

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

($\geq 140/90$ 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 plaques 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).

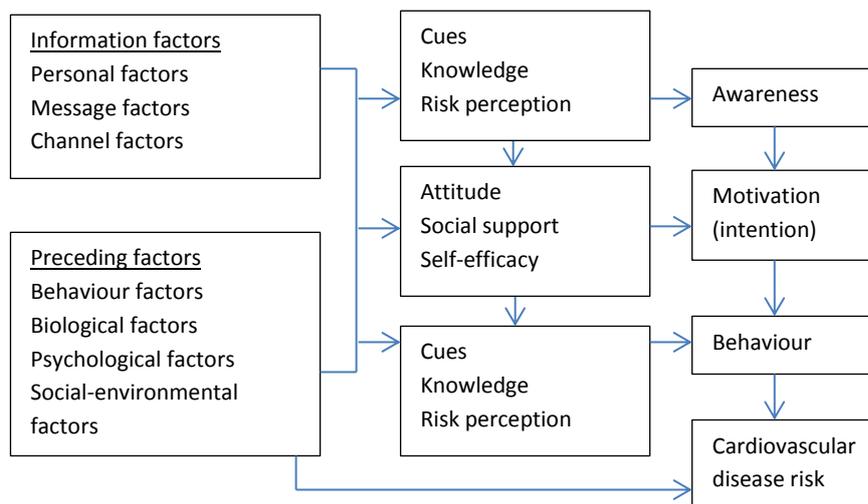


Figure 2: I-Change model 2.0

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

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 measures 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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