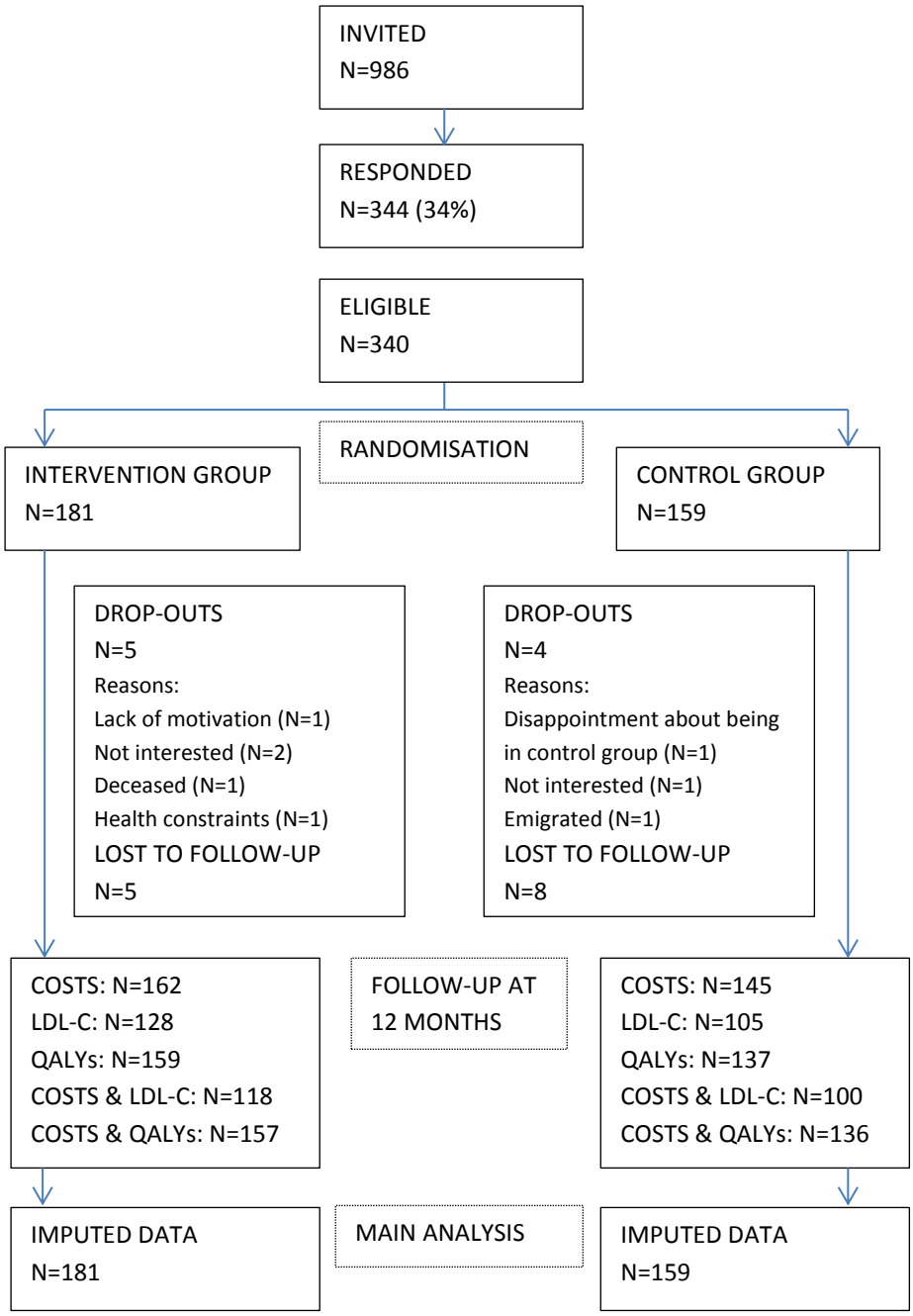


Figure 1: Flow of participants in the PRO-FIT project

Table 1: Baseline characteristics of people with Familial Hypercholesterolemia in the control and intervention group after multiple imputation, EMGO+ Institute for Health and Care Research, VU University Medical Center, Amsterdam, the Netherlands, 2009-2010

	Control group N=159	**Intervention group N=181**
Gender, N (% female)	90 (57)	104 (57)
Mean age in years) (SEM)	46.0 (1.0)	44.7 (1.0)
Mean BMI in kg/m^2 (SEM)	**27.1 (0.4)**	**26.0 (0.3)**
Statin use, N (% yes)	110 (69)	123 (68)
EQ-5D utility score$_1$(SEM)	0.9 (0.01)	0.9 (0.01)

$_1$ Assessed by the EuroQol-5D
N=sample size; SD=standard deviation; BMI=body mass index; Significant differences between control and intervention group (P<0.05) are printed in bold font. SEM=Standard Error of the Mean

Intervention compliance

Of the 181 participants in the intervention group, 95% received a PRO-FIT*advice log on account. The remaining 5% (9 participants) explicitly reported to have no interest in using *PRO-FIT*advice* and therefore, received no log on information. Subsequently, 49% of remaining 172 participants actually logged on and completed at least one out of 6 advice modules. Nearly all participants (99%) received the face-to-face counselling session and on average, 4.2 telephone booster calls were conducted with 181 participants.

Clinical outcomes

After 12 months, LDL-C had decreased in both groups and by 0.14 mmol/l more in the intervention group. The intervention group had 0.002 QALYs less than the control group. These between-group differences for LDL-C and QALYs were small and statistically non-significant (see Table 2).

Table 2: Pooled intervention effects on LDL-C and QALYs after 12 months among people with Familial Hypercholesterolemia after multiple imputation and adjustment for baseline values, EMGO+ Institute for Health and Care Research, VU University Medical Center, Amsterdam, the Netherlands, 2009-2010

Pooled effects (pooled mean (SEM))	**Control group N=159**		**Intervention group N=181**		**Intervention versus control**
	Baseline	Follow-up	Baseline	Follow-up	Mean difference (95% CI)
LDL-C (mmol/l)	3.7 (0.1)	3.6 (0.1)	3.7 (0.1)	3.5 (0.1)	-0.14 (-0.34-0.07)
QALYs achieved	-	0.9 (0.01)	-	0.9 (0.01)	-0.002 (-0.02-0.01)

LDL-C=low-density lipoprotein cholesterol ;QALY=Quality Adjusted Life Year; SEM=Standard Error of the Mean; the maximum QALY that can be achieved in one year is 1 unit.

Costs

Intervention costs are presented in Table 3 and mainly consisted of the costs of counselling (91%). Pooled mean costs and cost differences between the intervention and control group are presented in Table 4. Around one third of total costs in both groups consisted of medication costs. Primary care costs were statistically significantly lower in the intervention group in comparison with the control group. Secondary care costs in the control group were considerably higher than in the intervention group due to one extended hospitalization in this group. However, the difference in secondary costs was not statistically significant. Overall healthcare-related costs were €237 lower in the intervention group but this difference was not statistically significant (-1386-130).

Table 3: Overview of costs of the PRO-FIT intervention in Euros per participant, EMGO+ Institute for Health and Care Research, VU University Medical Center, Amsterdam, the Netherlands, 2009-2010

Cost category	**Included resources**	**Cost prices per unit[1]**	**Costs per participant**
Development			
Developmental costs of brochure and coaching logs	Content development (30 hrs) by junior researcher Concept development/graphic design (24 hrs) by graphic designer Final development (12 hrs) by brochure designer	€ 35.75/hr € 75/hr € 65/hr	€ 2.80
Computer-based part of intervention, including website and application for providing computer-tailored advice	Web development (12 hrs) by web- developer Registration website (once) Development/adjustment tailoring application by junior researcher (216 hrs) Account tailoring application	€ 65/hr € 53.95§ € 35.75/hr € 3930.25§	€ 5.44
Brochures, logs, website and tailoring application	Printing of brochure/coaching logs Hosting website Hosting tailoring application	€ 0.10/piece € 119.40/year§ € 171/year§	€ 1.64
Implementation based on 2700 participants and an implementation period of 5 years			
Training of lifestyle coaches	A 3-day Motivational Interviewing workshop 5 lifestyle coaches, 3 days, 8 hrs/day Supervisor, 3 days, 8 hrs/day	€ 5100§ € 38.38/hr € 35.75/hr	€ 3.94
Supervision of lifestyle coaches (10 meetings of 2 hours each)	Meeting rooms rental costs 5 lifestyle coaches Supervisor	€ 11.50/room/hr§ € 38.38/hr € 35.75/hr	€ 1.77
Counselling	1 face-to-face counselling session (45 mins) by lifestyle coach 5 telephone booster sessions (15 mins/session) by lifestyle coach Administrative work (25 mins/participant) by lifestyle coach Travelling (82 km/participant and 1 hr/participant)	€ 38.38/hr € 38.38/hr € 38.38/hr € 0.20/km, € 38.38/hr	€ 147.64
Total intervention costs			€ 163.13

[1]Salary costs were derived from the Collective Labour Agreement for Dutch Academic Medical Centers (CAO UMC) 2010 (for junior researcher, lifestyle coach and supervisor), or by price offers from web developers, graphic/brochure designers.

§ Costing was based on invoices/price offers. Hrs= hours; mins=minutes.

Table 4: Pooled mean differences in healthcare-related costs per participant in Euros between baseline and 12-months follow-up in the intervention and control group after multiple imputations, EMGO+ Institute for Health and Care Research, VU University Medical Center, Amsterdam, the Netherlands, 2009-2010

Pooled costs (pooled mean (SEM))	**Control group**	**Intervention group**	**Mean cost difference (95% CI)**
PRO-FIT intervention	0	163	163 (NA)
Primary care	**86 (17)**	**44 (8)**	**-43 (-86 - -11)**
Secondary care	461 (289)	121 (51)	-340 (-1406-24)
Medication$_1$	284 (29)	266 (23)	-17 (-91-54)
Total costs	831 (297)	594 (60)	-237 (-1386-130)

$_1$ Prescribed statins, SEM=Standard Error of the Mean, NA=Not Available
Costs are given in 2010 Euros

Cost-effectiveness

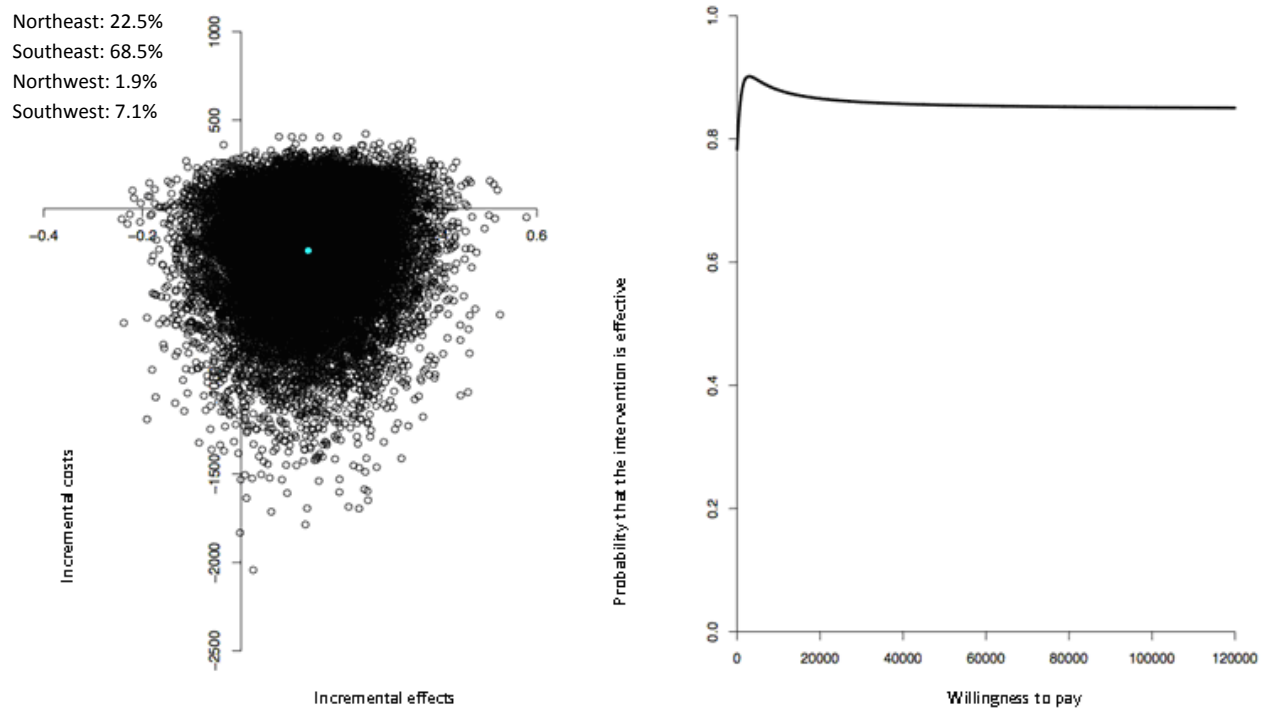
Assuming that the non-significant difference in LDL-C between intervention and control group can be attributed to the intervention, the main analysis showed that the pooled ICER for LDL-C was €1729 (see Table 5), indicating that a 1 mmol/l decrease in LDL-C concentration extra as a result of the PRO-FIT intervention saves €1729, compared to usual care. The CE-plane for LDL-C (Figure 2a) showed that 68% of the bootstrapped cost-effectiveness pairs were located in the southeast quadrant, the quadrant in which the intervention is dominant over usual care. The CEAC curve (Figure 2b) showed that if a decision maker is willing to pay €4000 for 1 mmol/l LDL-C reduction, the probability that the PRO-FIT intervention is cost-effective is 93%, but thereafter reduces to a maximum of 91%.

Table 5: Results for cost-effectiveness and cost-utility analyses, EMGO+ Institute for Health and Care Research, VU University Medical Center, Amsterdam, the Netherlands, 2009-2010

	Sample size			**Cost difference in Euros (95% CI)**	**Effect difference (95% CI)**	**ICER**	**Distribution CE plane (%NE / SE / SW / NW)**
	I	**C**					
Main analysis (CEA1)	181	159	LDL-C	-237 (-1386-130)	-0.14 (-0.34-0.07)	1729	22.5 / 68.5 / 7.1 / 1.9
	181	159	QALY	-237 (-1386-130)	-0.002 (-0.02-0.01)	145,899	9.7 / 30.9 / 44.2 / 15.2
Complete case analysis (CEA2)	118	100	LDL-C	-364 (-2030-238)	-0.14 (-0.37-0.08)	2012	4.6 / 8.0 / 55.7 / 31.7
	157	136	QALY	-301 (-1680-109)	-0.003 (-0.03-0.03)	100,347	6.5 / 25.4 / 52.5 / 15.6
Intervention costs as in RCT (CEA3)	181	159	LDL-C	-88 (-1248-277)	-0.14 (-0.34-0.07)	645	39.4 / 51.6/ 5.5 / 3.6
	181	159	QALY	-88 (-1248-277)	-0.002 (-0.02-0.01)	54,426	17.1 / 23.4 / 33.8 / 25.7
Hospital admission costs excluded (CEA4)	181	159	LDL-C	94 (-6-193)	-0.14 (-0.34-0.07)	-690	88.5 / 2.4 / 0.5 / 8.5
	181	159	QALY	94 (-6-193)	-0.002 (-0.02-0.01)	-33,676	38.9 / 1.2 / 1.7 / 58.2

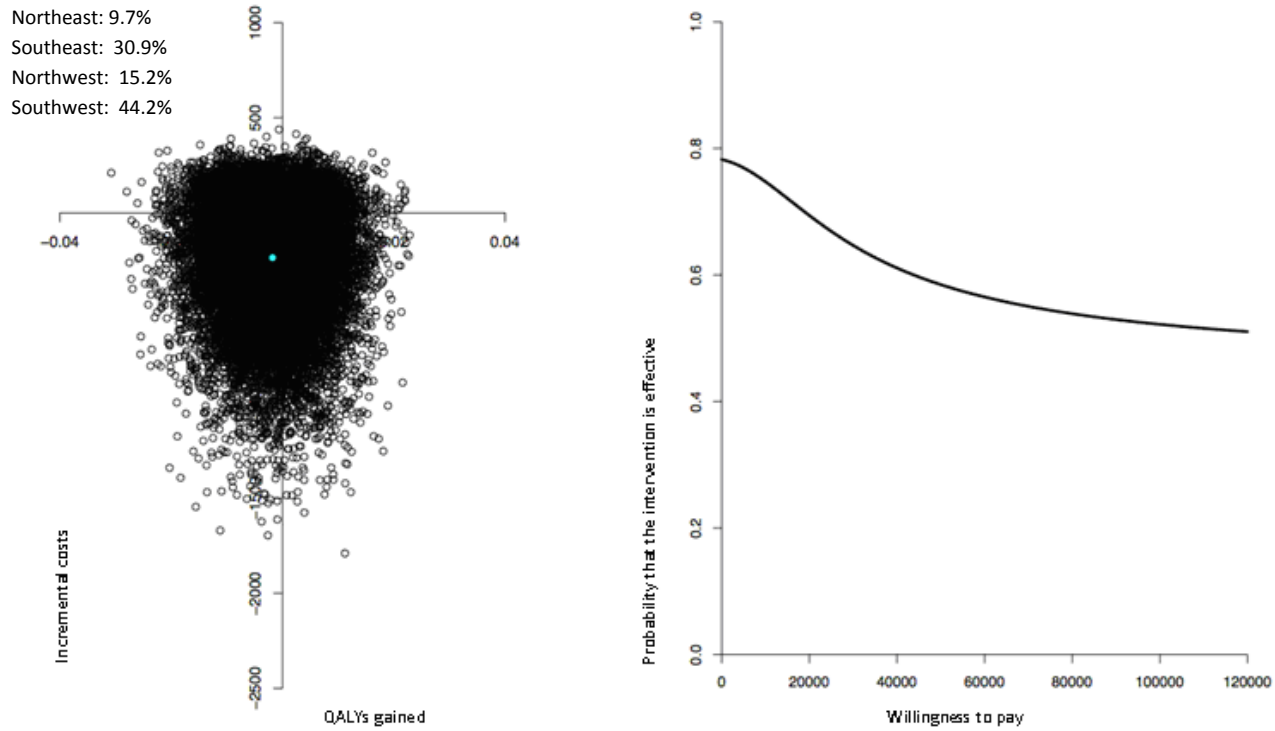
Cost-utility

The ICER of €145,899 per QALY indicates that 1 QALY lost as a result of the PRO-FIT intervention saves the healthcare sector €145,899, compared to usual care (see Table 5). In the CE plane (Figure 3a), most cost-utility pairs (44%) were located in the southwest quadrant, the quadrant in which less QALYs are gained at lower costs in the intervention group compared with usual care. The CEAC (Figure 3b) indicated that the probability of cost-utility of the PRO-FIT intervention compared to usual care ranged from approximately 75% at a ceiling ratio of €0 per QALY gained to 55% at a ceiling ratio of €120,000 per QALY gained.



Northeast quadrant of the CE plane: the intervention is more effective and more costly than usual care; Southeast quadrant of the CE plane: the intervention is more effective and less costly than usual care; Northwest quadrant of the CE plane: the intervention is less effective and more costly than usual care; Southwest quadrant of the CE plane: the intervention is less effective and less costly than usual care.

Figure 2a and 2b: Pooled cost-effectiveness plane and cost-effectiveness acceptability curve for the difference in LDL-C after 12 months



Northeast quadrant of the CE plane: the intervention is more effective and more costly than usual care; Southeast quadrant of the CE plane: the intervention is more effective and less costly than usual care; Northwest quadrant of the CE plane: the intervention is less effective and more costly than usual care; Southwest quadrant of the CE plane: the intervention is less effective and less costly than usual care.

Figure 3a and 3b: Pooled cost-effectiveness plane and cost-effectiveness acceptability curve for QALYs gained after 12 months

Sensitivity analyses

Results of the sensitivity analyses based on complete cases (CEA2) and based on the actual intervention

costs of the PRO-FIT intervention (CEA3) were similar to the results from the

main analyses (see Table 5). The CEA that excluded hospital admission costs led to smaller

cost differences and costs were lower in the control group.

DISCUSSION

The results of this study show that the PRO-FIT intervention was not cost-effective in comparison with usual care. No statistically significant differences were found in LDL-C, QALYs and health care costs after 12 months. Our study is the first to evaluate the cost-effectiveness of a lifestyle intervention compared to usual care in a FH sample. Other studies concluded that lifestyle interventions are cost-effective in reducing the long-term risk of type 2 diabetes and CVD. [22] However, our findings show no value in the addition of lifestyle advice to treatment with statins, which has already been shown to be cost-effective in people with FH. [23]

All further discussion and interpretation of the present results regarding cost-effectiveness should obviously be regarded with caution, since we cannot conclude that the non-significant decrease in LDL-C and related gain in QALYs were coincidental or caused by the intervention. For the sake of this economic evaluation, the found differences compared to the usual care were regarded as real and attributable to the intervention. Having conducted a CEA for an intervention for which no evidence of effect was found as compared to usual care seems to have limited value. Though, conducting CEAs while significant effects are lacking is of great importance, e.g. for systematic reviews on the cost-effectiveness of interventions. These reviews are often hampered by a publication bias, since CEAs are generally only conducted if an intervention was significantly effective and are therefore overrepresented. [24,25] Further, this study examines the joint distribution of costs and effects. This is relevant because even if costs and effects show no significant differences, the joint distribution could indicate that a treatment is cost-effective in comparison with control for some ceiling ratios. [26] In addition to the economic evaluation, the transparent oversight of the intervention costs and healthcare-related costs that we provided is relevant for policy-makers and future researchers planning a similar RCT.

Intervention costs were computed as if the intervention was implemented with full compliance. Taking into account the actual compliance during the trial would not lead to a substantial difference in intervention costs, as the proportion of participants that received face-to-face counselling was 99%. However, the intervention costs in this study were based on five telephone booster calls, whereas on average 4.2 were conducted during the trial. Consequently, the actual intervention costs are only slightly less (€155.46 instead of €163.13).
Secondary care costs in the control group were considerably higher than in the intervention group and this contributed most to the difference in total healthcare-related costs between the groups. Further analysis showed that this was caused by higher mean hospital admission costs associated with FH and/or CVD in the control group than in the intervention group. A sensitivity analysis excluding hospital admission costs showed that, in contrast to the main CEA analysis, costs in the intervention group were higher than in the control group, but this difference was not statistically significant and the intervention was still not considered cost-effective.

Limitations of this economic evaluation should be taken into consideration. At first, the evaluation was performed from a healthcare perspective, while Dutch guidelines recommend adapting a societal perspective. We chose this perspective since our central aim was to lower LDL-C with lifestyle changes, and no effects on productivity costs due to the intervention in the follow-up period were expected. Second, information on healthcare utilization and prescribed medication was obtained through a 12-month retrospective questionnaire. Shorter recall periods reduce the chance of recall bias, though more frequent measurements with a shorter recall period could have increased the chance of missing data, compared with one measurement with a recall period of 12 months. [27] Third, whereas intervention costs were complete, data on healthcare-related resource use and LDL-C/QALYs were missing for 36% and 14% of the participants respectively. To account for these missing data, multiple imputation techniques were used. Multiple imputation is preferred over complete case analysis. [27], since a complete-case analysis is inefficient, as the sample size is smaller and it ignores observed cost and/or effect data in the excluded participants. The advantage of using multiple imputation is that the uncertainty associated with imputing missing values is also taken into account in the pooled estimates.

In conclusion, an individually tailored lifestyle intervention in people with FH was not cost-effective compared to usual care. Due to the non-significant small effects found in the study, the conclusions should be regarded with caution.

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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 *Predisposing determinants*	**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 *Awareness phase*	**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 *Motivation phase*	**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 *Action phase*	**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 adoubling 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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SUMMARY

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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 (β=-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. Conclusive, implementation of the PRO-FIT intervention in practice appeared feasible, particularly PRO-FIT*advice, since it could be relative 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 behaviors 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.

SAMENVATTING

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In dit proefschrift werd de ontwikkeling en evaluatie beschreven van een leefstijlinterventie-op-maat (de PRO-FIT interventie) voor mensen met Familiaire Hypercholesterolemie (FH).

In het inleidende **hoofdstuk 1** werd de aanleiding voor het PRO-FIT project geschetst. Mensen met Familiaire Hypercholesterolemie (FH) hebben vaak een verhoogd LDL cholesterol (LDL-C) en een verhoogd risico op hart- en vaatziekten (HVZ), momenteel de belangrijkste oorzaak voor voortijdig overlijden in Westerse landen. De behandeling van mensen met FH met cholesterolverlagende medicijnen (statines) blijkt effectief in het verlagen van LDL-C waarden en het risico op HVZ. Echter, een interventie zal zich op zowel biologische als leefstijl-gerelateerde risicofactoren van HVZ moeten richten om het optreden van HVZ te voorkomen. Twee strategieën voor een optimale risicoreductie worden gesuggereerd: 1) het aanpakken van meerdere risicofactoren, en 2) het verlagen van LDL-C door het verbeteren van therapietrouw aan medicijnen. Naar aanleiding hiervan werd de ontwikkeling van de PRO-FIT interventie beschreven, gebaseerd op de meest belangrijke risicofactoren van HVZ en hun determinanten, die zijn beschreven in het I-Change model. Volgens dit model zijn er minstens drie stadia te identificeren in het proces van gedragsverandering: bewustzijn, motivatie en actie. Dit hoofdstuk sloot af met het formuleren van de doelen van de PRO-FIT interventie: 1) het verhogen van het bewustzijn van het risico op HVZ, 2) het verhogen van de motivatie om gedrag te veranderen op het gebied van bewegen, voeding, roken en therapietrouw, 3) het stimuleren van het aannemen en handhaven van een gezonde leefstijl, en 4) het verlagen van LDL-C waarden en het risico op HVZ.

Hoofdstuk 2 bevatte een systematische review over de effectiviteit van *computer-tailored* interventies ter bevordering van bewegen en gezonde voeding. Het betrof een upgrade van een in 2006 gepubliceerde review. Hiertoe werden literatuurdatabases doorzocht op gerandomiseerde gecontroleerde studies die zich hebben gericht op primaire preventie en volwassenen, gepubliceerd van September 2004 tot Juni 2011. Dit resulteerde in vijftig publicaties. De conclusie luidde dat, in vergelijking met de vorige review, een groter deel van de studies een positief effect van de *computer-tailored* interventies liet zien. Deze interventies bleken effectief in vergelijking met een controle groep waarbinnen geen of geen *computer-tailored* informatie werd gegeven en dit gold, in tegenstelling tot de vorige review, nu ook voor studies die zich hebben gericht op bewegen. De positieve effecten waren echter klein en beperkten zich tot studies met een follow-up tot 6

maanden. Verder lieten de resultaten zien dat er sinds 2004 meer studies zijn uitgevoerd met een lange follow-up periode, vooral op het gebied van gezonde voeding, en dat studies gericht op bewegen meer gebruik hebben gemaakt van objectieve uitkomstmaten. De conclusie in hoofdstuk 2 luidde dat toekomstige interventies die gebruik maken van *computer-tailoring* wordt aangeraden het volgende na te streven: 1) grotere en langdurige effecten, 2) meer gebruik van meer objectieve uitkomstmaten in studies gericht op gezonde voeding, en 3) meer gebruik van een controle groep die dezelfde informatie ontvangt, echter niet *computer-tailored*.

In **hoofdstuk 3** werd de ontwikkeling en evaluatie beschreven van de PRO-FIT interventie. In een gerandomiseerde gecontroleerde studie werden mensen met FH *at random* ingedeeld in een controle of interventie groep. In de interventie groep ontvingen deelnemers een leefstijlinterventie-op-maat, bestaande uit een combinatie van web-based en *computer-tailored* leefstijladvies (PRO-FIT*advies) en persoonlijke coaching door een leefstijlcoach met gebruik van Motivational Interviewing. Deelnemers in de controle groep ontvingen de zorg die zij normaal ontvingen en niet de interventie. De volgende biologische indicatoren van het risico op HVZ werden gemeten: systolische bloeddruk, glucose, body mass index, middelomtrek en lipiden (triglyceriden, totaal/LDL/HDL cholesterol). Secundaire uitkomsten waren leefstijlgedrag (roken, bewegen, voeding en therapietrouw) en psychologische correlaten en determinanten van leefstijlgedrag (kennis, attitude, risicoperceptie, sociale invloed, zelf-effectiviteit, *cues to action*, intentie en autonomie). Metingen van deze uitkomstmaten werden gepland aan het begin van de studie en na 3 en 12 maanden.

De effecten van de PRO-FIT interventie op leefstijlgedrag werden beschreven in **hoofdstuk 4**. Middels regressie analyses werden de verschillen tussen de interventie en controle groep na 12 maanden bekeken. In beide groepen werden geen significantie verschillen gezien in roken, bewegen, voeding (inname van verzadigde vetten en groente en fruit) en therapietrouw. Post-hoc analyses lieten een significante verlaging van de inname van verzadigde vetten zien bij vrouwen in de interventiegroep, in vergelijking met de controle groep (β=-1.03; CI -1.98- -0.03). Op basis van de resultaten kon worden geconcludeerd dat de PRO-FIT interventie niet superieur was ten opzichte van geen interventie op het gebied van verschillende leefstijldragingen bij mensen met FH.

In **hoofdstuk 5** werden de interventie effecten op biologische indicatoren van het risico op HVZ beschreven, namelijk systolische bloeddruk, glucose, body mass index, middelomtrek en lipiden triglyceriden, totaal/LDL/HDL cholesterol). Regressie analyses werden uitgevoerd om te zien of er na 12 maanden verschillen waren tussen de interventie en controle groep. Er werden geen significante

verschillen gevonden, LDL-C waarden waren gedaald in zowel de interventie als controle groep. Op basis van deze resultaten werd geconcludeerd dat de PRO-FIT interventie niet superieur was ten opzichte van geen interventie op het gebied van biologische indicatoren van het risico op HVZ bij mensen met FH.

De procesevaluatie werd beschreven in **hoofdstuk 6**. Volgens een systematisch procesevaluatie plan werden de volgende uitkomsten gemeten met betrekking tot de PRO-FIT interventie: het bereik, de geleverde/ontvangen dosis en de mate waarin de interventie volgens Motivational Interviewing werd uitgevoerd (MI fidelity). Hierbij werd gebruik gemaakt van data afkomstig uit de wervingsdatabase, de PRO-FIT website en coaching logboeken. MI fidelity werd gemeten met behulp van de MI Treatment Integrity (MITI 3.1.1.) code. Daarnaast werden regressie analyses uitgevoerd om verschillen in leeftijd, geslacht en LDL-C waarden tussen deelnemers en niet-deelnemers en de associatie tussen de dosis van de interventie en veranderingen in LDL-C en leefstijlgedragingen te bekijken. Resultaten laten zien dat een representatieve proportie (34%) van de beoogde doelgroep is geworven binnen het PRO-FIT project; deelnemers verschilden niet van niet-deelnemers in leeftijd, geslacht en LDL-C waarden. Van alle deelnemers ontving 95% een PRO-FIT*advies account. Slechts 49% logde in en rondde een van de vijf adviesmodules af. Bijna alle deelnemers ontvingen persoonlijke coaching en gemiddeld 4.2 telefoongesprekken. Geen van de persoonlijke coaching sessies bleek volgens MI uitgevoerd. De interventie bleek positief geassocieerd met LDL-C waarden en leefstijlgedragingen. Deze associatie was echter zwak en niet significant. Op basis van de resultaten werd geconcludeerd dat de implementatie van de PRO-FIT interventie in de praktijk haalbaar blijkt, vooral PRO-FIT*advies vanwege de hoge geleverde dosis. Echter, door het beperkte gebruik van PRO-FIT*advies maakt slechts de helft van de deelnemers optimaal gebruik van de PRO-FIT interventie zoals gepland.

In **hoofdstuk 7** werd de kosteneffectiviteit en kostenutiliteit van de PRO-FIT interventie gerapporteerd. LDL-C waarden, kwaliteit van leven en de gemaakte kosten werden gemeten aan het begin van de studie en na 12 maanden. Kosteneffectiviteit analyses werden uitgevoerd vanuit het perspectief van de gezondheidszorg. Op basis van de resultaten kon worden geconcludeerd dat de PRO-FIT interventie niet kosteneffectief was in vergelijking met de gebruikelijke zorg bij mensen met FH.

Hoofdstuk 8 omvatte een samenvattend hoofdstuk waarin de resultaten van het PRO-FIT project werden bediscussieerd vanuit verschillende perspectieven. Daarnaast werden in dit hoofdstuk aanbevelingen geformuleerd met betrekking tot de ontwikkeling en evaluatie van toekomstige

vergelijkbare interventies. Er werd geconcludeerd dat, ondanks een met theorie en bewijs onderbouwde aanpak dat zicht richtte op een hoog-risico populatie, leefstijlgedrag en biologische indicatoren van het risico op HVZ niet konden worden veranderd door een leefstijlinterventie-op-maat bij mensen met FH. Deze resultaten zijn niet in overeenstemming met andere interventie studies gericht op andere hoog-risico populaties. Samenvattend kan worden gezegd dat zowel de onderschatte heterogeniteit van de steekproef en de onvolledige implementatie van de PRO-FIT interventie waarschijnlijk hebben bijgedragen aan het ontbreken van een interventie effect. Er kan worden bevestigd dat cholesterolverlagende statines de meest effectieve behandeling zijn ter reductie van LDL-C waarden bij mensen met FH. Echter het feit dat we geen effect hebben kunnen aantonen van een leefstijlinterventie-op-maat betekent niet dat het bevorderen van een gezonde leefstijl geen additioneel effect kan hebben. Een integrale aanpak om het risico op HVZ te verlagen zal de volgende chronologische stappen moeten bevatten: 1) de screening van mensen met FH, 2) het initiëren van een cholesterolverlagende behandeling, 3) het communiceren van het risico op HVZ en de contributie van (te veranderen) risicofactoren, 4) het optimaliseren van therapietrouw, en 5) het aanbieden van leefstijladvies-op-maat gericht op mensen met FH.

BEDANKT!

Het dankwoord. *Het* sluitstuk van het verhaal. En waar begin je dan?

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ABOUT THE AUTHOR

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Karen Broekhuizen was born on the 30th of December 1979 in Delft, the Netherlands. After graduating from secondary school (Atheneum with beta curriculum) at the Christelijk Lyceum in Delft in 1999, she started her Medicine study at the Leiden University. After receiving her bachelor degree, she started a master in Health Sciences, with a specialisation in Prevention and Public Health. She successfully wrote her master thesis on the investigation of intervention fidelity in the New Life (Style) intervention study and graduated in 2007. In December 2007, she started working as a junior researcher at the Department of Public and Occupational Health at the EMGO+ Institute for Health and Care Research. Her PhD-project was called "Promoting a healthy lifestyle in people with Familial Hypercholesterolemia by an individually tailored lifestyle intervention" and was the start of the PRO- FIT project. Within this project, she developed an individually tailored lifestyle intervention and evaluated its cost-effectiveness in people with Familial Hypercholesterolemia in a randomised controlled trial. This thesis describes the content of the PRO-FIT project. Besides her work as a researcher, she was also involved in teaching activities and followed the postgraduate epidemiology program and several courses on health promotion, teacher professionalisation, and projectmanagement. Throughout the years, she participated as a (chief) editor and journalist in the boards of several popular-scientific magazines. Currently, she is working as a research scientist at TNO in Leiden on different lifestyle-related projects.