DOCTORAL THESES IN FOOD SCIENCES AT THE UNIVERSITY OF TURKU

Promoting Healthy Lifestyles with Personalized, APOE Genotype Based Health Information: The Effects on Psychological-, Health Behavioral and Clinical Factors

HANNA-LEENA HIETARANTA-LUOMA

DOCTORAL THESES IN FOOD SCIENCES AT THE UNIVERSITY OF TURKU
Food Chemistry

Promoting Healthy Lifestyles with Personalized, *APOE* Genotype Based Health Information:
The Effects on Psychological-, Health Behavioral and Clinical Factors.

HANNA-LEENA HIETARANTA-LUOMA

Food Chemistry and Food Development

Department of Biochemistry

TURKU, FINLAND – 2016

Food Chemistry and Food Development
Department of Biochemistry
University Consortium of Seinäjoki
University of Turku

Supervised by

Professor Anu Hopia, PhD
Functional Foods Forum
University of Turku, University Consortium of Seinäjoki
Seinäjoki, Finland

Professor Harri Luomala, PhD
Department of Marketing
University of Vaasa, University Consortium of Seinäjoki
Seinäjoki, Finland

Reviewed by

Professor Atte von Wright, PhD
Institute of Public Health and Clinical Nutrition
Department of Clinical Nutrition
University of Eastern Finland
Kuopio, Finland

Professor Anne-Marie Minihane, PhD
Department of Nutrition
Norwich Medical School
University of East Anglia
Norwich, UK

Opponent

Professor emeritus Matti Uusitupa, MD, PhD
Institute of Public Health and Clinical Nutrition
Faculty of Health Sciences
University of Eastern Finland
Kuopio, Finland

Research director

Professor Baoru Yang, PhD, Professor
Department of Biochemistry
University of Turku
Turku, Finland

ISBN 978-951-29-6401-7 (print)
ISBN 978-951-29-6402-4 (pdf)
ISSN 2323-9395 (print)
ISSN 2323-9409 (pdf)
Painosalama Oy – Turku, Finland 2016

To my family

TABLE OF CONTENTS

ABSTRACT

There is an increasing demand for individualized, genotype-based health advice. The general population-based dietary recommendations do not always motivate people to change their life-style, and partly following this, cardiovascular diseases (CVD) are a major cause of death in worldwide. Using genotype-based nutrition and health information (e.g. nutrigenetics) in health education is a relatively new approach, although genetic variation is known to cause individual differences in response to dietary factors. Response to changes in dietary fat quality varies, for example, among different *APOE* genotypes. Research in this field is challenging, because several non-modifiable (genetic, age, sex) and modifiable (e.g. lifestyle, dietary, physical activity) factors together and with interaction affect the risk of life-style related diseases (e.g. CVD). The other challenge is the psychological factors (e.g. anxiety, threat, stress, motivation, attitude), which also have an effect on health behavior. The genotype-based information is always a very sensitive topic, because it can also cause some negative consequences and feelings (e.g. depression, increased anxiety).

The aim of this series of studies was firstly to study how individual, genotype-based health information affects an individual's health form three aspects, and secondly whether this could be one method in the future to prevent lifestyle-related diseases, such as CVD. The first study concentrated on the psychological effects; the focus of the second study was on health behavior effects, and the third study concentrated on clinical effects. In the fourth study of this series, the focus was on all these three aspects and their associations with each other. The genetic risk and health information was the *APOE* gene and its effects on CVD.

To study the effect of *APOE* genotype-based health information in prevention of CVD, a total of 151 volunteers attended the baseline assessments (T0), of which 122 healthy adults (aged 20 – 67 y) passed the inclusion criteria and started the one-year intervention. The participants (n = 122) were randomized into a control group (n = 61) and an intervention group (n = 61). There were 21 participants in the intervention Ɛ4+ group (including *APOE* genotypes 3/4 and 4/4) and 40 participants in the intervention Ɛ4- group (including *APOE* genotypes 2/3 and 3/3). The control group included 61 participants (including *APOE* genotypes 3/4, 4/4, 2/3, 3/3 and 2/2). The baseline (T0) and follow-up assessments (T1, T2, T3) included detailed measurements of psychological (threat and anxiety experience, stage of change), and behavioral (dietary fat quality, consumption of vegetables, - high fat/sugar foods and –alcohol, physical activity and health and taste attitudes) and clinical factors (total-, LDL- HDL cholesterol, triglycerides, blood pressure, blood glucose (0h and 2h), body mass index, waist circumference and body fat percentage). During the intervention six different communication sessions (lectures on healthy lifestyle and nutrigenomics, health messages by mail, and personal discussion with the doctor) were arranged. The intervention groups (Ɛ4+ and Ɛ4-) received their *APOE* genotype information and health message at the beginning of the intervention. The control group received their *APOE* genotype information after the intervention. For the analyses in this dissertation, the results for 106/107 participants were analyzed. In the intervention, there were 16 participants in the high-risk (Ɛ4+) group and 35 in the low-risk (Ɛ4-) group. The control group had 55 participants in studies III-IV and 56 participants in studies I-II.

The intervention had both short-term (≤ 6 months) and long-term (12 months) effects on health behavior and clinical factors. The short-term effects were found in dietary fat quality and waist circumference. Dietary fat quality improved more in the Ɛ4+ group than the Ɛ4- and the control groups as the personal, genotype-based health information and waist circumference lowered more in the Ɛ4+ group compared with the control group. Both these changes differed significantly between the Ɛ4+ and control groups ($p<0.05$). A long-term effect was found in triglyceride values ($p<0.05$), which lowered more in Ɛ4+ compared with the control group during the intervention. Short-term effects were also found in the threat experience, which increased mostly in the Ɛ4+ group after the genetic feedback ($p<0.05$), but it decreased after 12 months, although remaining at a higher level compared to the baseline (T0). In addition, Study IV found that changes in the psychological factors (anxiety and threat experience, motivation), health and taste attitudes, and health behaviors (dietary, alcohol consumption, and physical activity) did not directly explain the changes in triglyceride values and waist circumference. However, change caused by a threat experience may have affected the change in triglycerides through total- and HDL cholesterol.

In conclusion, this dissertation study has given some indications that individual, genotype-based health information could be one potential option in the future to prevent lifestyle-related diseases in public health care. The results of this study imply that personal genetic information, based on *APOE*, may have positive effects on dietary fat quality and some cardiovascular risk markers (e.g., improvement in triglyceride values and waist circumference). This study also suggests that psychological factors (e.g. anxiety and threat experience) may not be an obstacle for healthy people to use genotype-based health information to promote healthy lifestyles. However, even in the case of very personal health information, in order to achieve a permanent health behavior change, it is important to include attitudes and other psychological factors (e.g. motivation), as well as intensive repetition and a longer intervention duration. This research will serve as a basis for future studies and its information can be used to develop targeted interventions, including health information based on genotyping that would aim at preventing lifestyle diseases. People's interest in personalized health advices has increased, while also the costs of genetic screening have decreased. Therefore, generally speaking, it can be assumed that genetic screening as a part of the prevention of lifestyle-related diseases may become more common in the future. In consequence, more research is required about how to make genetic screening a practical tool in public health care, and how to efficiently achieve long-term changes.

Keywords: *APOE*, attitudes, behavioral, cardiovascular risk markers, changes, clinical, dietary advice, dietary fat quality, genetic information, health behavior, health information, healthy lifestyle, intervention, nutrigenetics, predictors, psychological factors, threat experience, triglycerides, waist circumference

SUOMENKIELINEN TIIVISTELMÄ

Yksilöllisen, geenitietoon pohjautuvan terveysviestinnän tarve on lisääntynyt. Yleiset terveyssuositukset eivät aina motivoi elämäntapamuutoksiin ja osittain tämän seurauksena sydän- ja verisuonitaudit ovat suurin kuolinsyy maailmassa. Genotyyppiin pohjautuvan ravitsemus- ja terveys viestinnän (nutrigenetiikka) käyttö terveyskasvatuksessa on vielä suhteellisen uusi lähestymistapa, vaikkakin tiedossa on, että geneettinen vaihtelu aiheuttaa yksilöllisiä eroja vasteessa eri ruoka-aineisiin. Esimerkiksi, vaste rasvan laadun muutoksiin vaihtelee *APOE* genotyyppien välillä. Tutkimus tällä alalla on haastavaa, johtuen useista ei-muunneltavista (perimä, ikä, sukupuoli) ja muunneltavista (esim. elämätavat, ruokavalio, fyysinen aktiivisuus) tekijöistä, jotka yhdessä ja vuorovaikutuksessa toistensa kanssa vaikuttavat elämäntapasairausten (esim. sydän- ja verisuonitaudit) riskiin. Toinen haaste on psykologiset tekijät (esim. ahdistus, uhka, stressi, motivaatio, asenteet), joilla on myös vaikutusta terveyskäyttäytymiseen. Geenitietoon pohjautuva viestintä on aina hyvin herkkä aihe, koska sillä voi olla myös negatiivisia seurauksia (esim. depressiota, lisääntynyttä ahdistusta).

Väitöskirjatyössä selvitettiin, miten yksilöllinen, geenitietoon pohjautuva terveysviestintä vaikuttaa ihmisten terveyteen kolmella eri osa-alueella ja voiko geenitietoon pohjautuva terveysviestintä olla yksi mahdollinen menetelmä tulevaisuudessa elämäntapasairausten, kuten sydän- ja verisuonitautien ehkäisyssä. Geenitieto ja terveysviestintä pohjautuivat *APOE* geeniin ja sen vaikutuksiin sydän- ja verisuonitautien puhkeamisessa. Vaikutuksia selvitettiin psykologisissa (1. artikkeli), käyttäytymiseen liittyvissä (2. artikkeli) sekä kliinisissä tekijöissä (3. artikkeli). Neljännessä osatutkimuksessa selvitettiin näiden kolmen eri osa-alueen vuorovaikutusta.

Yhteensä 151 vapaaehtoista osallistui ensimmäisiin lähtötaso-mittauksiin. Heistä 122, tervettä, iältään 20–67 -vuotiasta henkilöä hyväksyttiin vuoden kestävään interventio-tutkimukseen. Heidät satunnaistettiin kontrolli- (n = 61) ja interventioryhmään (n = 61), joista 21 osallistujaa oli intervention Ɛ4+ ryhmässä (*APOE* genotyypit 3/4 ja 4/4) ja 40 osallistujaa intervention Ɛ4- ryhmässä (*APOE* genotyypit 2/3 ja 3/3). Kontrolliryhmään kuului 61 osallistujaa (*APOE* genotyypit 3/4, 4/4, 2/3, 3/3 ja 2/2). Lähtö- (T0) ja seurantamittauksissa (T1, T2, T3) oli kyselyjä psykologisista vaikutuksista (uhkan- ja ahdistuksen kokeminen, muutosvaihe), terveyskäyttäytymisestä (rasvan laatu, kasvisten käyttö, runsas rasvaisten ja sokeristen ruokien käyttö, alkoholin kulutus ja liikunta-aktiivisuus) sekä terveys- ja makuasenteista. Mukana oli myös kliinisiä mittauksia (kokonais-, LDL-, HDL kolesteroli, triglyseridit, verenpaine, verensokeri (0h ja 2h), painoindeksi, rasvaprosentti ja vyötärönympärys). Intervention aikana järjestettiin kuusi erilaista viestintätilaisuutta (luentoja terveellisestä elämäntavasta ja nutrigenomiikasta, viestejä sähköpostitse sekä henkilökohtainen keskustelu lääkärin kanssa). Interventioryhmä sai tietää oman *APOE* geenitietonsa intervention alussa, mutta kontrolliryhmä sai tietää sen vasta intervention päätyttyä. Yhteensä 106/107 henkilön tulokset analysoitiin tässä väitöskirjassa. Intervention korkean riskin (Ɛ4+) ryhmässä oli 16 henkilöä ja matalan riskin (Ɛ4-) ryhmässä 35 henkilöä. Kontrolliryhmässä oli 55 henkilöä osatutkimuksissa III-IV ja 56 henkilöä osatutkimuksissa I-II.

Interventiolla oli sekä lyhyt- (≤6 kk) että pitkäaikaisia (12 kk) vaikutuksia terveyskäyttäytymiseen sekä kliinisiin riskitekijöihin. Lyhytaikaisia vaikutuksia huomattiin ruokavalion rasvan laadussa ja vyötärönympäryksessä. Rasvan laatu parani tilastollisesti merkitsevästi enemmän

($p<0.05$) Ɛ4+ kuin Ɛ4- ja kontrolliryhmissä ja vyötärönympärys pieneni enemmän Ɛ4+ ryhmässä verrattuna kontrolliryhmään. Pitkäaikaisvaikutus huomattiin triglysedi-arvoissa, jotka alenivat enemmän Ɛ4+ ryhmässä verrattuna kontrolliryhmään. Lyhytaikaisvaikutuksia havaittiin myös uhkan kokemisessa, joka lisääntyi eniten Ɛ4+ ryhmässä geenitiedon saannin jälkeen ($p<0.05$), mutta väheni 12 kuukauden jälkeen, jääden kuitenkin hieman korkeammalle tasolle verrattuna lähtötasoon (T0). Lisäksi, osatutkimus IV havaitsi, että muutokset terveys- ja makuasenteissa, psykologisissa sekä käyttäytymistekijöissä eivät suoraan selittäneet muutoksia triglyseridissä ja vyötärönympäryksessä. Muutos uhkan kokemisessa saattoi kuitenkin vaikuttaa muutokseen triglyserideissä kokonais- ja HDL kolesterolin kautta.

Väitöskirjatyön tulokset antoivat viitteitä siitä, että yksilöllinen, geenitietoon pohjautuva terveysviestintä voisi olla yksi mahdollinen vaihtoehto tulevaisuudessa ehkäistä elämäntapasairausten puhkeamista myös julkisella sektorilla. Tulokset viittaavat siihen, että henkilökohtaisella *APOE* geenitietoon pohjautuvalla terveysviestinnällä on positiivisia vaikutuksia ruokavalion rasvanlaatuun sekä sydän- ja verisuonitautien riskitekijöihin, kuten triglyserideihin ja vyötärönympärykseen. Väitöskirjatyö osoitti myös, että psykologiset tekijät (ahdistus ja uhkan kokeminen) eivät todennäköisesti ole este geenitietoon pohjautuvan terveysviestinnän käyttämiselle terveillä aikuisilla. Saavuttaakseen kuitenkin pysyvän terveyskäyttäytymismuutoksen, on asenteiden sekä muiden psykologisten tekijöiden (esim. motivaatio) vaikutus otettava huomioon. Myös intensiivinen toisto sekä pidempi intervention kesto ovat tärkeitä seikkoja suunniteltaessa jatkotutkimusta. Tämä väitöskirjatyö tarjoaa perustan jatkotutkimukselle ja sen antia voidaan käyttää hyväksi suunniteltaessa räätälöityjä, geenitietoon pohjautuvaan terveysviestintään perustuvia interventioita elämäntapasairausten ehkäisemiseksi. Ihmisten kiinnostus yksilölliseen terveysneuvontaan on lisääntynyt, samalla kun myös geenitestauksen kustannukset ovat laskeneet. Joten yleisesti ottaen, voitaneen ehkä todeta, että geenitestaus osana elämäntapasairausten ehkäisyä tulee yleistymään tulevaisuudessa ja siksi lisää tutkimusta tarvitaan siitä, miten saada geenitestauksesta ja geenitiedon käytöstä toimiva työkalu julkisessa terveydenhuollossa ja miten saada pitkäaikaisia muutoksia aikaan.

Avainsanat: *APOE*, asenteet, geenitieto, interventio, kliininen, käyttäytymiseen liittyvät tekijät, muutos, nutrigenetiikka, psykologiset tekijät, ravitsemusneuvonta, ruokavalion rasvan laatu, sydän- ja verisuonitautien riskitekijät, terveelliset elämäntavat, terveyskäyttäytyminen, terveysviestintä, triglyseridit, uhkan kokeminen, vyötärönympärys

LIST OF ABBREVIATIONS

AD	Alzheimer disease
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
apoE	Apolipoprotein E
A-state	State-Anxiety
A-trait	Trait Anxiety
BMI	Body mass index
CD	Celiac disease
CHD	Coronary heart disease
CVD	Cardiovascular disease
DNA	Deoxyribonucleic acid
DTC	Direct-to-consumer
EPPM	Extended parallel process model
Ɛ4+	High risk group (include *APOE* 3/4 and 4/4)
Ɛ4-	Low risk group (include *APOE* 2/2, 2/3 and 3/3)
fP-Krea	Creatine (blood test for function of kidneys)
HDL	High-density lipoprotein
HTAS	Health and taste attitude scale
LDL	Low-density lipoprotein
MeS	Metabolic syndrome
p-ALAT	Alanine aminotransferase (blood test for function of liver)
P-TSH	Thyrotropin (blood test for function of thyroid)
RBD	Risk behavior diagnostic scale
RNA	Ribonucleic acid
SNP	Single nucleotide polymorphism
STAI	State-trait anxiety Inventory
TERVAS	Terveelliset valinnat – räätälöidyt syömisen ja liikkumisen mallit

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original articles referred to in the text by their Roman numerals.

I. Hietaranta-Luoma H-L, Hopia A, Luomala H, Puolijoki H (2014) Using *APOE* genotyping to Promote Healthy Lifestyles in Finland - Psychological Impacts: Randomized Controlled Trial. Journal of genetic counseling 1 – 39. doi: 10.1007/s10897-015-9826-8 (Hietaranta-Luoma et al. 2014)

II. Hietaranta-Luoma H-L, Tahvonen R, Iso-Touru T, Puolijoki H, Hopia A (2015a) An Intervention Study of Individual, *APOE* Genotype-Based Dietary and Physical-Activity Advice: Impact on Health Behavior. Journal of Nutrigenetics and Nutrigenomics 161–174. doi: 10.1159/000371743 (Hietaranta-Luoma et al. 2015a)

III. Hietaranta-Luoma H-L, Åkerman K, Tahvonen R, Puolijoki H, Hopia A (2015b) Using Individual, *APOE* Genotype-based Dietary and Physical Activity Advice to Promote Healthy Lifestyles in Finland – Impacts on Cardiovascular Risk Markers. Open Journal of Preventive Medicine. 05/2015. doi: 10.4236/ojpm.2015.55024. (Hietaranta-Luoma et al. 2015c)

IV. Hietaranta-Luoma H-L, Luomala H.T, Tahvonen R, Puolijoki H, Koivusilta L, Hopia A. Using Individual, *APOE* Genotype-Based Dietary and Physical Activity Advice to Promote Healthy Lifestyle: Associations between Psychological-, Behavioral- and Clinical Factors. J Nutrition Health Food Sci 3(4): 1-7. DOI: http://dx.doi.org/10.15226/jnhfs.2015.00151 (Hietaranta-Luoma et al. 2015a)

1 INTRODUCTION

General health recommendations (e.g. eating 500 g vegetables per day, consuming not more than 10E% saturated fat per day and undertaking endurance exercise at least twice a week) do not always motivate healthy people to change their lifestyle (Smith et al. 2004; Lovegrove and Gitau 2008; Minich and Bland 2013). Although these common health recommendations have been promoted globally for many years, lifestyle-related diseases (e.g. cardiovascular diseases (CVD)), are still the main cause of mortality and morbity in Finland, as well as worldwide (Vartiainen et al. 2010; Ordovás and Smith 2010; Borodulin et al. 2014) One reason can be the individual differences in responding to dietary changes because of nutrient-gene interactions (Kohlmeir 2013). A new approach and tool could be genotype-based nutrition and health information (e.g., nutrigenetics) that aims to affect health behavior and lower the risk of lifestyle-related diseases (e.g., obesity, diabetes, cardiovascular diseases) (Ong and Pérusse 2011). Currently, several commercial companies already offer genetic testing to the public (Bloss et al. 2011; Voils et al. 2012). However, genetic screening in the prevention of lifestyle-related diseases is not routine practice in public health care, which can be due the lack of know-how among health care professionals, the lack of resources, and the expense of the tests (Mountcastle-Shah and Holtzman 2000; Taloustutkimus Oy and The Finnish Innovation Fund 2013). In addition, a lack of clear guidelines and uniform policy is an obstacle to using genetic screening in public health care in Finland (Taloustutkimus Oy and The Finnish Innovation Fund 2013).

The number of studies focusing on using genetic information to promote lifestyle changes is limited (McBride et al. 2010) and the results have been contradictory (Harvey-Berino et al. 2001; Marteau et al. 2004; Frosch et al. 2005; Chao et al. 2008; Bloss et al. 2011; Markowitz et al. 2011). Marteau et al. (2010) found, in their review that genetic information did not generally motivate people to stop smoking or increase exercising, but it may have some favorable effects on diet and lifestyle (Marteau et al. 2010). The challenges to this research field emphasizes the multifactorial nature of lifestyle-related diseases (e.g. cardiovascular disease (CVD)), because they are influenced by many environmental, modifiable (e.g. unhealthy dietary habits, physical inactivity, smoking) and also genetic, non-modifiable factors (Raitakari et al. 1995; O'Neil et al. 1997; Ma et al. 2000; Lusis 2000; Schuit et al. 2002; Cho et al. 2009). Individuals are known to differ as regards gene-nutrition interactions, therefore another challenge is to target tailored health messages and develop targeted interventions and strategies that provided the best nutrition to the largest number of individuals (Kohlmeir 2013). There are several genes, which are known to affect our response to dietary components, especially dietary fat intake and dietary fatty acid composition while affecting the risk of metabolic diseases (Phillips 2013; Wetterstrand 2014). However, probably the most studied

dietary fat-gene interaction is related to the *APOE* gene. *APOE* has three major alleles: ε2, ε3, and ε4 and several studies have shown that carriers of *APOE* 4 allele have better response to dietary fat changes than other allele carriers, but at the same they have a higher blood cholesterol content and an increased risk of cardiovascular diseases than the carriers of other alleles (Masson et al. 2003; Minihane et al. 2007). However, controversial results have also found no connection at all between the different *APOE* genotypes and dietary fat (Minihane et al. 2000; Egert et al. 2010).

In addition to the multifactorial nature and targeting challenges, some challenges of using genetic screening also produce possible harmful psychological effects like fatalism, anxiety, depression, threat, and stress (Heshka et al. 2008; Collins et al. 2011); all of these may have an effect on health behavior. Usually, these psychological effects occurs quite soon after the genetic feedback, even within a few days or weeks, but these effects have been shown to be short-term (Heshka et al. 2008; Collins et al. 2011). In addition, genetic information, although individual, can also have a broader effect, affecting the whole family if the risk for the disease can be inherited (Marteau & Weinman 2006; Peterson 2005).

In this series of studies, the possibility to promote healthy lifestyles by genotype-based, personalized health information was investigated. The health information was tailored made and based on a real threat (measured *APOE* genotype) and an experience threat (measured by risk behavior diagnostic scale (RBD)) (Witte 2001). An Extended Parallel Process Model (EPPM) was used to create health messages (Witte 2001). The focus of the intervention was the effects on the psychological factors (state-anxiety, threat experience, stage of change), health behavior (dietary fat quality, consumption of vegetables, berries, fruits; consumption of alcohol and fatty and sugary foods; physical activity; health and taste attitudes), and cardiovascular risk markers (serum lipids, blood glucose, blood pressure, body mass index, waist circumference, fat percentage).The intervention included both an active communication period (during the first 6 months) and a follow-up period (during the last 6 months), during which the participants received no health communication from the research group. Secondary analyses were completed to clarify associations between different lifestyle factors (psychological, behavioral, and clinical). To best of the author's knowledge, no fully comparative studies using personalized health information based on the *APOE* genotype with an aim to promote a healthy lifestyle and lower CVD risk have been published to date. Concentrating on one health aspect at time: (1) psychological, (2) health behavioral and (3) clinical, was important to achieve the best possible benefit and understanding of this unique, very interdisciplinary research topic.

2 REVIEW OF THE LITERATURE

The review of literature is based on intervention research. The first chapter (2.1 Changing health behavior) describes the theory behind health behavior change and focuses more on the conceptual issues of this dissertation. The second and third chapter (2.2 Genetic testing for preventive purpose in lifestyle related diseases) (2.3 Nutrigenomics) focus more on the tools and methods to achieve health behavior change. The fourth chapter describes the actual risk factors (2.4 Cardiovascular diseases (CVD)), and the targets of health behavior change. The last chapter (2.5 Previous studies utilizing genetic testing to achieve nutrition- and clinical related changes) describes the previous studies and outcomes of using these tools to achieve health behavior change.

2.1 Changing health behavior

2.1.1 Definition of health behavior

Health behavior is a broad concept including the actions of individuals, groups and organizations, as well as background factors and consequences and it can be defined as a typical, individual model of choices in health related issues. Health behavior reflects a person's health beliefs, which usually means our lifestyle choices (e.g. dietary, smoking, physical activity, alcohol consumption).The definition also covers social change, policy development and implementation, improved coping skills, and an enhanced equality of life. (Glanz et al. 2008) Gochman (1997) has defined *health behavior* as “those personal attributes such as beliefs, expectations, motives, values, perceptions, and other cognitive elements, personality characteristics, including affective and emotional states and traits, and overt behavior patterns, actions, and habits that relate to health maintenance, to health restoration, and to health improvement” (Gohman 1997). According to Kasl and Cobb (1966a, 1966b) *health behavior* can also be divided to three categories: *(1) preventive health behavior, (2) illness behavior and (3) sick-role behavior* (Kasl and Cobb 1966a; Kasl and Cobb 1966b). The preventive health behavior was the focus of this dissertation study.

According to Salmela et al. (2010) health behavior change requires an individual to desire to change her/his behavior as well as environmental support for the change. There should not be obstacles in the environment to making a change, and the individual has to have the possibility and resources to change his/her health behavior (Salmela et al. 2010). In addition, the values and benefits of the change affect whether the individual is capable of making a change (Witte 2001).

2.1.2 Definition and characteristics of health communication

Health communication is the study and use of different methods to advice and affect the decisions of individuals and society to improve health by making health behavior changes (Freimuth and Quinn 2004). *Health communication* can be based on facts, emotions or experiences and it can be either factual or fictional (Torkkola 2002). The focus of *health communication* is usually placed on changing existing health behavior (Fitzgibbon et al. 2007) and proposing actions described in the health message. There are several strategies in the planning and implementation of health communication, depending on the aims of the communication (Hornik and Kelly 2007). The utilization of emotions in health communication has been a popular strategy over the past decades (Witte and Allen 2000; Fishbein and Cappella 2006) and it was also utilized in this present study. The *health communication* can be based on intimidation, if the health threats are individually modifiable (Ruiter et al. 2003). An emotion based *health communication* is more persuasive than one without emotions (Keller et al. 2002; Keller et al. 2003).

The planning and phrasing of the health message is important in order to produce the emotions necessary to motivate the health behavior changes. Chronology, persuasion, cogency, and appearance are critical points in the health message. The proposed change has to be described clearly and minutely in the message. In the emotion based *health communication* it is quite common to use a clearly described action instead of general recommendations (e.g. walk for 20 minutes a day NOT do more exercise) (Fitzgibbon et al. 2007).

2.1.3 Health behavior change theories

There is a wide spectrum of health behavior theories, which aim to explain the reasons for people's health behavior and how to influence health behavior (Glanz et al. 2008; Salmela et al. 2010). These theories can explain one or several factors in health behavior (e.g. motivation, attitude, intention) (Noar et al. 2007). However, nowadays there is no single correct theory or framework that governs the research and practice (Glanz et al. 2008). Instead of one single theory, it is possible to choose elements from several different theories for research work in order to further increase the understanding of health-related behaviors (Glanz et al. 2008).

Despite this current trend of combining theories, there are some health behavior theories or models which are the most popular (e.g. *Health Belief Model, Social Learning Theory, Social Cognitive Theory, Theory of Reasoned Action, Theory of Planned Behavior* and *The Transtheoretical Model/ Stages of Change)* (Glanz et al. 2008). These theories are cognitional-, behavioral or motivational based (Glanz et al. 2008). In addition, the other health behavior trend can be found in the so called *Fear Appeal Theories* (Witte 2001). The first fear appeal theory was *Fear-as-Acquired Drive Model,* which originated in the 1950s (Witte 2001). The other purely fear appeal theories were *the Parallel Process Model,* created by Leventhal (1970) and the *Protection Motivation Theory*, created by Rogers (1975) (Witte

2001). These theories suggest that a moderate amount of fear lead to the greatest health behavior change and they are based on creating risk message (Witte 2001).

In this dissertation, the *Extended Parallel Process Model (EPPM)* was used, which is based on one of the most widely used theories, the *Health Belief Model* and one of the fear-appeal theories the *Protection Motivation Theory. The Health Belief Model* contains several similar concepts (susceptibility, seriousness, benefits and barriers to a behavior, cues to action, and self-efficacy) to the *EPPM,* which predict peoples' actions in preventing, screening for, or controlling sickness conditions (Rosenstock 1974; Janz and Becker 1984). According to the *Protection Motivation Theory,* the motivation or intention to implement behavior change depends on two different, individual processes: (1) threat assessment and (2) evaluation of survival (Rogers et al. 1983). It is the first theory that also includes health communicating (Rogers et al. 1983).

The limitation of *the Health Belief Model* is that it is a purely cognitively based model and does not consider the emotional component of behavior (Glanz et al. 2008). The model does not take account fear and threat, which have been noticed to significantly predict perceived risk, benefits, self-efficacy, and actual behavior (Glanz et al. 2008). According to Witte (1992) fear is an essential part of health-related behavior, and he defines it as a negative emotion accompanied by a high state of arousal (Witte 1992). On the other hand, the traditional *Fear-Appeal Models* do not place much credence on people's self-efficacy, motivation and the way in which people initially process risk messages (Witte 2001). In contrast to the conventional *Fear-Appeal Models, EPPM* suggests that two appraisals act consequently (Witte 2001). First, the threat appraisal must generate a particular perceived threat before people even consider the recommended response in the efficacy appraisal (Witte 2001). In addition, EPPM makes distinction between threat and fear, as well as the danger control process and the fear control process (Witte 2001).

Extended Parallel Process Model (EPPM) (Fig. 1)

EPPM was created at the beginning of the 1990s, and it is a combination of the previous theoretical perspectives, mainly based on the Health Belief Model and Protection Motivation Theory (Witte 2001). The Bandura's self-efficacy concept is also used in EPPM (Bandura 1977) (Witte 2001). EPPM combines elements from fear appeal and behavioral change theories to explain the different responses to health threats (Witte 2001).

According to the Extended Parallel Process Model (EPPM), people's reaction towards a health communication depends on four things: How threatening and seriously people perceived the disease, how susceptible they are to the disease, how great their self-efficacy is to implement the proposed method (for example: I am able to exercise regularly in order to prevent cardiovascular disease), and how efficient people consider the proposed method (for example: Doing exercise regularly prevents cardiovascular disease) (Witte 2001). According

to EPPM a health message works when it brings about a suitable amount of fear, but at same time allows the individual to feel that he/she has enough self-efficacy to observe the proposed action (Witte 2001). As long as self-efficacy and response efficacy are more powerful feelings than fear and susceptibility then the health message is working correctly. In this ideal situation, people work with the danger instead of the fear and they are able to act to prevent the threat (e.g. cardiovascular disease threat). (Witte 1992)

There are a few studies which have utilized the EPPM model and usually, the threat has been some disease (e.g. cancer, AIDS, CVD, Asthma or Influenza) (Witte 1991; Witte et al. 1998; McKay et al. 2004; Goei et al. 2010; Prati et al. 2012; Krieger and Sarge 2013). Further, Wong & Cappella used smoking as a threat (Wong and Cappella 2009). To the best of the author's knowledge, the study of McKay et al. (2004) is reportedly the only study so far (in addition this dissertation) to use EPPM in the context of CVD risk. Their recommended response was to increase the consumption of B-vitamin-rich foods and multivitamins. The health threat was CVD. Their outcomes were promising, although they had several limitations in their data. (McKay et al. 2004). For example, those participants who received a high efficacy message, had a higher food response and vitamin response efficacy and in addition, they had higher scores for their vitamin attitude compared to the group who received a low efficacy message (McKay et al. 2004).

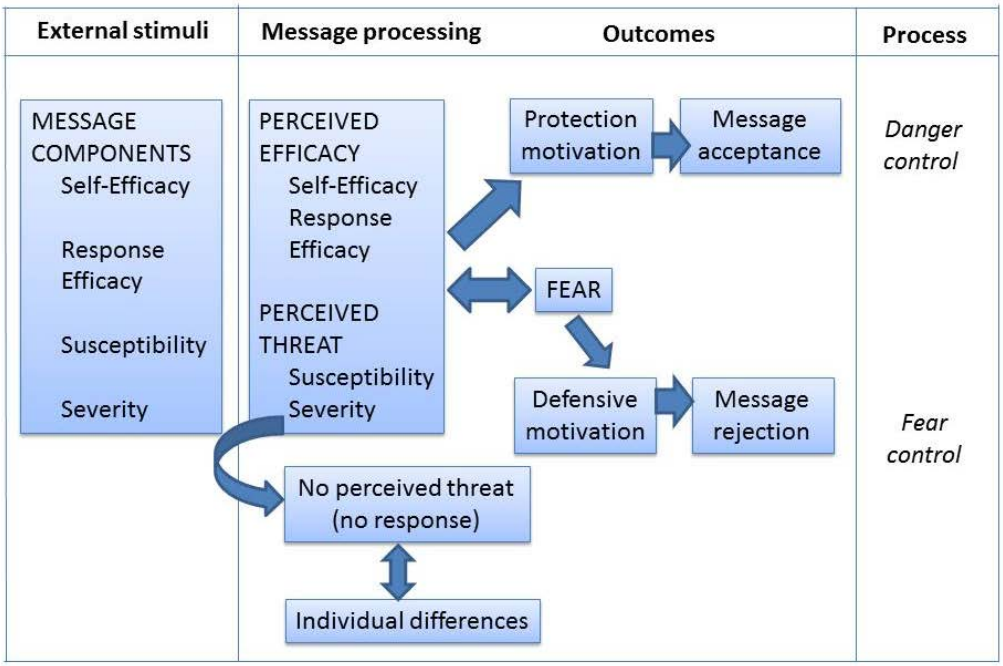

Figure 1. The Extended Parallel Process Model (EPPM) (according to Witte et al. 2001).

Health and taste attitudes

The basic assumption behind the concept of attitudes and health behavior is that attitudes in some way guide, influence, direct, shape, and predict health behavior (Kraus 1995). However, despite several previous studies over the last decade propounding different aspects of the attitude-behavior-link, it is still questionable, how much these attitudes and beliefs about diet and lifestyle affect our responses to dietary recommendations (Glasman and Albarracín 2006; Hearty et al. 2007; Smith et al. 2008). There are few basic facts which have an effect on how the attitude-behavior-link works. First of all, attitudes, which people hold with the confidence, predict behavior better than ambivalent or inconsistent ones (Glasman and Albarracín 2006; Hearty et al. 2007). In addition, easily recollected attitudes (accessibility) predict behavior better than attitudes that are difficult to recall and attitudes based on direct experience promote greater attitude-behavior consistency than those based on indirect experience (Kraus 1995). According to Kraus et al. (1995) and Cooke & Sheeran's (2004) accessibility and stability are the most important aspects of attitudes as regards affecting health behavior (Kraus 1995; Cooke and Sheeran 2004). The stability of information associated with attitudes may increase attitude-behavior correspondence (Doll and Ajzen 1992).

Moreover, health and taste attitudes have been shown to have an effect on health behavior (Hearty et al. 2007; Roininen et al. 2001; Zandstra et al. 2001) as permanent lifestyle change demands continuous work and usually requires several changes at the same time. Health-related attitudes especially have proved to be good predictors of healthy food choices in the diet (Zandstra et al. 2001; Roininen et al. 2001; Hearty et al. 2007). However, some studies have found no connection between health related attitudes and health behavior (Lloyd et al. 1993; Barker et al. 1995). Lloyd et al. (1993) observed that participants with a high-fat diet had similar attitudes to dietary changes compared with participants who had a low-fat diet ((Lloyd et al. 1993). Some studies have found that by affecting parental eating attitudes it is possible to attain good and stable changes in children's health behavior (Talvia et al. 2011). Eating behavior and food choices are established early in life and they have a long-term impact (Mikkilä et al. 2005). Talvia et al. (2010) found in their longitudinal, child-oriented dietary intervention, that a parental high *general health interest* was associated with dietary indicators of healthy eating (e.g., low intake of saturated fat, high intake of fiber, and high consumption of vegetables and fruits). This also had an effect on the children's dietary quality (Talvia et al. 2011).

Furthermore, health-related attitudes vary between different countries, socioeconomic status, gender, and age (Kearney et al. 1998; Roininen et al. 2001; Hearty et al. 2007; Biltoft-Jensen et al. 2009; Talvia et al. 2011). Some previous studies have shown that Americans were the most health- and the least pleasure-oriented and French the least health- and the most pleasure-oriented, while Belgian and Japanese participants were between these two groups (Glanz et al. 1997; Rozin et al. 1999). Glanz et al. (1997), for example, noticed that Americans

were more realistic in estimating their dietary fat than the Dutch (Glanz et al. 1997). In addition, literature has shown that women, older people, and those who are more highly educated usually have a more positive attitude toward health-related issues (Kearney et al. 1998; Roininen et al. 2001; Hearty et al. 2007; Biltoft-Jensen et al. 2009; Talvia et al. 2011), and that aging increases interest in health and nutrition, partly due to disease avoidance (Olsen 2003).

2.2 Genetic testing for preventive purpose in lifestyle related diseases

Although health education and general health recommendations—related to healthy eating, exercise and non-smoking—have been promoted globally for many years, there is a considerable challenge in tailoring this information to individuals (Kreuter et al. 1999). Lifestyle related diseases (e.g. CVD) are still a major cause of death in Finland and worldwide, and genetic factors in combination with the an individual's own lifestyle choices (e.g. dietary habits, physical activity, smoking) affect the risk for CVD (Vartiainen et al. 2010; Ordovás and Smith 2010; Borodulin et al. 2014). Partly because of this there is a need for individualized information and new tools to promote healthy lifestyle changes (Gramling et al. 2003; Smith et al. 2004). Genetic information, including susceptibility to illness, is one method to motivate people to change unhealthy lifestyles (Lovegrove and Gitau 2008). Genetic information can act as a motivator if a person already has a risk factor for a disease (e.g., high cholesterol, overweight) and they want to change their health behavior in a relatively easy way (Fishbein and Cappella 2006; Stewart-Knox et al. 2009). Both the genetic susceptibility and the already existing risk factor (e.g. high cholesterol) can together increase the disease threat (e.g. CVD) and motivate further the need for lifestyle changes. However, the number of threat experiences should be moderate, and not induce fear (Witte 1992). The use of genetic profiling and providing risk information is intended to provoke people into being concerned about their lifestyles.

2.2.1 Definition and categories of genetic testing

The official definition of genetic testing varies between countries, context, tested material, method, and purpose. There are often overlaps with the term "genetic testing", "genetic information" and "genetic counseling" and there is no standard definition (Varga et al. 2012). However, according to the European Commission (2004) the genetic testing is the analyses performed on human DNA and RNA, genes and chromosomes to identify inheritable or acquired genotypes, mutations, phenotypes, or karyotypes that can cause a specific disease or conditions (European Commission 2004). Another general and more technical definition is for example in Hungary: "Genetic test is a laboratory test aimed at disclosing DNA and/or

chromosome variations and their specific protein products, which are accompanied by or predict effects that have an adverse influence of human health. Types of genetic test include diagnostic, presymptomatic, predictive, heterozygote and prenatal tests. Genetic screening is a wide-range programmed genetic test provided to a population or a group of population for the purpose of identifying certain genetic characteristics in asymptomatic persons" (Varga et al. 2012).

The methods used for genetic screening also create some challenges to giving a precise definition. Molecular genetic tests (or gene tests) study single genes or short lengths of DNA to identify variations or mutations that lead to a genetic disorder (Kohlmeir 2013). Chromosomal genetic tests analyze whole chromosomes or long lengths of DNA to see if there are large genetic changes, such as an extra copy of a chromosome, that cause a genetic condition (Kohlmeir 2013). Biochemical genetic tests study the number or activity level of proteins; abnormalities in either can indicate changes to the DNA that result in a genetic disorder (Kohlmeir 2013).

Genetic testing can be either diagnostic or predictive testing (Evans et al. 2001). A diagnostic test is similar to a conventional medical test, such as a basic blood count, as they both give information about a current condition (Aktan-Collan 2001). In contrast, predictive genetic testing provides information about the probability of contracting the disease, with uncertainty (Aktan-Collan 2001). In lifestyle related diseases, (e.g. CVD) the result of genetic testing gives only the susceptibility to contract a disease. Several factors (e.g., biological, learned, sociocultural, material-economic) affect the onset of life-style related diseases.

There are several options when performing the genetic testing. Traditionally (pathological) genetic testing includes diagnostic, screening, and predictive tests for a disease (e.g. looking for breast cancer or Alzheimer disease) (Nyrhinen 2007; Kohlmeir 2013). These are usually done in health care situations with a doctor and a genetic counselor. The new area is in nonpathological testing (e.g. nutrigenetic tests). It is possible to discover the interactions between diet and genotypes on health and disease by nutrigenetic testing. These tests are usually commercial or direct-to-consumer testing. The commercial tests are done for profit and it can be either pathological or nonpathological (Kohlmeir 2013). The difference in the direct-to-consumer tests is that there is a physician or genetic counselor involved in the process. The direct-to-consumer tests do not offer a possibility of genetic counseling and an individual is alone with the genetic testing results. In addition, the nutritional advice given with the tests is very general without any emotional support. (Kohlmeir 2013) Predictive, nutrigenetic testing was used in this dissertation.

2.2.2 Definition of genetic information

Genetic information has certain properties, which distinguishes it from other health information. Human genetic data has a special status, because genetic information, although personal can reveal future health risks and also affect the whole family, particularly as the risk for a disease can be inherited (Peterson 2005; Marteau and Weinman 2006; Nyrhinen 2007; Kohlmeir 2013). Genetic information includes information about an individual's and also their family members genetic tests, their medical history, the individual's request for, or receipt of genetic services, or participation clinical trials with the genetic testing (Kohlmeir 2013). The term 'genetic information' does not have an established definition, but it covers the all information about an individual's genome. The genome alone or in combination with the environmental factors can influence risk of the disease. The genetic information is the hereditary information about genes, gene products or other inherited characteristics contained in chromosomal DNA or RNA that are derived from individual, families or population s (Kohlmeir 2013). The *raw* genetic information is the particular genetic variants (e.g. Taq1 t (rs731236) or/and gene sequence (e.g. CCCATAGGAACA…). The *derived* genetic information consists of the explanation and meaning of the raw genetic information (e.g. …you have susceptibility to higher cholesterol). The derived genetic information reports only on the information an individual is tested for, not any extra results, which may not have any meaning for the individual or they do not necessary want to hear (e.g. … susceptibility to Alzheimer disease). (Kohlmeir 2013) In this dissertation the term 'genetic information' was used to define derived genetic information.

2.2.3 Genetic counseling

The definition of genetic counseling has been described as follows: "The genetic counseling is the process of helping people to understand and adapt to the medical, psychological, and familial implications of genetic contributions to disease. There are three steps in this process: "(1) interpretation of family and medical histories to assess the chance of disease occurrence or recurrence, (2) education about inheritance, testing, management, prevention, resources and research, and (3) counseling to promote informed choices and adaptation to the risk or condition." (Resta et al. 2006)

This definition does not determine who is qualified to give genetic counseling. Nowadays, the trend is that healthy individuals, who want to learn about their genotype, for example, in order to diminish anxiety, uncertainty, or make personal and medical decisions, need genetic counseling. This creates opportunities as well as challenges for many physicians and doctors in a growing, preventive genetic testing field; this is because there is a lack of know-how among health care professionals and a lack of resources (Mountcastle-Shah and

Holtzman 2000; Taloustutkimus Oy and The Finnish Innovation Fund 2013). Genetic counseling requires a team effort from a number of different fields, such as nutrition, dietetics, genetics, biochemistry, and molecular biology (Juma et al. 2014).

2.2.4 Psychological and ethical aspects of genetic testing

As genetic testing can either reveal a susceptibility to or a decreased risk for a disease, or be neutral, the psychological and ethical issues are also of concern when receiving results. Genetic information, although personal, can also affect the whole family, particularly as the risk for a disease can be heritable (Marteau & Weinman 2006; Peterson 2005).

In several previous studies, genetic information has been related to harmful psychological effects like fatalism, anxiety, depression, threat, and stress (Heshka et al. 2008; Collins et al. 2011). These psychological effects can occur quite soon after the genetic-risk feedback is given, even within a few days or weeks, but these changes usually also disappear quickly (Heshka et al. 2008; Collins et al. 2011). The genetic risk information can cause stress and anxiety, but at the same time it may alert people to the potential impact of their lifestyle choices, give hope and strengthen will and commitment (Aatre and Day 2011). The genetic information can also cause a sense of relief for a non-carrier, so it may also have some unfavorable consequences for the health-related behavior of those with a low risk. It can provide an explanation for their unhealthy lifestyle because there is no recognized genetic susceptibility to the disease (Lerman et al. 1997; McBride et al. 2002; Ito et al. 2006; Marteau and Weinman 2006; Lovegrove and Gitau 2008).

In addition, the timing of the dissemination of genetic information has been shown to affect psychological responses. In the context of intense emotion and threat experience, people may not understand the genetic information and the risk properly, particularly if the results are opposite of those they expected (Smith et al. 2004; Heshka et al. 2008; Sanderson et al. 2009). At the same time, threat can be felt to be too frightening or too minor, depending on the emotional context (Smith et al. 2004; Heshka et al. 2008; Sanderson et al. 2009).

In the context of genetic testing, four ethical principles have often described: the principles of autonomy, privacy, equality, and beneficence (Nyrhinen 2007). These principles emphasize the importance of informed consent, which means that individuals have the right to be informed, or not to be informed, have the right to privacy and confidentiality, and the right to control their own information (Teicher-Zallen 2009; Gefenas et al. 2011; Kohlmeir 2013). There are only a few situations where the genetic testing is compulsory (e.g. paternity testing in newborn child) (Kohlmeir 2013), otherwise, individuals have the freedom to choose whether they receive the results of gene test (Kohlmeir 2013). Other important ethical issues are clinical efficacy of revealing susceptibility to a disease, for which there is no treatment (e.g. Alzheimer disease), misdiagnoses (false positives or false negatives), misinterpretation of genetic results, too much unnecessary information and misuse of genetic information (e.g.

education, employment, insurance) (Lovegrove and Gitau 2008; Gefenas et al. 2011; Kohlmeir 2013). One concern is the lack of health literacy skills, because genetic information is not always fully understood and there are differences in how people interpret and understand their results (Henneman et al. 2002; Marteau et al. 2004; Lillie et al. 2007; Claassen et al. 2010; McBride et al. 2010). The consultation and information are important, because they have a significant impact on the understanding of gene results and the experience of worry (Henneman et al. 2002).

2.3 Nutrigenomics (Fig.2)

Nutrigenomics is a recently launched multidisciplinary research field, which focuses on many aspects; complex gene-environment interactions, the effects of nutrients on these interactions, the mechanism behind these nutrient effects and genotypes, and how these interactions affect the balance between health and disease (DeBusk 2009). The use of genotype-based nutrition and health information that aim to affect health behavior and lower the risk of lifestyle-related diseases (e.g., obesity, diabetes, cardiovascular diseases) is a relatively new approach in health education (Smith et al. 2004; Lovegrove and Gitau 2008; Ong and Pérusse 2011).

Nutrigenomics and nutrigenetics are defined as the science of the effect of genetic variation on dietary response and the role of nutrients and bioactive food compounds in gene expression (Ordovas and Corella 2004; Trujillo et al. 2006; Kaput 2008; Corella and Ordovas 2009; Ferguson 2009; Simopoulos 2010). There is also a difference between the definitions of 'Nutrigenetics' and 'Nutrigenomics'. Nutrigenetics is a science that explores the interactions of our inherited genome and nutrition (dietary responses) and the use of this information in practice (Simopoulos 2010; Kohlmeir 2013). The term 'nutrigenetics' was used for the first time by Dry R. O Brennan in 1975 (Farhud et al. 2010). Nutrigenomics is a broader concept, which includes all genetic differences (nutrigenetics), and also gene regulation by nutrients, gene expression and epigenetics (effects of DNA and RNA modifications on gene properties and behavior) (Simopoulos 2010; Kohlmeir 2013).

There is wide spectrum of genetic-dietary interactions. Genetic differences are known to affect almost every nutrient metabolism in some way (protein-, carbohydrates-, lipids-, sterols-, minerals-, vitamins-, trace elements-, alcohol metabolism) and disorders or deficiencies in a gene may cause health problems, which vary in severity. In phenylketonuria disease, for example, conversion of phenylalanine to amino acid L-tyrosine is defective, which leads to an accumulation of phenylalanine in blood (Kohlmeir 2013). Tyrosine is needed for the synthesis of proteins, compounds acting neurotransmitters, hormones (adrenaline, noradrenaline and dopamine), and melanin (Kohlmeir 2013). Excessive amounts of phenylalanine metabolites and a deficiency of tyrosine cause irreversible damage to the central nervous system (Kohlmeir 2013). However, fortunately all these deficiencies in genetic-dietary interactions are not so harmful. In lactose-intolerance disorder, for example, the gene (*LCT* gene), which

encodes the lactose-digesting enzyme (*Lactase*) is missing or is not working completely (Kohlmeir 2013). Several other genes' polymorphs can also affect the property of lactose intolerance. A mutation in *MCM6* gene, for example, enables people to tolerate lactose and dairy products and it is common in Europe (Kohlmeir 2013). The lactose-intolerance disorder causes abdominal cramps, bloating, or diarrhea, when drinking milk with lactose. The world-wide prevalence of lactose-intolerance disorder is 60-70 % and it is very common in Finland (Kohlmeir 2013).

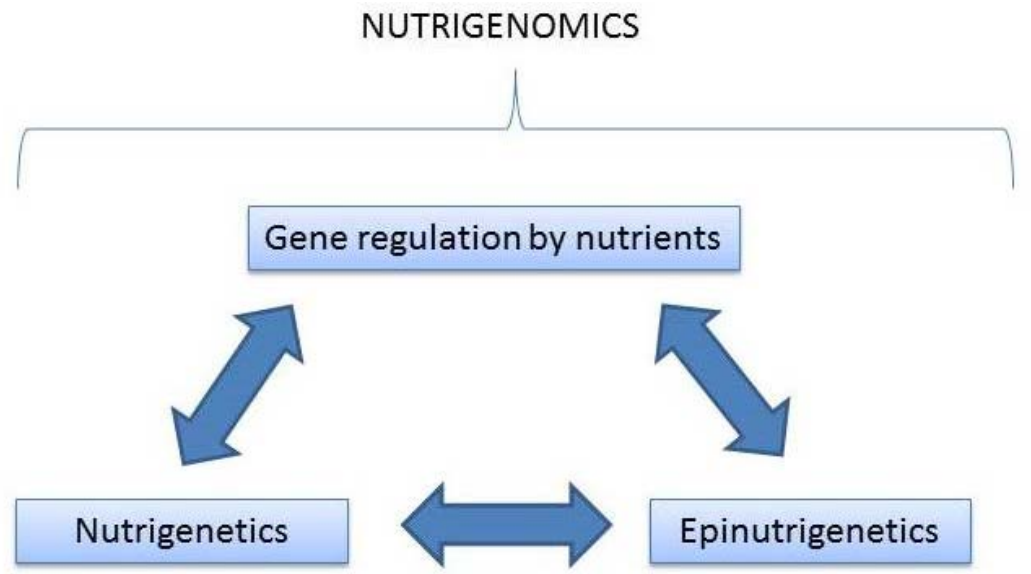

Figure 2. Nutrigenomics (according to Kohlemeir 2013).

2.3.1 Nutrigenomics in lipid and cholesterol metabolism

In the past few decades nutrigenomics has concentrated on lipid and cholesterol metabolism, especially those genetic differences which predispose to obesity, higher cholesterol, and metabolic syndrome (MeS) (Kohlmeir 2013). The research in this field is relatively new compared with carbohydrate- or protein metabolism and evidence, the effects of genetic variations on heterogeneity in lipid responses is still limited, but suggestive (Koriyama et al. 2012; Kohlmeir 2013). However, the research in this field is increasing and will continue to do so in the future. This is because chronic diseases (e.g. cardiovascular diseases) are a major cause of death worldwide and lipid and cholesterol metabolism have a central role in preventing these diseases (Lovegrove and Gitau 2008; Koriyama et al. 2012). Multiple genes, rather than one single gene, together with environmental factors and especially the mechanism of dietary components in lipid metabolism are currently popular research topic, and will also be in the future (Koriyama et al. 2012).

Although the evidence is limited, there is wide spectrum of genetic variants which have observed to affect the response to dietary fat and sterol intake and only a few that are the most known are presented in this dissertation study. Genes, *CD36* and *FTO*, for example, have been associated with obesity (Keller et al. 2012; Moleres et al. 2012). The response toward saturated fat differs between *CD36* and *FTO*-gene variants. Lack of the *FTO* variant (rs9939609), for example, may protect from obesity, even if an individual eats considerable amounts of saturated fat (Moleres et al. 2012). In addition, the *APOA2* gene has been found to have a role in protecting against the development of metabolic syndrome (Smith et al. 2012). This protection effect varies between different variants and especially in carriers with the *APOA2 – 265C/C* genotype, low saturated fat intake has been associated with the lower BMI than other genotypes (Smith et al. 2012).

Several genes also have functions in cholesterol metabolism (e.g. *APOE*, *APOA1, APOA4, APOB*, FADS, *MTP, MTTP (-493T/T), ABCG5*) (Koriyama et al. 2012; Kohlmeir 2013). These genes have several variants, which may either have or not have an effect on LDL or HDL cholesterol and the data is still partly contradictory on this point (Koriyama et al. 2012; Kohlmeir 2013). The findings are mainly based on individual studies, for example high polyunsaturated fatty acid (PUFA) has been associated with the higher HDL cholesterol concentration among *APOA1 – 75A* carriers (Ordovas et al. 2002), and carriers with the *FADS1* (rs174546, T-allele) tended to have about 5 % lower serum cholesterol concentration, if their dietary alpha-linoleic acid (ALA) was greater than 1.4 g/day (Dumont et al. 2011). In addition, the gene *ABCG5* with the two C-alleles have been associated with higher blood cholesterol concentration compared with the carriers of G-alleles (Herron et al. 2006) and *APOA4* 360His variant carriers have a decreased cholesterol response to cholesterol intake (Ordovas et al. 1995).

Nutrigenetics and APOE gene

Overall, the most studied gene in dietary fat response and cholesterol metabolism is *APOE* gene (Minihane et al. 2007; Lovegrove and Gitau 2008), and it is the most convincing. The response of individuals to dietary fat varies (Masson et al. 2003; Minihane et al. 2007) and this heterogeneity is partly dependent on three major *APOE* alleles ε2, ε3 and ε4 (Lovegrove and Gitau 2008). The apolipoprotein (apoE) contains 299 amino acids and it has many functions in cholesterol and lipoprotein metabolism (e.g. low-density (LDL)-, high-density (HDL)- and very low-density (VLDL) lipoprotein and chylomicron metabolism) (Koriyama et al. 2012). The apoE binds several lipoprotein receptors (Koriyama et al. 2012). There is evidence that *APOE* 4 carriers usually have a higher blood cholesterol content and an increased risk for cardiovascular diseases than the carriers of other alleles (Masson et al. 2003;

Ordovas and Corella 2004; Minihane et al. 2007), but on the other hand they are more responsive to changes in dietary fat than other *APOE* carriers (Masson et al. 2003; Ordovas and Corella 2004; Carvalho-Wells et al. 2012).

Several studies have found a difference in LDL cholesterol level between ε2 and ε4 alleles, the level being higher among carriers of the ε4 allele (Kuusisto et al. 1995; Pablos-Méndez et al. 1997; Bercedo-Sanz et al. 1999; Minihane et al. 2000; Corella et al. 2001; Beilby et al. 2003; Marques-Vidal et al. 2003; Rastas et al. 2004; Shin et al. 2005). Shin et al. (2005), for example found in their study of healthy people (age 45 – 74 y, n = 1232 (female)) that LDL cholesterol among *APOE* 2 carriers was 2.8 mmol/l, while it was 0.6 mmol/l higher among *APOE* 4 carriers (Shin et al. 2005). Higher LDL cholesterol has also been found among carriers of *APOE* 4 allele compared to *APOE* 3 carriers (Srinivasan et al. 1999; Sheehan et al. 2000; Ranjith et al. 2004; Saito et al. 2004; Almeida et al. 2006), although the difference was minor between the *APOE* 4 carriers and 3 carriers compared with the difference in *APOE* 4 carriers and 2 carriers. Sheehan et al. (2000), for example found in their study of healthy people (aged 19 – 67 y) that LDL cholesterol level among the carriers of *APOE* 4 allele was 2.86 mmol/l, while among carriers of *APOE* 3 allele it was 2.39 mmol/l and among carriers of *APOE* 2 allele 2.27 mmol/l (Sheehan et al. 2000). The age, gender, disease status, and drug use may also bring some variations in serum lipids levels and responses to changes in dietary fat among different *APOE* genotypes (Lovegrove and Gitau 2008). Carvalho-Wells et al. (2010) study found that age has a remarkable effect on lipid concentration on the different *APOE* genotypes(Carvalho-Wells et al. 2010). Their study indicated that total- and LDL cholesterol, and triglyceride content were higher and HDL cholesterol was lower with individuals of *APOE* 2 allele compared to individuals with *APOE* 4 allele in a subgroup that were 50 years or under, whereas in the subgroup over 50 years the results were the opposite (Carvalho-Wells et al. 2010).

Masson et al. (2003) in their systematic review (46 studies) studied the connection between different *APOE* genotypes and responses to dietary fat. A significantly different number of LDL, HDL-cholesterol or triglycerides responses were found in 19 studies, mostly in the LDL-cholesterol (12 studies) of which *APOE*4 individuals tended to be the most responsive (8 studies) (Masson et al. 2003). In addition, the recent study by Carvalho-Wells et al. (2012) found a greater responsive in triglyceride content to dietary fat manipulation among *APOE* 3/4 genotypes compared with the *APOE* 3/3 genotypes (Carvalho-Wells et al. 2012).

Although the review by Masson et al. (2003) showed that individuals with the *APOE* 4 allele appear to be most responsive to changes in dietary fat, their study also concluded that carriers of the *APOE* 4 allele may not be the most responsive to changes in other aspect of diet (Masson et al. 2003). In addition, several controversial or no associations at all have been presented (Minihane et al. 2000; Masson et al. 2003; Olano-Martin et al. 2010; Egert et al. 2010; Liang et al. 2013). Liang et al. (2013), for example did not find a different response

toward fish oil fatty acids eicosapentaenoic (EPA) among *APOE* genotypes. The only significant response was seen in HDL-cholesterol among *APOE* 2 carriers (Liang et al. 2013). Further, Minihane et al. (2000) showed in their studies that *APOE* ε4 carriers' total cholesterol and LDL cholesterol increased after a fish oil supplementation, and HDL cholesterol decreased compared with *APOE* ε3 carriers (Minihane et al. 2000). In addition, Egert et al. (2010) found that *APOE* ε3 carriers had a better response to quercetin (flavonols) supplementation than *APOE* ε4 carriers (Egert et al. 2010). The differences were revealed in systolic blood pressure, HDL cholesterol, and the ratio of LDL:HDL cholesterol (Egert et al. 2010). Several previous studies have also demonstrated the connection of *APOE* 2 and 4 alleles to higher triglyceride content than *APOE* 3 allele (Dallongeville et al. 1992; Luc et al. 1994; Tiret et al. 1994; Haffner et al. 1996; Tammi et al. 2000; Haddy et al. 2002). Additionally, some studies with mice have also found connections between a high-fat and high-cholesterol diet and extensive atherosclerotic plaques caused by a high- fat and cholesterol diet and the *APOE* 2/2 genotypes (Sullivan et al. 1998; Mihovilovic et al. 2007). This connection was not found in *APOE* 3/3 genotypes.

The *APOE* also have other nutritional related functions, including vitamin E, D and K metabolism (Kohlmeier et al. 1998; Lovegrove and Gitau 2008; Huebbe et al. 2010; Huebbe et al. 2011; Vermeer 2012). Some previous studies have found that individuals with the *APOE* 4 allele are better able to tolerate D vitamin deficiency compared with the carriers of other *APOE* alleles (Ulrik Gerdes 2003; Huebbe et al. 2011). This is the case mainly in circumstances in which vitamin D production or intake is decreased (e.g. high geographical latitude, dark skin, or insufficient dietary supplementation) (Ulrik Gerdes 2003; Huebbe et al. 2011). Higher D-vitamin concentrations among *APOE* 4 carriers may be due to a better absorption of dietary fats and renal retention (Huebbe et al. 2011). Further, the *APOE* 4 allele can be associated with lower vitamin E retention in peripheral tissue (Huebbe et al. 2010) and a lower level of vitamin K concentration in blood. Both, *APOE* 4 allele and deficiency of vitamin E has also been associated with an increased risk for Alzheimer disease (AD). Lower vitamin K concentration among *APOE* 4 carriers has been associated with an increased risk for osteoporosis and bone fractures (Kohlmeier et al. 1998). Increased alcohol consumption has also associated with an increased LDL-cholesterol level among *APOE* 4 carriers (Ordovas 2002).

Prevalence of APOE genotypes (table 1)

The most common *APOE* allele in all human populations is *APOE* 3, but there are great regional differences in number of *APOE* 4 carriers (Lehtimäki et al. 1990; Corbo and Scacchi 1999; Schiele et al. 2000). Humans with *APOE* 4 allele are more common in ethnic and aboriginal groups such as African Pygmies and the Khoi San, as well as aborigines of Malaysia and Australia (Corbo and Scacchi 1999). In Europe, there is a geographical limit between South and North in prevalence of the *APOE* 4 allele (Corbo and Scacchi 1999; Minihane et

al. 2000; Schiele et al. 2000; Singh et al. 2006) (table 1). Among northern Europeans, 30 % are *APOE* 4 carriers, whereas in South Europe correspondingly less than 20 % (Schiele et al. 2000). Singh et al. (2006) observed the same phenomenon, although the prevalence of the *APOE* 4 allele was approximately 20 % in Northern Europe (e.g. Norway, Finland) (Singh et al. 2006) (table 1). Furthermore, previous studies observed that frequency of *APOE* 4 allele was higher among young Finns compared with most other populations (France, Germany, Scotland, USA, Canada, New Zealand, Singapore, Japan), but there were no regional differences in incidence of *APOE* genotypes. (Ehnholm et al. 1986; Lehtimäki et al. 1990; Corbo and Scacchi 1999; Schiele et al. 2000; Juonala et al. 2004).

Table 1. Prevalence of *APOE* alleles in select countries worldwide (Singh et al. 2006; Minihane et al. 2007)

		ApoE alleles		
Country	n	ε4 -%	ε3 -%	ε2 -%
Nigeria	781	25.2	68.4	6.4
Norway	798	19.8	74.4	5.8
Finland	1577	19.4	76.7	3.9
New Zealand	426	14.1	73.9	12.0
UK	621	13.7	72.2	14.2
Germany	1557	13.6	78.2	8.2
USA	1209	13.5	78.6	7.5
France	1228	12.1	77.1	10.8
Spain	614	7.8	84.2	8.0
India	4450	7.3	88.7	3.9
China	518	6.5	84.3	9.2
Italy	633	6.3	89.7	4.0
Turkey	8366	6.1	86.0	7.9

2.3.2 Utilization of nutrigenetics by nutritional genetic testing

Some researchers have predicted that nutritional genetic testing will become a routine and as commonplace as having a blood cholesterol test, thus changing the practice from generalized treatments to early detection and prevention based on a personal, genetic susceptibility (Lovegrove and Gitau 2008). The one assumption is that genetic testing will increase interest in healthy nutrition (Kohlmeir 2013). Utilizing nutrigenetic testing in genetic-nutrition related diseases, which can be controlled only by increasing, decreasing, or avoiding some food or food ingredient have been routine for several years (Ferguson 2014). Increasing folate, for example, is important for women whose metabolism works differently, to prevent neural tube defects in unborn children (Pogribna et al. 2001) and avoiding lactose in dairy products is important for people with an absence of the lactose-digesting enzyme lactase in the small

intestine (Kohlmeir 2013). However, a new approach is to modify the standard nutrition therapy by using nutritional genetic testing. This can be one tool that can be combined with individual nutrition advice, such as increasing unsaturated fat intake to effect cholesterol level in prevention of life-style related diseases (e.g. CVD) (Ferguson 2014). However, using nutrigenetic testing is only viable if it brings actionable information based on convincing evidence (Kohlmeir 2013). The evidence has to come from a sufficient and comparable target population, and the genetic analysis has to be reliable (Kohlmeir 2013). The challenge in utilizing nutritional genetic testing in lifestyle-related diseases is the multifactorial nature of these diseases. The onset of the lifestyle-related disease (e.g. CVD) is affecting several genes, genetic-nutrition interactions and lifestyle factors (e.g. dietary, smoking, alcohol consumption, physical activity).

Partly due to these challenges, and also to the lack of know-how and resources among health care professionals the utilization of nutritional genetic testing in the prevention of lifestyle related diseases is still in its infancy in public health care (Bloss et al. 2011; Rahman et al. 2012; Voils et al. 2012). This fact has offered an opportunity to several commercial companies (DTC) to offer nutritional genetic testing to the public (Bloss et al. 2011; Rahman et al. 2012; Voils et al. 2012). Supplying the information for the genetic test is kept very simple in these DTC tests. The consumer is receives a simple sample collection kit from the testing company and usually takes a sample by noninvasive swabs from the inside of the cheek. After a few weeks, the tests results are returned as a printed or electronic report. A broad spectrum of these tests is available (e.g. for B vitamin metabolism, hearth health, alcohol metabolism, cholesterol metabolism, weight management) (Ferguson 2014) and the majority of these tests are based on one single nucleotide (SNP).

There are also some ethical aspects to DTC nutritional genetic testing, which have been discussed previously in this dissertation (Chapters 2.2.1 and 2.2.4). The nutritional advice offered by DTC testing companies, is usually very generic and rarely meets the real need (Kohlmeir 2013). Consequently, the one challenge is to ensure an opportunity for appropriate genetic consultation for everyone. Nevertheless, DTC nutritional genetic testing can either decrease health care costs by increasing the prevalence of early detection and prevent the lifestyle related disease or it can increase the costs by burdening the health care system with individuals who have ‘excessive anxiety and worry. Another special concern in DTC genetic testing is the lack of comprehensive service standards and validity of test interpretations (Kohlmeir 2013). In addition, an individuals’ personal genetic information may not sufficiently protected, although the companies convince so (Kohlmeir 2013).

2.4 Cardiovascular diseases (CVD)

The cardiovascular diseases (CVD) consist of several disease conditions, which affect the heart and blood vessels (e.g. atherosclerotic heart disease, coronary heart disease (CHD), and

ischemic heart disease). Despite the major, favorable changes in cardiovascular diseases risk factors (CVD) over the past few decades, CVD are still the main cause of mortality and morbidity in Finland as well as worldwide (Vartiainen et al. 2010; Ordovás and Smith 2010; Borodulin et al. 2014). The prevalence of CVD has increased clearly over the past 100 years (Ordovás and Smith 2010).

2.4.1 Association of *APOE* genotype with cardiovascular diseases (CVD)

The majority of studies have indicated an interaction between *APOE* genotypes and CVD, although there is discrepancy in the evidence of this causal relationship and other gene-nutrient interactions (Lovegrove and Gitau 2008). This research field is very broad and there are several controversial results published (Gustavsson et al. 2012). However, there are some large studies, which support associations of *APOE* genotype with CVD (Song et al. 2004; Bennet et al. 2007; Holmes et al. 2014). The meta-analysis of Song et al. (2004), for example, showed that carriers of the *APOE* 4 allele may even have a 42-percent higher risk for CVD compared with the carriers of the *APOE* 3/3 genotype, although the evidence was based partly on studies which with less than 500 coronary cases (Song et al. 2004). However, the meta-analysis of Bennet et al. (2007) from over 86 000 healthy participants and from 37 850 coronary cases (in total 203 studies) reported somewhat parallel results. The highest risk to Coronary heart disease (CHD) was among the carriers of the *APOE 4* allele, however, it was only 6 % higher compared with the *APOE* 3/3 genotype. The lowest risk was among carriers of *APOE 2* allele, being 26 % lower compared with the carriers of *APOE 4* allele. (Bennet et al. 2007) A very recent, systematic review and meta-analysis from over 130 000 individuals, also observed similar linear association ($p = 0.046$) between *APOE* genotypes and CHD risk (ε2/ε2, ε2/ε3, ε3/ε3, ε3/ε4, ε4/ε4); the risk being higher among carriers of *APOE 4* allele and lower among carriers of *APOE 2* allele (Holmes et al. 2014).

As reported previously in this dissertation (Chapter 2.3.1 Nutrigenetics and *APOE*), the main role of *APOE* concerned with lipid metabolism and cholesterol absorption, which have major effects on cardiovascular disease risk. In addition, it has been suggested that *APOE* genotype also effects other cardiovascular risk factors (Rantala et al. 1997; Helkala et al. 2001; Saito et al. 2004; Carvalho-Wells et al. 2010). High blood pressure has been associated with the presence of the *APOE* 4 allele (Rantala et al. 1997), but also with the *APOE* 2 allele (Couderc et al. 1993; Helkala et al. 2001; Cho et al. 2009). Furthermore, Helkala et al. (2001) found that carriers of the *APOE* 2 allele had a higher fasting glucose and 2 h blood glucose than *APOE* 3 and 4 carriers (Helkala et al. 2001). Previous and also some recent studies have also associated smoking with the increased risk of CHD among *APOE 4* carriers (Humphries et al. 2001; Gustavsson et al. 2012; Grammer et al. 2013). Gustavsson et al. (2012), for example, found that smoking increases the CHD risk ($P = 0.009$) among female *APOE 4* allele carriers, but not in male *APOE 4* allele carriers and Grammer et al. (2013) reported higher

CVD risk and mortality (P = 0.034) among 'current-smokers with *APOE 4* allele' compared with the 'ex-smokers with *APOE 4* allele' or 'not-smokers, with the *APOE 4* allele' (Gustavsson et al. 2012; Grammer et al. 2013). However, very recent review and meta-analysis did not find this connection (p = 0.19) between smoking, *APOE* genotypes, and CHD risk (Holmes et al. 2014).

2.4.2 Risk factors for cardiovascular disease (Fig.3)

The genetic factors in combination with the environment (e.g., unhealthy dietary habits, physical inactivity and smoking) play an important role in the prevalence of CVD (Lusis 2000; Cho et al. 2009). While gender, age, genetics, race and ethnicity are non-modifiable risk factors for CVD, modifiable key risk factors include obesity, smoking, high serum total cholesterol and elevated systolic and diastolic blood pressure (Borodulin et al. 2014; Ferguson 2014; Juma et al. 2014). Generally, men and older people have more CVD risk factors than women and younger people. Previous studies suggest that women's advantage toward CVD risk factors compared with men is their insulin sensitivity (Nuutila et al. 1995; Willeit et al. 1997; Cnop et al. 2003; Moran et al. 2008; Ferrara et al. 2008; Ervin 2009; Kim and Reaven 2013).

It has been shown that unhealthy lifestyle habits (e.g. physical inactivity, smoking, excessive consumption of alcohol and saturated fat and low consumption of vegetables) are closely linked to an increased risk of cardiovascular diseases (Raitakari et al. 1995; O'Neil et al. 1997; Ma et al. 2000; Schuit et al. 2002; Lukasiewicz et al. 2005). In addition, these risk factors tend to accumulate (Raitakari et al. 1995; O'Neil et al. 1997; Ma et al. 2000; Schuit et al. 2002; Artaud et al. 2013; Robinson et al. 2013).

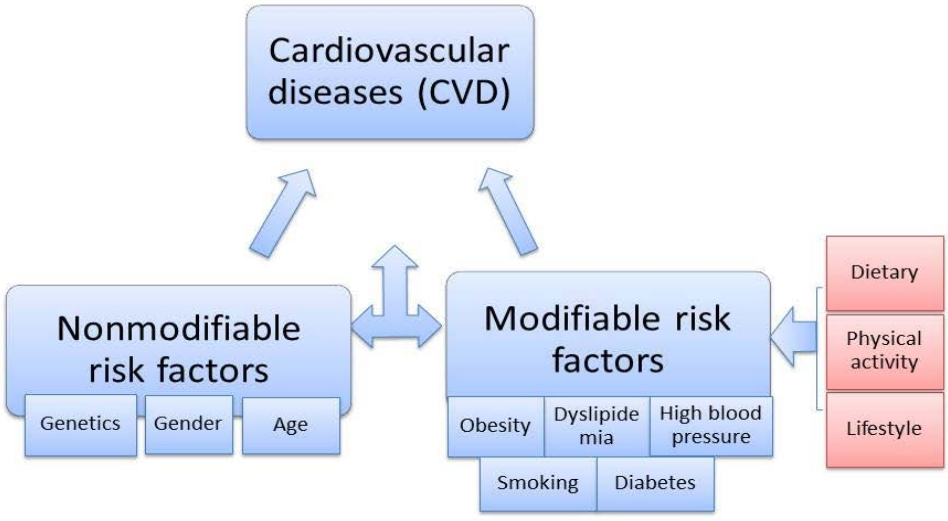

Figure 3. Modifiable and non-modifiable risk factors related to CVD. (derived from Juma et al. 2014)

Obesity

Overweight in adults is categorized based on body mass index (BMI), which is calculated dividing weight (kg) by height (m) squared. BMI under 18.5 kg/m^2 indicates underweight, BMI from 18.5 – 24.9 kg/m^2 indicates normal weight and BMI 25.0 kg/m^2 or higher indicates overweight (Tarnanen et al. 2011). However, classifying individuals as having 'normal weight' or being 'obese' only based on BMI is not correct. Overweight can be due to an increased amount of muscle tissue and BMI does not take a note the distribution of body fat. An accumulation of fat on the central part of the body is a more accurate and independent criterion for obesity and risk factors for metabolic disorders (Misra and Vikram 2003). Waist circumference reveals on amount of visceral fat and fat in the area of the abdominal cavity and it is one main criteria for metabolic syndrome (Mes) (Alberti et al. 2005). *Normal* waist circumference for men is ≤94 cm and for women ≤80 cm. Over 102 cm for men and over 88 cm for women indicates *significant health risk.*

In addition, body fat percentage can have an impact on obesity. Women have higher body fat percentage compared with men due to hormonal reasons (Lemieux et al. 1994). *Normal* body fat percentage for men is 8 - 21.9 % and for women 21 - 33.9 and it depends on age (Anonymous. Finnish electronic medical book. 2009). Smoking, excessive alcohol consumption, and low intake of dietary fiber are known to increase central fat accumulation (Barrett-Connor and Khaw 1989; Dallongeville et al. 1998; Ludwig et al. 1999; Koh-Banerjee et al. 2003; Canoy et al. 2005; Lukasiewicz et al. 2005)

Obesity is one of the main, well known, modifiable risk factor to cardiovascular diseases and it is usually a consequence of unhealthy dietary and physical inactivity, although several genes have also known to predispose to obesity (Hubert et al. 1983; Jonsson et al. 2002; Sharma 2003; Haslam and James 2005; Kohlmeir 2013). The gene most often linked to fat mass and obesity is the FTO gene (Phillips et al. 2012). Some studies have also found genetic predisposition (variants in the UCP gene) to higher waist circumference (Martinez-Hervas et al. 2012).

Obesity has been shown to increase risk for hypertension and diabetes, which also increases the risk for CVD (Sharma 2003; Lindström 2006). It has also shown that risk factors tend to accumulate (Raitakari et al. 1995; Schuit et al. 2002; Pronk et al. 2004; Lukasiewicz et al. 2005; Poortinga 2007; Artaud et al. 2013; Robinson et al. 2013). The longitudinal study (23 year follow-up, n = 22 025) of Jonsson et al. (2002) demonstrated that obesity was associated to CVD mostly, if participants were also smokers (Jonsson et al. 2002).

Obesity prevalence has increased throughout the world, although at the same time underweight and malnutrition have also increased in developed countries (Silventoinen et al. 2004). In Finland, overweight is still a major concern (Helakorpi et al. 2008; Vartiainen et al. 2010; Helakorpi et al. 2011; Helldán et al. 2013; Borodulin et al. 2014), although the increase in BMI has slowed down in men and the BMI of women has stayed constant during the past

few years (Borodulin et al. 2014). This similar, favorable trend has also been observed in United States (Flegal and Carroll 2010). The major concern is the increasing overweight of younger people (National Institute for Health and Welfare; Ogden et al. 2014). Large regional differences in BMI are also present (Borodulin et al. 2014) and overweight is more common in the western part of Finland (Southern Ostrobothnia) than in the whole of Finland (Helakorpi et al. 2011; Hietaranta-Luoma et al. 2011; Helldán et al. 2013).

Dyslipidemia (high serum lipids)

Dyslipidaemia can be defined as a disorder where there is an abnormal amount of lipids in the blood (Koriyama et al. 2012). These lipids include Low Density Lipoprotein (LDL), High Density Lipoprotein (HDL) and Triglycerides (Tg). The total cholesterol consists of these three lipids (LDL, HDL and Tg). Reference values (Finland) for total cholesterol is under 5.0 mmol/l, for LDL cholesterol under 3.0 mmol/l, triglyceride content under 1.7 mmol/l, HDL cholesterol over 1.0 mmol/l (men) and over 1.3 mmol/l (women) (Tarnanen et al. 2013). The American Heart Association and National Institute of Health have also set recommended cholesterol and triglyceride levels: the recommended total cholesterol is under 5.2 mmol/l (200 mg/dL) and HDL cholesterol is over 1.03 mmol/l (60 mg/dL), optimal LDL cholesterol is under 2.6 mmol/l (100 mg/dL) and triglyceride content under 1.7 mmol/l (151 mg/dL) (American Heart Association; National Institute of Health).

There is a considerable amount of data demonstrating that dyslipidaemia increases the risk for CVD and the link between high serum lipids and CVD have been accepted worldwide (Koriyama et al. 2012). The worldwide MRFIT – project (Multiple Risk Factor Intervention Trial) for 350 000 middle-aged men, demonstrated a clear positive correlation between total serum cholesterol (over 240 mg/dl) and coronary risk ratio (Stamler et al. 1986). Dietary aspects and physical activity have a central role in serum lipids (discussed later in this dissertation in the chapter on dietary aspects and physical activity) (Koriyama et al. 2012).

Over the past few years, the total cholesterol has started to increase again in Finland after the remarkably favourable change since 1970s (Borodulin et al. 2014). A similar trend has also been observed in Sweden between 2008 and 2010 (Ng et al. 2012). The pooled total cholesterol mean in 2007 was 5.36 mmol/l in men and 5.14 mmol/l in women. After five years (2012) the corresponding values were 5.43 mmol/l in men and 5.29 mmol/l in women. The only area where total cholesterol has continued to decrease during the last five years was in Helsinki/Vantaa and this trend was only in men. (Borodulin et al. 2014)

Hypertension (high blood pressure)

Hypertension is defined as disorder where the pressure in the arteries that carry blood from the heart to the rest of the body is too high. Blood pressure is divided into systolic blood pressure and diastolic blood pressure. The systolic blood pressure is the pressure in the arteries

as the heart contracts and the diastolic pressure is the pressure in the arteries as the heart relaxes. Normal blood pressure is 130/85 mmHg or under, blood pressure between 130/85 mmHg - 140/90 mmHg is satisfactory, but needs checking once a year and a blood pressure of 140/90 mmHg or above is at a raised level. (Duodecim and Suomen Verenpaineyhdistys 2009, käypähoitosuositukset)

It is well known that elevated blood pressure is related to increased risk of cardiovascular disease and mortality (Kannel 1995; van den Hoogen et al. 2000; Zhang et al. 2006). The study by Kannel et al. (1995) estimated that hypertension increases the risk of CVD to 2 to 3 fold compared with the normal blood pressure (Kannel 1995).

Hypertension with the diabetes has been noticed to further increase the risk of CVD (Strong Heart Study,12 years follow-up) (Zhang et al. 2006).

Trends in Finland have been favorable in systolic blood pressure, but over the past few years (2007 – 2012) the diastolic blood pressure has increased both in men and women, being over the recommended level in men (85.5 mmHg) (year 2012) (Borodulin et al. 2014). Although the diastolic blood pressure has decreased dramatically over the past forty-five years, it is still over the recommended level in men (134.4 mm/Hg) (Borodulin et al. 2014).

Smoking

Smoking is a well-recognized health risk. Further, it affects cardiovascular and cancer morbidity and also causes abdominal obesity, and increases the risk for type 2 diabetes (Barrett-Connor and Khaw 1989; Marti et al. 1991; Canoy et al. 2005; Patja et al. 2005). As described previously in this dissertation (chapter *obesity*), smoking has been observed to increase CVD risk together the obesity (Jonsson et al. 2002). Daily smoking has decreased in Finland, in the last few years. The change has been favorably dramatic in men over the past decades. In women, smoking has increased until 2002 and decreased after that (Borodulin et al. 2014). From men, 19 % and from women 13 % smoked daily in year 2012 (Helldán et al. 2013).

Dietary aspects

Diet has a major role in the prevention of lifestyle-related diseases, such as cardiovascular diseases (Mente et al. 2009). The occurrence of dyslipidaemia is mainly affected by dietary composition, especially dietary fat quality, smoking, blood pressure, and body mass index (Koriyama et al. 2012).The Finnish nutrition recommendations, compiled by the National Nutrition Council, gives comprehensive dietary guidelines and these recommendations are also suitable for preventing CVD (e.g. decrease cholesterol level or blood pressure) (Fogelholm et al. 2014). However, there are recommendations with a little more detailed for the people, who already have CVD and these guidelines are compiled by the Finnish Heart Association (Finnish Heart Association 2015).

The Finnish nutrition recommendations follow the 'plate model' and 'food triangle', in which the foundational and largest level consist of vegetables, fruits and berries and the top of the triangle consist of delicacies (e.g. snacks, candies, sausages, pizza, biscuits). The amount of saturated fat should be under 10 E% and at least 500 g vegetables, fruits and berries should be include in the daily diet. In addition, in order to keep the blood pressure within a normal range (≤130/85 mmHg), the daily salt intake should be only 5g. The wholegrain products (e.g. low-salt bread), potatoes and non-fat or low-fat dairy products should include in the daily diet. Fish is recommended to be eaten 2-3 times in week and the intake of low-fat/salt red meat (e.g. bovine, swine, and sheep) is not more than 500 g in a week. Bread is recommended to be spread with vegetable-based margarine and oil-based dressing is recommended for salads. The diet should include only a little salt and sugar. (Fogelholm et al. 2014)

There are several studies which have indicated the effects of dietary fat quality on serum lipids (Masson et al. 2003; Minihane et al. 2007; Ordovas et al. 2007). Excessive amounts of saturated fat and sugary foods indicate higher triglyceride values (Matikainen 2009). In addition, a high fiber diet (e.g. vegetables, berries and fruits + whole grain cereals) has shown to have favorable effects on total and LDL-cholesterol (Wood et al. 1983; Anderson 1985; Brown et al. 1999).

Over the past decades, dietary composition (e.g. dietary fat quality, consumption of vegetables, fruits and berries and salt intake) has improved. However, in the last few years the trend has been the opposite, especially in dietary fat quality and salt intake (Fogelholm et al. 2014).

Excessive alcohol consumption is also one important risk factor for CVD, because it has been associated with the increased LDL cholesterol and triglyceride level, especially among *APOE* 4 carriers (Ordovas 2002; Matikainen 2009). There is evidence that moderate alcohol consumption (one proportion in a day) can protect against cardiovascular risk factors, but increased consumption (over 2 proportions in a day) clearly increases the risk for CVD (Ronksley et al. 2011). Excessive alcohol consumption has unfavorable effects on lipid metabolism and blood pressure and it increases the risk of obesity (Lukasiewicz et al. 2005; Ronksley et al. 2011).

Alcohol consumption increased dramatically between the years 1980 and 1990 in Finland, but after that consumption has been constant in both men and women (Helldán et al. 2013). In 2012, 38 % of men consumed at least eight doses of alcohol in a week and 27 % of women consumed five units of alcohol in a week (Helldán et al. 2013).

Physical activity

The development and compilation of the international and national guidelines for physical activity in adults (18-64) has been focus in past few years. (Anonymous. The Office of Disease Prevention and Health Promotion. 2008; Suomalaisen Lääkäriseuran Duodecimin

asettama työryhmä. 2012). Every kind of physical activity, which is regular, a moderate burden, and takes at least 10 minutes is significant in terms of health. The Physical Activity Recommendation in Finland is to partake in endurance exercises at least twice a week, for least 30 minutes at the time (Suomalaisen Lääkäriseuran Duodecimin asettama työryhmä. 2012; Fogelholm et al. 2014). In addition, physical activity, related to muscular condition is recommended twice a week (Suomalaisen Lääkäriseuran Duodecimin asettama työryhmä. 2012; Fogelholm et al. 2014). Physical activity has a remarkable role in the prevention of CVD. Endurance exercise especially, (e.g. walking, running, skiing, biking) promote health and prevent life-style related diseases (e.g. CVD and diabetes) (Fogelholm et al. 2014). In addition, regular physical activity affects the maintenance of normal weight and has favorable effects on serum lipids (Wood et al. 1983; Benzer et al. 1998). Several favorable effects on mental health have also been found (Mason and Holt 2012), which can further affect the maintaining normal weight and prevent other cardiovascular risk factors.

Although leisure-time physical activity has increased in Finland, other physical activity (e.g. exercise in work or work travel) has decreased (Peltonen et al. 2008; Helldán et al. 2013).

2.5 Previous studies of utilizing genetic testing to achieve nutrition-and clinical related changes (Tables 2 and 3)

Utilizing genotype-based health information and nutritional genetic testing purely to promote healthy lifestyles (e.g. diet, physical activity, and cholesterol) and prevent lifestyle-related diseases is quite a new research field and a very limited number of studies have been conducted in this areas. This dissertation included an overview of only 16 studies between 2001 and 2015 (Tables 2-3) and Marteau et al. (2010) included in their review only seven clinical studies. Both reviews found that the results were conflicting and the favorable changes limited. Eight of the included studies in this dissertation review found significant favorable changes (e.g. intentions to eat healthy diet, increase vitamin and supplement intake, decrease sodium intake, weight reduction or controlling, increase vegetables consumption) (Frosch et al. 2005; Roberts et al. 2005; Smerecnik et al. 2007; Arkadianos et al. 2007a; Chao et al. 2008; Conradt et al. 2009; Vernarelli et al. 2010; Meisel et al. 2012; Egglestone et al. 2013; Meisel and Wardle 2014; Meisel et al. 2015 (Table 2-3). In addition, Marteau et al. (2010) observed that genetic information did not motivate people to stop smoking or increase exercising, but it may have some favorable effects on diet and lifestyle (Marteau et al. 2010a).

No study about using genotype-based health information to prevent CVD, which considered the psychological, health behavioral, and clinical factors has been done before this dissertation study. Research into life-style related diseases is challenging as it is dependent on several genes and many lifestyle factors (e.g. dietary, physical activity, smoking), which affect interactions and therefore the disease risk. Partly because of this, most of the research has focused on testing the effects of genetic information to prevent cancers such as breast,

ovarian, lung, and colon cancers. Genetic information has, for example, motivated people to have more mammograms (Halbert et al. 2004; Watson et al. 2004; Collins et al. 2005; Claes et al. 2005; Kinney et al. 2005; McBride et al. 2010). O'neill et al. (2008) and Quach et al. (2009) studied the effect of breast cancer (BC) genetic testing on dietary and physical activity and found no differences between the high-risk (BRCA 1/2+) or low-risk (BRCA 1/2-) group (O'Neill et al. 2008; Quach et al. 2009).

Preventing obesity or weight management has been the most popular topic in the context of promoting healthy lifestyles with the genotyping (Harvey-Berino et al. 2001; Frosch et al. 2005; Rief et al. 2007; Arkadianos et al. 2007b; Conradt et al. 2009; Meisel et al. 2012; Meisel and Wardle 2014; Wang et al. 2014; Meisel et al. 2015) (Table 2). Three of these studies found that positive obesity gene status did not affect BMI, weight, body fat percentage, fasting glucose, serum lipids, confidence or motivation to lose weight, or attitudes to eat a healthy diet in the short-term (<6 months) (Harvey-Berino et al. 2001; Rief et al. 2007; Conradt et al. 2009) (Table 2). In Harvey-Berino et al. (2001) a pilot study of 30 obese women, obesity related gene (b3-adrenergic receptor) was screened and it was found that there was no differences in confidence to lose weight ($p = 0.42$) or in eating self-efficacy ($p = 0.65$) between the 'positive gene group' and the 'negative gene group' after genetic feedback (Harvey-Berino et al. 2001). The study Rief et al. (2007) was conducted with 410 obese people and the results were compared between the two intervention groups: a 'group, with counselling and genetic information' and a 'group with counselling, without genetic information' and a control group. The study did not find any significant differences in BMI, restraint in eating, body acceptance, or self-efficacy between the groups after six months (Rief et al. 2007). The Conradt et al. (2009) study was similar to the Rief et al. (2007) study, but they measured BMI, attitudes about weight loss goals, weight-related self-blame, coping, and body shame. They did not find any significant differences between the intervention groups, but a difference of ($p<0.05$) was found in the "likelihood of losing 5 % body weight" between the intervention and control groups and in "satisfaction with 5% weight loss" between the intervention group (without genetic information) and control group (Conradt et al. 2009).

Short-term effects were found in the study by Frosch et al. (2004), which observed that imaginary, genetic susceptibility to obesity indicated stronger intentions to eat a healthy diet ($p = 0.02$) and in the study by Meisel et al. (2015), it was noticed that the 'intervention group, with genetic feedback' had significantly higher thoughts ($p = 0.003$) about or had started controlling their weight compared with the 'control group, with only advice' (Frosch et al. 2005; Meisel et al. 2015).

A long-term effect was found in the Arkadianos et al. (2007) study, which observed that nutrigenetic tests affected BMI reduction over a 300 day period (Arkadianos et al. 2007b) (Table 2). This Arkadianos et al. (2007) study is good example of the importance of longer follow-up. BMI reduction was quite similar in both groups (non-tested group and nutrigenetic

test group) during first 300 days. After 300 days, the BMI increased in both groups, but the increase was clearly greater in the non-tested group (3.25 kg/m^2) compared with the tested group (0.65 kg/m^2 ($p = 0.023$). Among the non-tested group, BMI was at the higher level after 300 days compared with the baseline (weight as % of baseline: 103.2 % (non-tested group) and 95.6 % (nutrigenetics group). (Table 2)

The other conditions or disease studied have been Alzheimer disease (AD), diabetes, Familial hypercholesterolemia (FH) and hypertension (Marteau et al. 2004; Roberts et al. 2005; Chao et al. 2008; Taylor and Wu 2009; Vernarelli et al. 2010; Grant et al. 2013) (Table 3). Chao et al. (2008), in their randomized, controlled, clinical testing (n = 53 (Ɛ4+ group), n = 58 (Ɛ4- group), n = 51 (control group)), for example, reported that the *APOE*4+ group had 2.73 times more ($p = 0.02$) Alzheimer disease (AD) specific health behavior changes (increased exercise, vitamin intake and dietary changes) compared with *APOE*4- group (Chao et al. 2008) (Table 3). On the contrary, Marteau et al. (2004) found in their randomized, clinical testing that the genetic testing of FH did not have an impact on smoking, diet, exercise, and medication adherence in three groups (mutation (n = 74), no mutation (n = 139) and no genetic diagnosis (n = 103)) 6 months after the diagnostic assessment. This study also found that cholesterol medication was considered more effective ($p = 0.02$) in lowering the cholesterol level than diet among the mutation group. (Marteau et al. 2004) (Table 3) However, the follow-up period was longer (over one year) in the study of Chao et al. (2008) compared with the study of Marteau (2004) (six months), which may have had an effect on the more favorable results in the study of Chao et al. (2008). (Table 3) It has been shown that a longer and more intensive intervention period is more effective than a shorter and less intensive intervention when achieving a permanent lifestyle change (e.g. weight reduction, dietary changes) (Maderuelo-Fernandez et al. 2014; Wallace et al. 2014)**.** It is also possible that people consider Alzheimer disease a more severe condition and not as preventable as hypocholesteremia.

The recent studies in the nutritional genetic testing field have been focused on utilizing or imitating the commercially direct-to-consumer genetic (DTC) testing in preventing life-style related diseases (Bloss et al. 2011; Nielsen and El-Sohemy 2012; Bloss et al. 2013; Egglestone et al. 2013; Nielsen et al. 2014) (Table 3). This has brought new trends and progress into this research field, because these kinds of studies are much easier to conduct without laborious clinical experiments and face-to-face consultation. However, it also brings some challenges and ethical problems, which have been discussed previously in this dissertation (Chapters 2.2.1 and 2.2.4). These DTC studies, included in this review consist of a wide spectrum of several life-style related genetic tests and assessments (e.g. dietary (salt-, fat-, fiber-, fruit- and vegetables consumption), physical activity, smoking, anxiety, test related distress, intention to complete the health behavior screening test and changes in perceptions of personalized nutrition) (Table 3). Their experimental design differs somewhat from ordinary, clinical, nutritional genetic testing (e.g. all consultation is given by mail). Study of Nielsen & El-

Sohemy (2012) and Nielsen et al. (2014), for example, was clinical, randomized and controlled, including two groups (intervention group, n = 92, which received DNA-based dietary advice and control group, n = 46, which received only general dietary advice). Advice and consultations were only given by mail or electronically (Table 3). This study had similar elements to the experimental design of this dissertation study. Further, Bloss et al. (2011 & 2013) (n = 2037), Nielsen & El-Sohemy (2012) and Nielsen et al. (2014) (n = 138) did not observe any significant changes in nutritional-related outcomes between baseline and follow-ups (3 months, 6 months (Bloss et.al), 12 months), when using genetic screening to impact on health behavior (Bloss et al. 2011; Nielsen and El-Sohemy 2012; Bloss et al. 2013; Nielsen et al. 2014) (Table 3). However, on the contrary, the purely commercially direct-to-consumer genomic testing of Egglestone et al. (2013) showed that consumers, who had already received and completed the genetic testing ('consumer group', n = 189) had significantly better health behavior scores than potential consumers (n = 86), who were either considering the receiving or purchasing the test (Egglestone et al. 2013) (Table 3). The significant difference ($p = 0.03$) was in fruit and vegetables consumption between the 'consumer' group and 'potential consumer' group, as a sufficient fruit and vegetables intake was reported by 53.9 % of 'consumer group, and 38.8 % of 'potential consumer' group (Egglestone et al. 2013) (Table 3).

The preventing life-style related diseases by genotype based health information is a new and growing research field and partly because of this there is great variation in the follow-up durations, methods, assessments and diseases or conditions which it is intended to prevent (Tables 2-3). Only five studies of those included in this dissertation review had a follow-up period of over 10 months, seven of the studies used randomization, and only four studies included personal genetic counseling; this does not give a very convincing picture of these studies. However, based on the studies included, it can be concluded that genotype based information may have favorable effects on health promotion, but longer follow-ups and genetic counseling must be included. Using genotype based health information to promote healthy lifestyles and prevent cardiovascular diseases is very challenging due to the many modifiable and non-modifiable risk factors and also the ethical aspects. However, this dissertation study aims to give one, unique view on this very recent, but gradually growing research field. The empirical research of this dissertation study has been presented in the next chapters.

Table 2. Summary of utilizing genetic testing to achieve nutritional- and clinical related changes in prevention of obesity or in weight management (in years 2001 – 2015).

Reference	Condition	Study population	Groups	Method	Assesments (changes)	Measuring points	Findings
Harvey Berino et al. (2001)	Obesity	30 obese white women, (age 57 y)	GENE+ (n = 18), GENE- (n = 12)	Clinical genetic testing	Confidence, self-efficacy to weight management.	Baseline, immediately after genetic screening	No differences between the groups.
Frosch et al. (2005)	Obesity	249 university students (age = 20.5 y), self-identified a being "average weight".	imaginatory, genetic susceptibility to obesity group' (n = 125),' no imaginatory susceptibility group' (n = 124)	Experimental, imaginatory, randomised trial	Intentions to eat a healthy diet, attitudes, perveived behavioral control, perceived social norms	Baseline	Imaginatory, genetic susceptibility group' indicated significantly ($p<0.05$) stronger intentions to eat a healthy diet and lower perceived behavioral control compared 'no imaginatory susceptibility group'. No differences in other factors.
Rief et al. (2007)	Obesity	410 obese individuals (age = 45.7 y)	intervention group with counseling and genetic infromation' (n = 147), 'intervention group with counseling and without genetic information' (n = 147), 'control group' (n = 116)	Clinical, genetic testing	BMI, restraint eating, body acceptance, self-efficacy	Baseline, after consultation, 6 months	No differences between the groups.
Conradt et al. (2009)	Obesity	411 individuals (age = 45.6 y)	intervention group with counseling and genetic information' (n = 148), 'intervention group with counseling, without genetic information' (n = 147), 'control group' (n = 116)	Clinical, genetic testing	BMI, attitudes about weight loss goals, weight-related self-blame, coping, body shame.	Baseline, 6 months	Significant difference ($p<0.05$) in "likelihood of losing 5% body weight" between intervention and control groups and in "satisfaction with 5% weight loss" between intervention group (without genetic information) and control group. No differences between intervention groups.
Wang et al. (2014)	Obesity	Source population consist of 3238 individuals (age = 52.8 y).	genetic risk feedback group', 'lifestyle risk feedback group', 'both genetic and lifestyle risk (combined) feedback, 'control group (no risk feedback)'	Randomized, controlled, clinical genetic testing with the online risk feedback (Obesity Risk Communication Study)	Health behaviors (dietary, physcial activity), behavioral intentions, weight, psychological responses	Baseline, 3 months	NOT PUBLISHED YET.
Arkadianos et al. (2007)	Weight management	93 individuals (age = 45.8 y) with a history of failures at weight loss.	nutrigenetic test group' (n = 50), 'non-tested group' (n = 43)	Clinical, nutrigenetic test	BMI, fasting glucose, serum lipids (total, HDL, LDL cholesterols).	100 days, 300 days, over 300 days	Nutrigenetic test group' had significantly ($p<0.05$) bigger weight loss over 300 days follow-upt compared with non-tested group. No differences in other factors or shorter follow-ups.
Meisel et al. (2012); Meisel et al. (2014); Meisel et al. (2015)	Weight gain / control	279 first-year university students (age = 20.5 y)	intervention group, with genetic feedback and advice (n = 139), control group, only with advice (n = 140)	Randomized, controlled, clinical genetic testing	Body composition (weight, body fat), motivation to avoid weight gain (stage of change), fatalism	Baseline, 1 month, 8 months	Intevention group was significantly ($p<0.05$) more in the contemplation stage (thinking about controlling their weight) and the action stage (having started to control weight) compared with the control group. No differences in other factors.

Table 3. Summary of utilizing genetic testing to achieve nutritional- and clinical related changes in prevention of hypertension, diabetes, familial hypercholesterolemia (FH), Alzheimer disease (AD) and several other lifestyle-related diseases (in years 2004 – 2014).

Reference	Condition	Study population	Groups	Method	Assesments (changes)	Measuring points	Findings
Smerecnik et al. (2007)	Hypertension	146 individuals (age = 58.7 y)	genetic suscebtibility for salt-sensitivity blood pressure group', 'not-genetic suscebtibility group'	Clinical, genetic testing	Intention to adopt a salt-destricted diet, stage od change	Baseline, after informed genetic predisposition to having a salt-sensitive blood pressure	The stage of change had effect on adopting salt-restricted diet. In the *precontemplation* and *contemplation* stages, 'the genetic suscebtibility group' reported higher intentions ($p < 0.001$) to restict salt intake compared with 'not-gentic suscebtibility group'
Taylor & Wu (2009)	Hypertension	98 African-American women (age = 55+ y)	one group, with the genetic counseling and risk assesment for hypertension	Clinical, genetic testing	Diet (sodium and potassium intake), physical activity, blood pressure, BMI	Baseline, 6 months	Significant decrease ($p<0.005$) was found in sodium intake from baseline to 6 months follow-up. No differences in other factors.
Marteau et al. (2004)	FH	341 families (age 56.1 y) and 128 adults relatives (age = 46.5 y) with a history of FH	mutation group' (n = 74), 'no mutation group' (n = 139), 'non-genetic diagnosis group' (n = 103)	Randomised clinical genetic testing.	Perceived control over FH, - cholesterol, - heart disease, dietary, physical activity, smoking, medications, emotional state, ilness perceptions, perceptions of the diagnosis	Baseline, 1 week, 6 months	Mutation group' believed significantly more ($p<0.01$) that their cholesterol levels were controlled by their genetic compared with other groups. They also preferred significantly more ($p<0.05$) the medication, instead of diet in reducing their cholesterol level compared with the other groups. No differences in other factors.
Grant et al. (2013)	Diabetes	108 overweight participants (age = 57.9 y)	higher diabetes genetic risk group' (n = 42), 'lower genetic risk group' (n = 32), 'control group' (n = 34)	Randomized, controlled, clinical genetic testing with the genetic counseling.	Confidence and motivation to make diabetes-related lifestyle changes (exercise, weight loss, adoption of a low-fat diet) and stage of change for achieving these behaviors, conrete weight loss	Baseline, 12 weeks (3 months)	Significant difference ($p<0.05$) was in stage of change in exercise between 'lower genetic risk'- and 'control group'. 'Lower genetic risk group' had less intent to exercise compared with the 'control group'.
Roberts et al. (2005); Chao et al. (2008)	AD	162 participants (age = 53 y)	apoE4+ (n = 53), apoE4- (n = 58), control group (n = 51)	Randomised, controlled clinical genetic testing	Health behavior factors (diet, physical activity, vitamin E supplement), psychological factors (anxiety, depression)	Baseline, 6 weeks, 6 months, 12 months	ApoE4+ group had 2.73 times more favorable health behavior changes (increased exercise, vitamin intake and dietary changes) compared with apoE4- group. No differences in psychologigal factors .
Vernarelli et al. (2010)	AD	272 individuals (age = 58.1 y) with family history of AD	apoE4+ group (n = 111), apoE4- group (n = 161)	Randomized, clinical genetic testing (REVEAL)	Dietary, physical activity, dietary supplement use	Baseline, 6 weeks	ApoE4+ group did statistically more any health-behavior changes ($p<0.05$), especially in dietary supplement use ($p<0.001$) compared with the apoE4- group. The most commonly reported supplement changes were in vitamin E.
Bloss et al. (2011); Bloss et al. (2013)	Several health conditions	2037 individuals (age = 46.7 y) completed the 3 months follow-up; 1325 individuals (age = 47.5 y) completed the 12 months follow-up	One group.	Commercially, direct-to-consumer genetic testing	diet (fat intake), physical activity, anxiety, test related distress, intention to complete the health behavior screening tests	Baseline, 3 months, 6 months, 12 months	Test related distress significantly ($p<0.001$) decreased between 6 months and 12 months follow-ups. No differences in other factors or follow-ups.
Egglestone et al. (2013)	Life-style related diseases, based on health behavior factors.	275 participants (mode age group 30 - 44 y)	Consumer group, which had completed the tes, (n = 189), 'potential consumer group, which were considering the receive or purchase test' (n = 86)	Commercially, direct-to-consumer genomic testing	Dietary (salt-, fat-, fibre-, fruit- and vegetables consumption), smoking, physical activity, health anxiety.	Baseline	Consumer group' had significantly ($p<0.05$) better health behavior scores than 'potential consumer group'. Significant difference was in fruit and vegetables consumption between the 'consumer' group and 'potential consumer' group.
Nielsen & El-Sohemy (2012); Nielsen et al. (2014)	Life-style related diseases (increased risk of myocardial infarction, serum ascorbic acid defiency, overconsuming sugars and sodium-sensitive hypertension.	138 individuals (age 26 y)	intervention group, with DNA-based dietary advice' (n = 92), 'control group, with general dietary advice' (n = 46)	Randomized, controlled, clinical genetic testing with advices only mail or electronically, mimic the nature of the direct-to-consumer (DTC) genetic testing.	Opinions of sources for personal genetic information and personalized nutrition advice, changes in perceptions of personalized nutrition and genetic testing, sharing of information, utility of personalized nutrition	Baseline, 3 months, 12 months	No differences between the groups.

3 AIMS OF THE STUDY

The overall aim was to study how personalized genotype based health information affects an individual's health.

More specific objectives of the study were:

1. To study the psychological effects of personal genetic information, provided by different *APOE* genotypes, as a tool to promote lifestyle changes. (Paper I)

2. To study the health behavioral and attitude effects of receiving personal genetic information, using *APOE* genotypes as a tool for promoting lifestyle changes. (Paper II)

3. To study the clinical (cardiovascular risk markers) effects of receiving personal genetic information, using *APOE* genotypes as a tool for promoting lifestyle changes. (Paper III)

4. To study the associations between psychological-, health behavioral and clinical factors in context of *APOE* based genetic feedback, all factors for CVD. (Paper IV)

4 MATERIAL AND METHODS

4.1 Project organization

This one-year intervention study was part of the 'Healthier food choices, tailored models for eating and exercises' (TERVAS) project (2009 – 2012) in Southern Ostrobothnia, Finland. The study involved the University of Turku, the University of Vaasa, the Seinäjoki Central Hospital and Natural Resource Institute Finland (Luke; earlier MTT). Permission was received from the Ethics Committee of the Central Hospital in Southern Ostrobothnia, Finland.

The researcher group included a principal researcher, a medical doctor, a researcher of biotechnology, a certified nutritionist, a clinical chemist, professors of nutrigenomics, food science and consumer sciences and medical laboratory technologists. The managers of the study were Anu Hopia Professor of Food Science, University of Turku and Hannu Puolijoki Professor, Medical Doctor, the Central Hospital in Southern Ostrobothnia. The author was the principal researcher and she was responsible for the general coordination of the study, including planning of the practical implementation of the research and intervention activities, recruiting and advising assistants, and the design of the study questionnaires and forms in collaboration with the other members of the research team.

4.2 Population and design (Papers I – IV) (Table 4 and Fig. 4)

All the participants were healthy adults, aged 20 to 67 years and a major proportion of participants had already previously participated in the TERVAS study through a questionnaire (n = 1706), which was randomly sent to 4,000 people in Southern Ostrobothnia. In this questionnaire, participants had the opportunity to report their willingness to participate in further studies; 520 people agreed to this further participation. Half of the participants were randomized into this intervention (n = 260). The first contact was made by telephone, when participants were asked whether they were willing to participate in the intervention along with questions about their demographic details and state of health. They were also given information about the study (schedule, measurements, genetic testing). Every participant who was identified as being on long-term medication (e.g., diabetes, cholesterol, blood pressure, psychiatric) or having a disease (e.g., diabetes, psychiatric) was excluded at this phase (n = 145). A minor proportion of the participants were recruited through newspaper advertisements (n = 36). (Table 4, Fig. 4)

Baseline interviews with all participants (n = 151) were conducted and the first measurements were taken. In this baseline interview, their health state was screened, using a generally used form, which means that they were asked about any medication; diseases, and use of functional products which affect cholesterol absorption (e.g. plant stanols and sterols).

They were also asked about alcohol consumption, smoking habits, physical activity, and how they perceived their own health. In this first interview, the participants gave their written consent to participate in the intervention. All participants had the opportunity to refuse to see their blood and gene results: no one refused.

After these interviews, the participants (n = 130) were given blood tests (including their serum's lipids, blood glucose (0h and 2h), basic blood count (e.g. hemoglobin), the kidneys function (fP-Krea), liver (p-ALAT) and thyroid (P-TSH)), and anthropometric measurements (e.g. blood pressure, Body Mass Index, waist circumference and body fat percentage). They also completed questionnaires on psychological factors (threat, anxiety, the stage of change) and behavioral factors (including diet, alcohol consumption, physical activity and health and taste attitudes). On the basis of the first interview (n = 21) and blood tests (n = 8), participants, who had long-term medication (e.g., diabetes, cholesterol, blood pressure, psychiatric medication) or chronic conditions (e.g., diabetes or mental disorders) were excluded (n = 29). These people were directed to public health care. Other inclusion criteria included: blood pressure under 160/99 mm/Hg, hemoglobin over 120 g/l, proper kidney, liver and thyroid function (fP-Krea <115 umol; p-ALAT 10 – 35 U/I (women), 10 – 50 U/I (men);P-TSH 0.30 – 4.20 mU/l). Individuals who were overweight (BMI 20 – 35 kg/m^2), had slight hyperlipidemia (total cholesterol < 8 mmol/l, triglycerides < 4.5 mmol/l) or impaired glucose tolerance (fasting glucose < 7.0 mmol/l and glucose two hours after challenge < 11.0 mmol/l) were included in the study. After the first screening, the final number of participants for the intervention was 122. (Table 4, Fig. 4)

After these first measurements (T0), all participants attended a lecture on healthy lifestyle and diet held by a qualified nutritionist (chapter 4.2.3).

This study was single-blinded as the principal researcher, and a medical doctor, followed the anxiety measurements of the participants. The participants (n = 122) were randomized into a control group (n = 61) and an intervention group (n = 61).

After eight weeks, immediately after all genotype results were ready and available, the intervention groups (Ɛ4+ and Ɛ4-) received their *APOE* genotype information and health message by mail. This information was sent together with a tailored health-risk message based on their *APOE* genotype (Table 5, chapter 4.2.4 Health messages, Appendix 1-8). The specific threat communicated to the participants was, in this case, CVD, and the effect of the *APOE* genotype on CVD was emphasized for each participant in the intervention groups.

Within two weeks of receiving their messages and genotype information (T1), all participants also received web-based questionnaires on psychological factors (e.g. threat and anxiety experiences, the stage of change) and behavioral factors (e.g. diet, physical activity, alcohol consumption, health and taste attitudes). (Table 4, Fig. 4). About two weeks was assumed to be sufficient time for the participants to ponder the results, but not too long in order to be able to capture the first psychological responses (e.g. threat and anxiety experience).

After 12 weeks, all the participants were offered the opportunity to attend genetic counseling and a lecture was given by a professor of nutrigenomics and nutrigenetics. At this point, the intervention group also had the possibility to have a personal discussion with a medical doctor. Seven people used this opportunity. (Chapter 4.2.3 Lectures and Consultations) After five months the health messages and gene information were repeated (Fig 4).

At the six-month measurement point (T2), the participants were given blood tests (including the cholesterol level, blood glucose (0 h) and basic blood picture) and other measurements (e.g. Body Mass Index, fat percent, waist circumference, blood pressure). These measurements were the same as those taken at the baseline, except for the gene tests and glucose tolerance 2-hours tests. At this phase of the intervention, participants again received web-based questionnaires on behavioral factors (e.g. diet, alcohol consumption, physical activity and health and taste attitudes); this was before they took part in the six-month clinical measurements. Psychological factors (e.g. threat, anxiety and the stage of change) were not gauged at this time. (Table 4, Fig. 4)

The final measurements, after 12 months (T3), were very similar to the six-month measurements (T2). In this phase participants (n = 117) took part in a glucose tolerance 2-hour test and answered questionnaires regarding threat, anxiety, and the stage of change. (Table 4, Fig. 4) After 12 months, the control group also had the opportunity to obtain further information about their own *APOE* genotype and the opportunity to consult with a medical doctor. This session was similar to the intervention group. Three people used this opportunity for a personal discussion with a doctor. (Chapter 4.2.3 Lectures and consultation)

Of all 122 participants, five people withdraw from the intervention, and participants who had started cholesterol, blood pressure or diabetes medication during the intervention were excluded (n = 4). There were 113 participants who completed the study. For the analyses, participants who had missing values in their answers (n = 4, (Papers I, II); n = 5 (Papers III, IV)) or transpired to be outliers were excluded (n = 2). Thus, results for 107 (Papers I, II) and 106 (Papers III, IV) participants were analyzed. (Fig. 4)

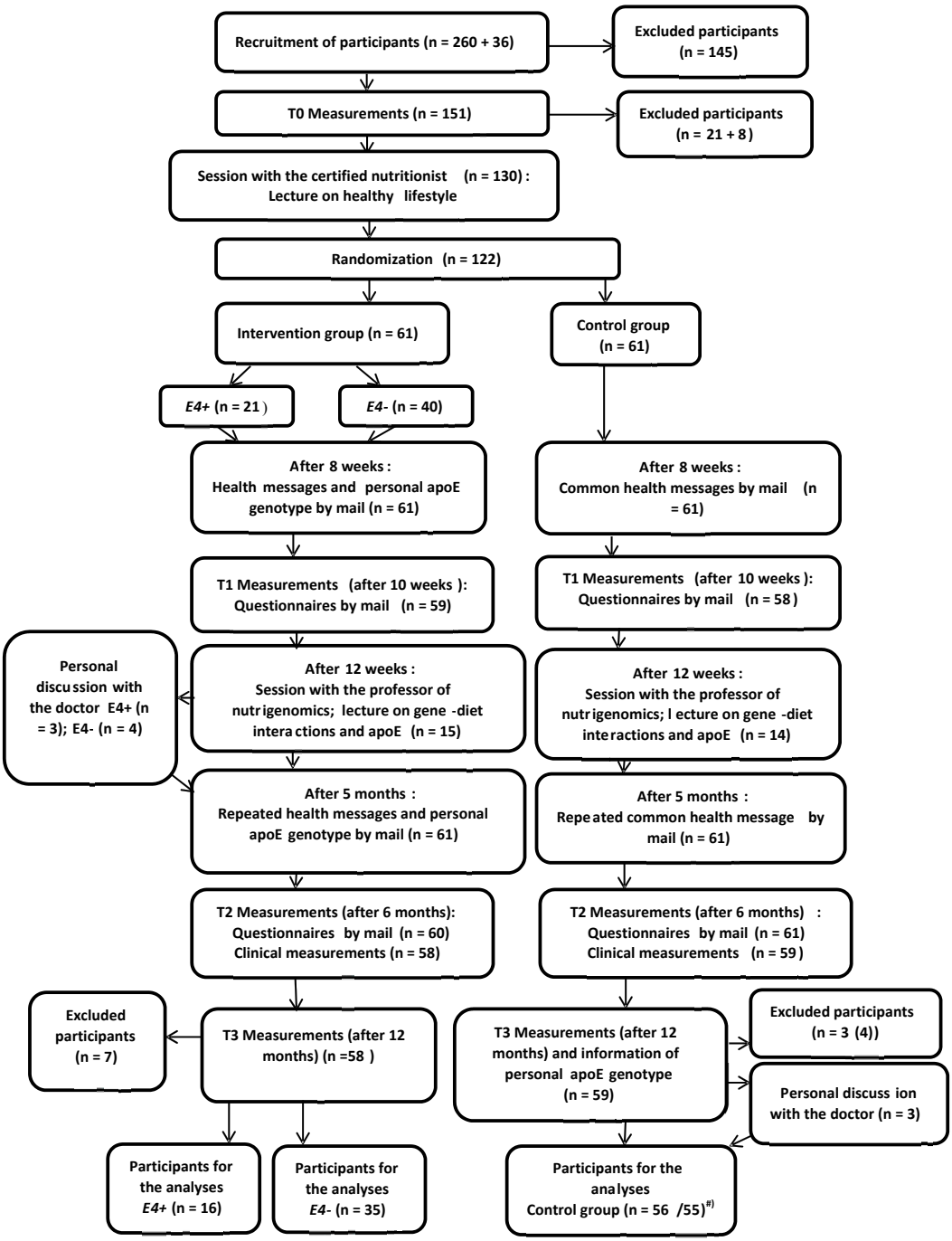

Figure 4. General procedure of the intervention.

#) There were 56 participants in the studies I and II and 55 participants in the studies III and IV.

Table 4. Schedule of measurements.

	Baseline (T0)	10 weeks (T1)[#)]	Six months (T2)	12 months (T3)
Baseline Interview	x	NM	NM	NM
ApoE gene test	x	NM	NM	NM
Psychological measurements	x	x	NM	x
State Anxiety (A-State)	x	x	NM	x
Trait Anxiety (A-Trait)	x	x (NA)	NM	x (NA)
Threat	x	x	NM	x
State of change	x	x	NM	x
Behavioral measurements	x	x	x	x
Dietary fat quality	x	x	x	x
Consumption of vegetables	x	x	x	x
Consumption of high fat and sugar foods	x	x	x	x
Consumption of alcohol	x	x	x	x
Physical activity	x	x	x	x
Health and taste attitude (HTAS)	x	x	x	x
Clinical measurements	x	NM	x	x
Serum's lipids	x	NM	x	x
Blood glucose (0h)	x	NM	x	x
Blood glucose tolerance (2h)	x	NM	NM	x
Blood pressure	x	NM	x	x
Body Mass Index	x	NM	x	x
body Fat Percentage	x	NM	x	x
Waist circumference	x	NM	x	x

[#)] two weeks after receiving gene results.

x (measured)

NM (not measured)

NA (not analyzed in statistically). A-Trait is personal property and it was only used as an background variable.

4.2.1 Intervention groups

There were two intervention groups: a high risk group (Ɛ4+), including individuals with the *APOE* genotype 3/4 or 4/4 and low risk group (Ɛ4-), including individuals with the *APOE* genotypes 2/3 and 3/3. Both intervention groups received their genetic information at the beginning of the intervention. They received tailored health messages during the intervention and they had the opportunity to have a discussion with the doctor after the genetic feedback. Altogether, 51 participants remained in the intervention: 16 in high-risk group and 35 in low-risk group. Genotypes *APOE* 3/4 (n = 15) and 4/4 (n = 1) were included in group Ɛ4+ and genotypes 2/3 (n = 8) and 3/3 (n = 27) were included in group Ɛ4-.

4.2.2 Control group

At the beginning of the intervention, 61 participants were randomized into a control group. Altogether, 56 (Papers I – II) and 55 (Papers III - IV) participants remained in the intervention. In the control group, the participants had genotypes 3/4 (n = 11), 4/4 (n = 1), 2/3 (n = 6), 3/3

(n = 37 (36)), and 2/2 (n = 1). The control group received their genetic information at the end of the intervention (after 12months). During the intervention, they received only general information about the study together with general health information on lifestyle and CVD risk, based on health and nutrition recommendations and studies from the National Institute for Health and Welfare, Finland. At the end of the intervention, they also had an opportunity to have a discussion with the medical doctor.

4.2.3 Lectures and consultation

The first communication session, held by a certified nutritionist was arranged on the same day as the first measurements (T0). This lecture was compulsory and the purpose of the lecture was that every participant would have the same basic knowledge regarding a healthy diet and lifestyle. It was essential that participants would understand the importance of eating healthy food and the role *APOE* plays in cardiovascular health. During the lecture, it was emphasized that healthy choices are cornerstone factors for decreasing risks for lifestyle diseases, such as CVD, and that genomics have a limited role in increasing or decreasing risks for lifestyle diseases. In addition, the connection between the *APOE* gene to Alzheimer disease (AD) was mentioned, due to ethical reasons (*APOE* 4 allele increases the risk to having AD). However, the aim was to focus on the role of *APOE* in cardiovascular health.

The second communication session was arranged after the intervention group received their gene results (3 months after baseline). This lecture was elective, held by a professor of nutrigenomics and it focused more on gene-diet interactions and function o of the *APOE* gene than the first lecture. Twenty nine participants attended this lecture (Fig. 4).

Both groups (intervention and control group) also had an opportunity for a private discussion with a medical doctor about their blood- and gene test and how these results have affected them physically and mentally. The intervention group had this opportunity after the genetic feedback (3 months after baseline) and the control group had the same opportunity after the intervention (12 months after baseline). Seven participants from the intervention group (Ɛ4+ (n = 3), Ɛ4- (n = 4)) and three participants from the control group used this opportunity (Fig. 4). These personal discussions were arranged as recommended the Ethical committee.

4.2.4 Health messages (Table 5, appendix 1-8)

The health information (message) was based on the analyzed *APOE* genotype and it was performed using the Extended Parallel Process Model (EPPM) (Witte 2001). The specific risk communicated to the participants in the study concerned CVD, and the effect of the *APOE* genotype on CVD risk was emphasized for each participant in the intervention groups by using one of the four different kinds of health messages. All the tailored health information comprised of four different parts: response efficacy, self-efficacy, susceptibility, and severity

(Witte 2001). The combinations of messages were high real threat + high experience threat, high real threat + low experience threat, low real threat + high experience threat, and low real threat + low experience threat. If people had a high CVD threat experience and they also had an actual threat (Ɛ4+), a health message was created to reassure and intensify self-efficacy and efficacy. Those, who lacked the threat of a risk of CVD and also experienced no actual threat (Ɛ4-), received a message, which aimed to inform these participants about the disease. Participants, who had high actual threat (Ɛ4+), but did not feel a threat as regards the received message, the message was aimed to add susceptibility. The message for participants, who had a high threat feeling, but no actual threat (Ɛ4-) comprised items about increasing self-efficacy and susceptibility.

In practical terms, the message for the Ɛ4+ group emphasized that a dietary change (e.g., improvement of fat quality) and increased exercise would be especially important for their genotype in order to lower the cholesterol level and prevent CVD. The information for the Ɛ4- group emphasized the interaction between environmental factors and the genotype and highlighted the significance of the individual's own lifestyle. The control group received only general information about the study together with general health information on lifestyle and CVD risk, based on health and nutrition recommendations and studies from the National Institute for Health and Welfare, Finland. This message did not consider the *APOE* genotype or threat experience.

Table 5. Health messages.

Group	Based	Model	Specific Risk	Aim	Example
Ɛ4+	*apoE* genotype 3/4 or 4/4	Extended Parallel Process Model (EPPM) (Witte 2001)	CVD	To emphasize the importance of the genotype on influencing dietary changes (e.g., improvement of fat quality) and increasing exercise to lower cholesterol level to prevent CVD	*"…you have apoE 3/4 genotype, which means that you have hereditary higher cholesterol and bigger risk to get CVD, but especially YOUR cholesterol has good response to lifestyle changes…"*
Ɛ4-	*apoE* genotype 3/3, 2/3 or 2/2	Extended Parallel Process Model (EPPM) (Witte 2001)	CVD	To emphasize the interaction between environmental factors and the genotype and highlight the significance of the individuals' own lifestyle.	*"…your apoE genotype doesn't increase risk to higher cholesterol and CVD, but apoE is only ONE factor - your own lifestyle has big weight preventing CVD…"*
Control	general health and nutrition recommendations and studies from the National Institute for Health and Welfare, Finland.	-	CVD	To give general health information on lifestyle and CVD risk.	*"…genome may predispose to CVD, but healthy diet, regular physical activity, minor alcohol consumption and maintenance normal BMI lower clearly the CVD risk…"*

4.2.5 Assessments of *APOE* genotype

The whole blood samples at baseline for the *APOE* assay were taken at the South Ostrobothnia Central Hospital laboratory. Genomic DNA was extracted from the blood samples, as described by (Miller et al. 1988). The genomic region containing two SNPs (rs429358:p.Cys130Arg and rs7412: p.Arg176Cys) was amplified using the primers 5'-GCCTACAAATCGGAACTGGA and 5'-ACGAGGTGAAGGAGCAGGT and sequenced with the MegaBACE 1000 (Amersham Biosciences, UK). The three major *APOE* isoforms were determined by these SNPs, which translate into the common (epsilon) protein isoforms ε2 (130Cys/176Cys), ε3 (130Cys/176Arg), and ε4 (130Arg/176Arg). DNA extractions and genotyping were conducted at the Natural Resource Institute Finland (Luke; earlier MTT).

4.2.6 Psychological assessments (Paper I)

The study participants completed three psychological assessments (T0, T1, T3) (Table 4) during the intervention - their validated anxiety (State-Trait Anxiety Inventory, STAI), threat (Risk Behavior Diagnostic Scale, RBD) and stage of change (The Transtheoretical Model of Behavior Change) questionnaires (Spielberger C, Gorsuch RL 1970; Spielberger C 1971; Witte 2001; Prochaska JO 2005).

STAI measures both State Anxiety and Trait Anxiety. The State Anxiety (A-State) is an emotional feeling for which the intensity may change under different circumstances and it describes the feelings at the moment. The Trait Anxiety (A-Trait) is a personal property, which differs among individuals and it describes general feelings. (Spielberger C, Gorsuch RL 1970; Spielberger C 1971).

Threat experience, measured by RBD, describes the perceived Health Threat, which was related to cardiovascular diseases in the present study. It comprises items of Response Efficacy, Self-Efficacy, Susceptibility and Severity. (Witte 2001)

Stage of change describes a motivation for lifestyle change ("Have you considered a lifestyle change?") and it comprises five stages: (1) pre-contemplation, (2) contemplation, (3) preparation, (4) action, and (5) maintenance (Prochaska JO 2005). In dissertation study included the first four steps.

4.2.7 Health behavioral assessments (Paper II)

All the study participants were asked to answer five different health behavior questionnaires four times (T0, T1, T2, T3) during the intervention (Table 4). The dietary fat quality –assessment was based on the questionnaire of the Finnish Heart Association (Finnish Heart Association 2010). This questionnaire has nine items and it describes how large a part of an individual's diet has unsaturated and saturated fat.

In the questionnaire on vegetables, fruits, and berries questions were asked about the portions of these in daily consumption, and it was based on the National Institute of Health and Welfare, in Finland, and also the report of the FIN-D2-D project (Peltonen et al. 2008; Saaristo et al. 2009)

Questions were asked about the weekly consumption of high fat/sugar. The foods were divided the six categories: pizza, hamburgers and kebab, salty pastries (e.g., meat pies), salty snacks (e.g., potato chips), sweet pastries (e.g., biscuits), chocolate, and candies. Sweetened beverages were also categorized into high sugar fruit drinks or high sugar soft drinks (e.g., Coca-Cola©). This questionnaire was created in cooperation with the research team and based on the report of National Institute for Health and Welfare, Finland (Helakorpi et al. 2008).

The study participants were asked the frequency and weekly portions of alcohol consumption and in addition the frequency of leisure time physical activity. These questionnaires were based on the report of the National Institute for Health and Welfare, Finland (Helakorpi et al. 2008).

4.2.8 Health and taste attitude assessments (Paper II)

The study participants completed the validated health and taste attitude questionnaires (HTAS) four times (T0, T1, T2, T3) during the intervention (Roininen et al. 2001). The HTAS measures the importance of the health and taste aspects in the food choice process and it consists of six different dimensions (1) general health interest, (2) light product interest, (3) natural product interest, (4) craving for sweet foods, (5) using food as a reward, and (6) pleasure. The first three dimensions represent the health attitude, and the other three dimensions the taste attitude. (Roininen et al. 2001) (Table 4)

4.2.9 Clinical assessments (Paper III)

The clinical assessments were arranged three times (except two hours after challenge blood glucose test two times (T0, T3)) during the intervention: at the baseline (T0), after six months (T2) and at the end of the intervention (T3). Measurements were performed in the Department of Clinical Chemistry, at the Central Hospital of Southern Ostrobothnia, Finland. Blood samples and blood pressure (systolic/diastolic) were taken by medical laboratory technicians. Metabolic Syndrome (MeS) was also assessed based on worldwide definitions (Alberti et al. 2005). (Table 4)

Serum lipids (total-, LDL-, HDL cholesterol, triglycerides) and blood glucose (fasting glucose (0h), 2 h after challenge (2h)) were analyzed according to standard guidelines by enzymatic photometry, The Architect c8200 analyzer (Abbot Diagnostic, Abbot Park, IL, USA).

Blood pressure was analyzed with using an oscillometric method, i.e., two measurements, in a sitting position, using the right arm, after 15 minutes of rest.

Anthropometric analyses (Body Mass Index, body fat percentage) were conducted by Body Composition Meter (Omron BF 500). Weight was analyzed with light indoor clothes, and height without shoes. Waist circumference was measured by a measuring tape, midway between the lowest rib and the iliac crest.

For the inclusion/exclusion of the participants, the Complete Blood Count (CBC) (Sysmex XE-5000, Kobe, Japan) and the kidney function (fP-Krea), liver (p-ALAT) and thyroid (P-TSH) were assayed in a baseline (T0).

4.2.10 Explained changes and predictors (Paper IV)

Study IV combined the results of the three previous Papers (I, II, III) by analyzing associations between psychological-, behavioral- and clinical changes. It focused on explaining the changes, which were statistically clearest in the previous studies (I, II, III). The changes were cardiovascular threat experience (T0-T1), based on Risk Behavior Diagnostic Scale (RBD) (Witte 2001), dietary fat quality (T0-T1) based on questionnaire of Finnish Heart Association (Finnish Heart Association 2010), triglyceride values (T0-T2) based on standard guidelines by enzymatic photometry, The Architect c8200 analyzer (Abbot Diagnostic, Abbot Park, IL, USA) and waist circumference (T0-T2) based on tape measurements, midway between the lowest rib and iliac crest.

Predictors, were included in the analysis in following order, group (Ɛ4+, Ɛ4-, control), sex, age, psychological assessments (Trait-Anxiety (T0), State Anxiety (T0-T1), stage of change (T0-T1), behavioral assessments (T0-T1; dietary fat quality, consumption of vegetables, consumption of high fat and sugar foods, consumption of alcohol, physical activity), attitude assessments (T0-T1; health and taste attitude (HTAS (Roininen et al. 2001)) and clinical assessments (T0-T2; Total-, LDL- HDL cholesterol, blood glucose (0h), blood pressure, Body Mass Index, body Fat Percentage,). In addition, the explained changes (threat experience, dietary fat quality, triglyceride values and waist circumference) were included as predictors, when explaining the other changes that were statistically clearest.

4.2.11 Statistical methods

Data management and analysis were performed using SPSS (IBM) Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0 Armonk, NY: IBM Corp. In Papers I-III, the preliminary analyses (exploring normality, missing values, and outliers) were done before the final analyses. Normality was analyzed from residuals with the Kolmogorov-Smirnov method and histograms. Variables, (*State-anxiety*, *dietary fat quality, consumption of high fat/sugar foods, and alcohol*, *BMI* and *waist circumference)* which were not normally distributed were transformed and modified. The main variables were adjusted for their own baseline scores (T0) by covariance analyses. In addition state-anxiety was adjusted for trait-anxiety.

In Papers I-III, the main effects of the adjusted scores were analyzed by a mixed between-within subject analysis of variance (a combination of repeated-measures ANOVA and a between-groups ANOVA; General linear models, repeated measures). A Chi-Square –test was used to analyze the frequencies. Pairwise comparisons were conducted using the Bonferroni method. The effects of the lecture and personal discussions with the doctor at measuring point T3 were analyzed using covariance analyses (one-way ANCOVA).

In Paper IV, changes (Δ) between T0 and T1/T2 measuring points were calculated. Changes (Δ) between T0 and T1/T2 measuring points were calculated. Preliminary analysis (exploring normality, multicollinearity, missing values and outliers) were done before final analyses. Hierarchical multiple regression was used to analyze predictors for the changes in threat experience, dietary fat quality, triglyceride values and waist circumference. In regression analysis, the variable indicating the group (Ɛ4+, Ɛ4-, control) was forced into the model after which a forward stepwise method was used to find out the statistically strongest predictors (models (a) to (c)).

Randomization and the power analysis

The included participants (n = 122) were randomized into a control group and an intervention group. The randomization was done by using the random sampling method of Microsoft Excel. Participants who received the first 61 random numbers were put into the intervention group and the remaining 61 participants were put into the control group. The randomization was done before genotype results were available, so the intervention group sizes differed. This difference was purely due to the number of carriers with *APOE* 3/4 and 4/4.

Effect sizes (*Partial Eta Squared*) and observed power were analyzed by SPSS program. Statistical power analysis was conducted by G*Power program (Faul et al. 2007). It was done after the intervention, when analyzing results. Based on the power analysis, F-test (sensitivity) was used to calculate minimum, detectable effect sizes with the power of 0.80 and the appropriate F-test for the main variables was ANOVA (Repeated measures, between factors) and for the effects of lecture and discussion and A-Trait ANCOVA (Main effects and interactions).

The effect sizes (f) were for the main variables (A-State, threat, stage of change) 0.190 and for analyses of covariates (the effects of lecture and discussion and A-Trait) 0.275.

5 RESULTS

5.1 Baseline results (Papers I – IV) (Table 6 and 7)

Altogether 113 individuals completed the study of which the psychological and behavioral factors were analyzed for 107 participants and the clinical factors for 106 participants. Of the total of 107 (106) individuals who were analyzed, 69.2 percent were females, with a mean age of 47.0 (standard deviation, S.D.: 12.1) years (range: 20–67 years). There were significant differences ($p < 0.001$) in the age between the women and the men who participated in the study (women: 44.2 years (S.D.: 11.4) *versus* men: 53.3 years (S.D.: 11.4)). (Table 6)

Approximately one-fourth (26.2%) of the participants had an E4 allele (3/4, 4/4) placing them at an increased risk for CVD. Sixteen participants with the high-risk genotype (*APOE* 3/4, 4/4) were randomized in the high-risk intervention group and 12 participants in the control group. Thirty-five participants with the low risk genotype (*APOE* 2/3, 3/3, 2/2) were in the low-risk intervention group and 44 in the control group. Differences between the groups were not significant. (Table 6)

The A-Trait was mild (Spielberger C, Gorsuch RL, Lushene PR, Vagg Pra 1983); approximately 31.7 and varied between 21 and 50. (Table 6)

Clinical measurements were also analyzed at the baseline between the different *APOE* genotypes. The total population (n = 106) was divided into two groups: *APOE* 4+ (n = 28), including participants with the *APOE* 3/4 and 4/4 genotypes and *APOE*4- (n = 78), including *APOE* 2/2, 2/3 and 3/3 genotypes. Mean total cholesterol was 5.20 mmol/l, LDL cholesterol 3.10 mmol/l, HDL cholesterol 1.52 mmol/l and triglycerides 1.18 mmol/l. Average body mass index was 25.8 kg/m^2. (Table 7) The metabolic syndrome (Alberti et al. 2005) was present in 18.9 % of the total participants and 24.2 % of the men and 16.4 % of the women.

The differences between the groups (*APOE*4+ and *APOE*4-) were minor at the baseline. The *APOE*4+ group had a higher total, LDL and HDL cholesterol than the *APOE*4- group and correspondingly the *APOE*4- group had higher triglyceride content, blood glucose (0h and 2h), blood pressure (systolic and diastolic), BMI, fat percent, and waist circumference than the *APOE*4+ group. The only significant difference was in body fat percentage ($p = 0.003$) as it was 28.5 % in *APOE*4+ group and 33.9 % in *APOE*4- group. (Table 7)

Table 6. Demographics and background variables of included (107/106) participants.

	Total	Ε4+ group	Ε4- group	Control group
Number of participants (n)[#)]	107 (106)	16	35	56 (55)
Age (years, mean (SD))	47.0 (12.1)	47.8 (12.3)	47.3 (11.2)	46.7 (12.9)
Men (years, mean (SD))	53.3 (11.4)[***)]			
Women (years, mean (SD))	44.2 (11.4)			
Female, sex %, (n)	69.2 (74)	62.5 (10)	85.7(30)[*)]	60.7(34)[*)]
ApoE genotype %, (n)				
E3/E3	59.8 (64)	0 (0)	77.1 (27)	66.1 (37)
E3/E4	24.3 (26)	93.8 (15)	0 (0)	19.6 (11)
E2/E3	13.1 (14)	0 (0)	22.9 (8)	10.7 (6)
E4/E4	1.9 (2)	6.2 (1)	0 (0)	1.8 (1)
E2/E2	0.9 (1)	0 (0)	0 (0)	1.8 (1)
Trait-Anxiety (mean (SD))	31.7 (6.5)	33.7 (7.9)	30.3 (5.9)	31.9 (6.5)
Moderate anxiety % (n)	12.3 (13)	18.8 (3)	8.8 (3)	12.5 (7)
Participants in personal disscussion % (n)	9.3 (10)	18.8 (3)	11.4 (4)	5.4 (3)
Partipants in the lecture of nutrigenomics % (n)	27.1 (29)	56.3 (9)	17.1 (6)	25.0 (14)

[#)] In studies I and II included in 107 participants and in studies III and IV included in 106 participants.
[*)] $p<0.05$
[***)] $p<0.001$

Table 7. Comparison of baseline clinical measurements between the *APOE*4+ (3/4, 4/4) and *APOE*4- group (2/2, 2/3, 3/3).

	Total	ApoE 4+ group (n = 28)	ApoE 4- group (n = 78)
Measurement	Mean (SD) (baseline)	Mean (SD) (baseline)	Mean (SD) (baseline)
Total cholesterol (mmol/l)	5.20 (0.95)	5.26 (0.90)	5.15 (0.96)
LDL cholesterol (mmol/l)	3.10 (0.81)	3.26 (0.74)	3.07 (0.83)
HDL cholesterol(mmol/l)	1.52 (0.35)	1.52 (0.40)	1.52 (0.33)
Triglycerides (mmo/l)	1.18 (0.60)	1.06 (0.55)	1.22 (0.61)
Blood glucose (0h) (mmol/l)	5.50 (0.43)	5.48 (0.45)	5.53 (0.42)
Blood glucose (2h) (mmol/l)	5.90(1.32)	5.52 (1.33)	5.98 (1.30)
Blood pressure, *systolic* (mmHg)	129.3 (16.6)	127.0 (17.4)	130.1 (16.4)
Blood pressure, *diastolic* (mmHg)	77.1 (9.0)	75.8 (9.2)	77.6 (8.9)
Body Mass Index (BMI) (kg/m^2)	25.8 (3.8)	24.7 (3.0)	26.1 (4.0)
body Fat Percentage (%)	32.5 (8.2)	28.5 (6.8)[**)]	33.9 (8.3)[**)]
Waist circumference (cm)	85.9 (11.2)	84.2 (10.6)	86.6 (11.4)

[**)] $p<0.01$

5.2 Intervention results (Papers I – III)

The intervention had some effects on psychological, health behavioral and clinical factors. The effects were both short-term and long-term.

5.2.1 Psychological results (Paper I, Fig. 5)

State Anxiety

State anxiety (A-State) was mild (Spielberger C, Gorsuch RL 1970; Spielberger C 1971) in every group at every measurement point and varied from 27.9 to 36.1. The adjusted baseline scores were 30.8 in every group (Paper I). The A-State increased during the first 10 weeks in the Ɛ4+ (Δ+3.1) and control (Δ+2.2) groups, but decreased in both groups (Ɛ4+ group, Δ-1.5; control group Δ-0.1) during the last 10 months, although remaining at a higher level than at the baseline. In the Ɛ4− group, the A-State decreased (Δ-0.1) after genetic feedback, but increased (Δ+1.1) between the measuring points T1 and T3. Experience of the A-State was significantly different in every group at the T0 measuring point compared with T1 measuring point (p=0.006) (Paper I). However, throughout the intervention period (12 months), there were no significant differences between the groups in their experiences of the A-State, although the trend in Ɛ4− was opposite to the Ɛ4+group and control groups (Paper I, Fig. 5).

Threat experience

Every group had positive scores for the threat experience, which means that none of the groups felt any fear towards CVD (Witte et al. 2001) (Paper I). The mean threat experience among the total population was 5.0 (S.D.: 7.1) at the baseline. The adjusted baseline scores were 5.0 in every group (Paper I). Threat was experienced most strongly by the Ɛ4+group (Δ-3.5) after they had received their personal genetic information, but it decreased (Δ+1.5) after 12 months, although remaining at a higher level than at the baseline (T0). Threat experience decreased in the Ɛ4− group (Δ+2.0) after the first 10 weeks, but increased (Δ-0.3) a little towards the 12 months period. In the control group, the changes were similar to those in the Ɛ4+group, but were smaller (T0-T1: Δ-0.8; T1-T3: Δ+1.5). (Paper I; Fig. 5). There was almost no significant difference (alpha value 0.017) between the Ɛ4+ and Ɛ4− groups as regards threat experience (p=0.034) (Paper I). At the T3 measurement point, the threat experience was still at a higher level in Ɛ4+group (2.5) than in Ɛ4− group (6.7) and control group (5.7) (Paper I; Fig. 5). **NOTE. In the threat experience, the lower the scores, the higher the threat experience.**

Stage of change

At the start of the intervention, every group was on average at stage 2 (contemplation, getting ready, consider lifestyle change within the next 6 months) and after the intervention each of

the groups were at stage 3 (preparation, ready, have planned lifestyle change within next month) (Fig. 5, Paper I). The stage of change was significantly different at the baseline (T0) compared with T1 and T3 measuring points ($p<0.001$) in every group (Paper I). The greatest change was in the Ɛ4+group (ΔT0-T1), but the differences were minor and there were no significant differences between the groups (Paper I, Fig. 5).

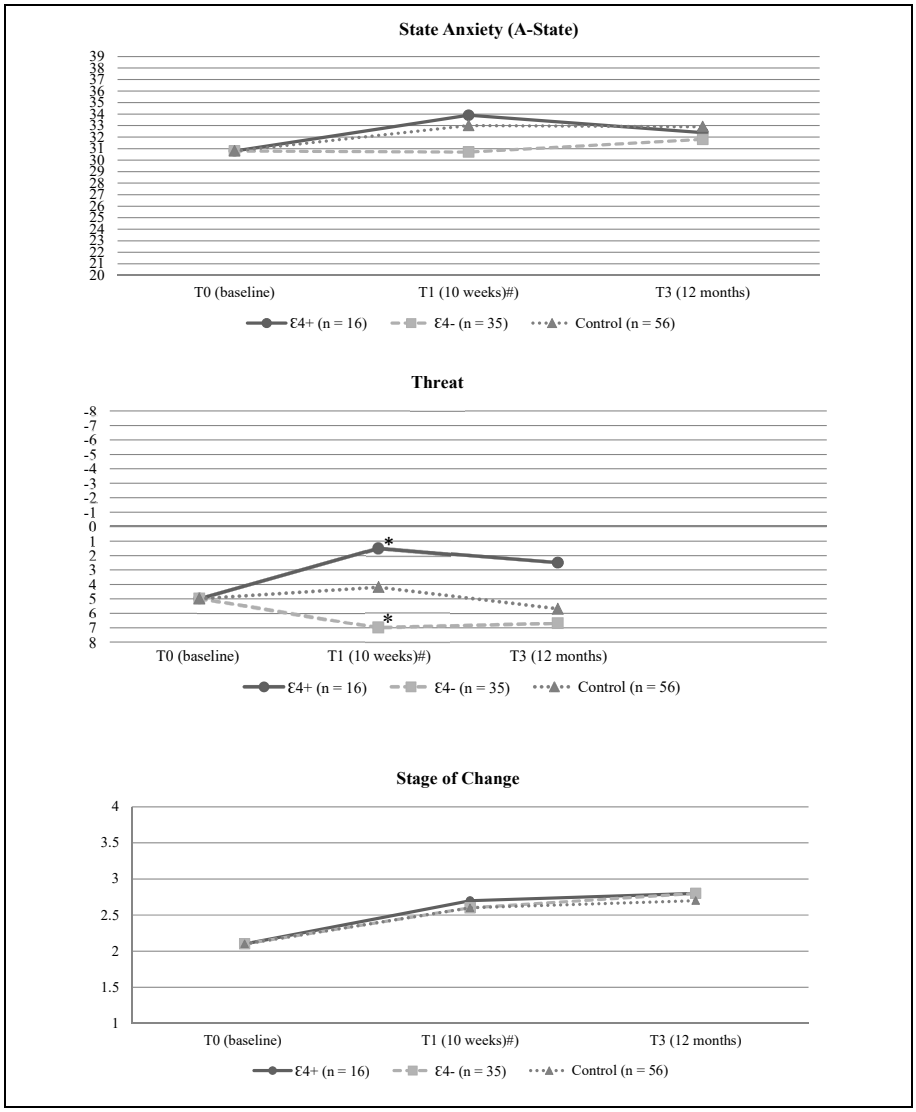

Figure 5. Changes in state anxiety, threat experience, and stage of change during the intervention.

*) p = 0.034 (alpha value 0.017)

NOTE. In threat experience, the lower the scores, the higher the threat experience.
The detailed scores and statistical tests are presented in Paper I.

5.2.2 Health behavioral results (Paper II, Fig. 6 and 7)

Dietary fat quality

Saturated fat intake was higher than recommended, belonging to the category '*most of dietary fat was saturated and only a minor part unsaturated',* scores: 10-17 (Finnish Heart Association 2010) in every group (adjusted scores 16.3) (Paper II, Fig. 6). The intake of unsaturated fat increased and saturated fat decreased in every group after the genetic feedback (T1). The change was greatest in the Ɛ4+ group (ΔT0–T1: +3.8), and there was a statistically significant difference between the Ɛ4+ and the control group ($p = 0.048$) (Paper II). Towards the end of the intervention and during the last 6 months with no active health communication (T3), the intake of saturated fat again increased and unsaturated fat decreased in both intervention groups. This unfavorable change in scores was higher in the Ɛ4+ group (ΔT2–T3: –1.7) than in the Ɛ4– group (ΔT2–T3: –0.2). In the control group, fat quality improved slightly even during the last 6 months of the intervention (ΔT2–T3: +0.2) (Paper II). Although the dietary fat quality deteriorated during the last 6 months of the intervention, the fat quality of the diet was improved at the end of the intervention (T3) compared with the baseline values (T0) for every group (Paper II, Fig. 6). Dietary fat scores were 18.7 (Ɛ4+ group), 18.3 (Ɛ4- group) and 17.8 (control group) after the 12 months (T3), this score belongs to the category '*acceptable in terms of fat quality and amount of unsaturated fat,* scores: 18-22 (Finnish Heart Association 2010). However, this total improvement (T0–T3) was not significant in any group. (Paper II)

Consumption of vegetables, fruits and berries, foods containing excessive fat and sugar and alcohol

The average vegetable, berry and fruit consumption at the baseline was 2.3 portions a day, which is below the recommended level in Finland (at least five portions in a day, one portion being for example 1 apple or handful of carrot pieces) (Paper II). Vegetable, fruit, and berry consumption increased slightly in every group during the intervention, being highest after six months (Ɛ4+ group: 3.0 portions, Ɛ4- group 3.0 portions and control group: 2.6 portions) (Paper II, Fig. 6). However, the differences between the groups were minor and not statistically significant (Paper II).

Mean consumption of foods containing excessive fat and sugar was 9.9 times/week at the baseline (Paper II). There was a decreasing trend in the consumption of foods containing excessive fat and sugar during the first 10 weeks (T1) in every group, being 8.2 times/week in Ɛ4+ group, 8.4 times/week in Ɛ4- group and 9.6 times/week in control group (Paper II, Fig. 6). After six (T2) and 12 months (T3), their consumption increased nearly to the baseline level of the Ɛ4+ group (9.0 times/week), but in the Ɛ4- group the consumption decreased further during the later six month period, being 6.7 times/week (T3) (Paper II, Fig. 6). Consumption

was 8.8 times/week in the control group after 12 months (12). The total decrease (T0-T3) of foods containing excessive fat and sugar was significantly different in Ɛ4- group compared with the control group ($p<0.05$). (Paper II)

The alcohol consumption was moderate during the intervention, being 2.4 doses/week at the baseline in every group (adjusted scores) and after 12 months 2.3 (Ɛ4+ group), 2.6 (Ɛ4- group) and 2.7 (control group) doses/week (Paper II, Fig. 6). At the baseline, alcohol was consumed the most (at least twice a week) by the control group (42.9 %) and the least by the Ɛ4+ group (18.8 %) (Paper II, Fig. 7). Of the participants in the Ɛ4- group 34.3 % consumed alcohol at least twice a week at the baseline (Paper II, Fig. 7). However, the changes in alcohol consumption after the disclosure of personal genetic information were minor, and there were no statistically significant differences between the groups (Paper II).

Leisure-time physical activity

Leisure-time physical activity (at least two times in a week) at the baseline was engaged in by 75.0 % of participants in the Ɛ4+ group, 80.0 % of Ɛ4- group and 66.1 % of control group (Paper II, Fig. 7). Genetic feedback had only a minor impact on physical activity. The greatest difference was ΔT0–T1 between the Ɛ4+ and the Ɛ4– group. Physical activity increased by 6.3% in the Ɛ4+ group but decreased by 17.1% in the Ɛ4– group; however, the difference was not significant. (Paper II, Fig. 7)

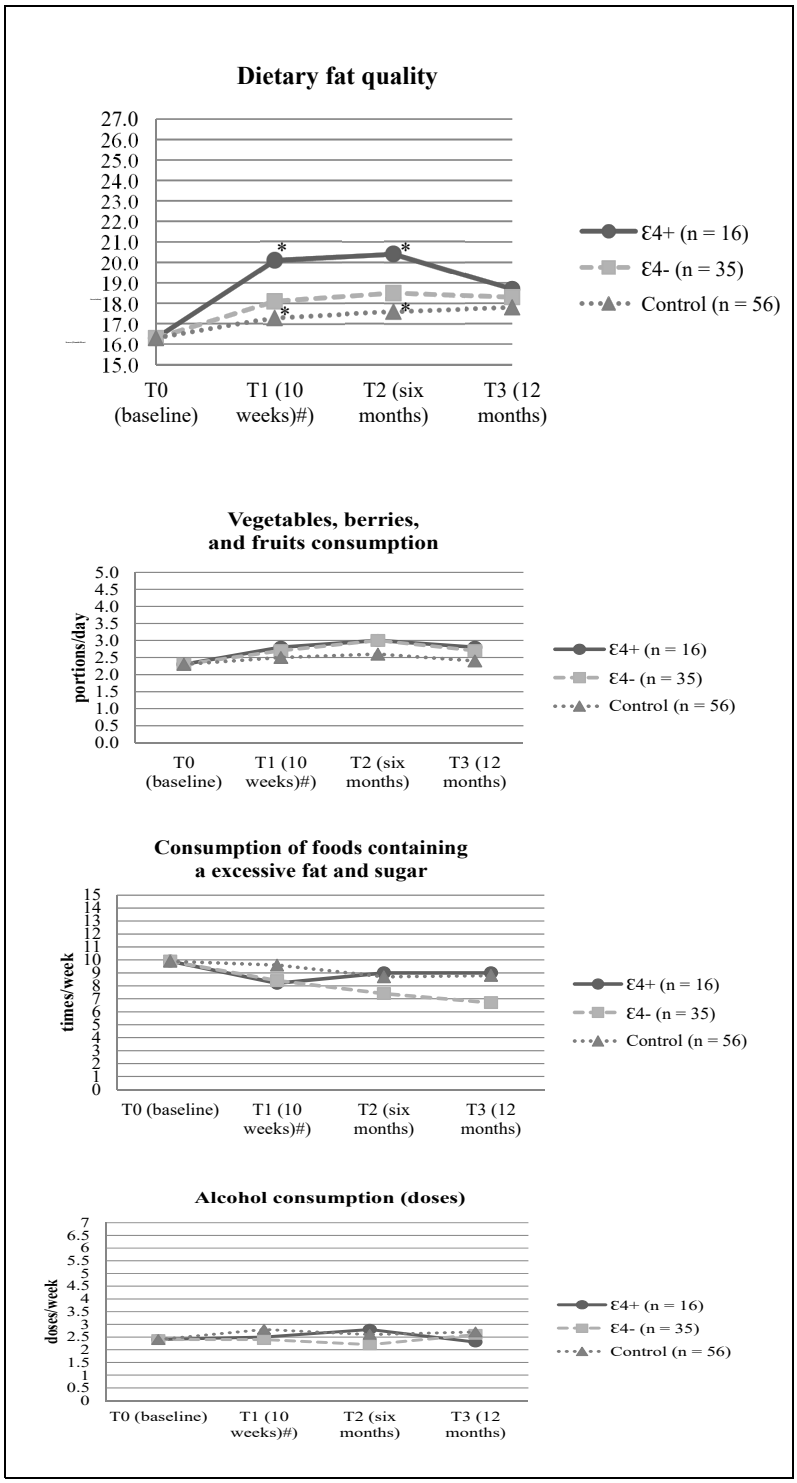

Figure 6. Changes in health behavior factors during the intervention
*) p = 0.48, #) two weeks after genetic feedback
NOTE. Detailed scores and statistical tests have presented in Paper II.

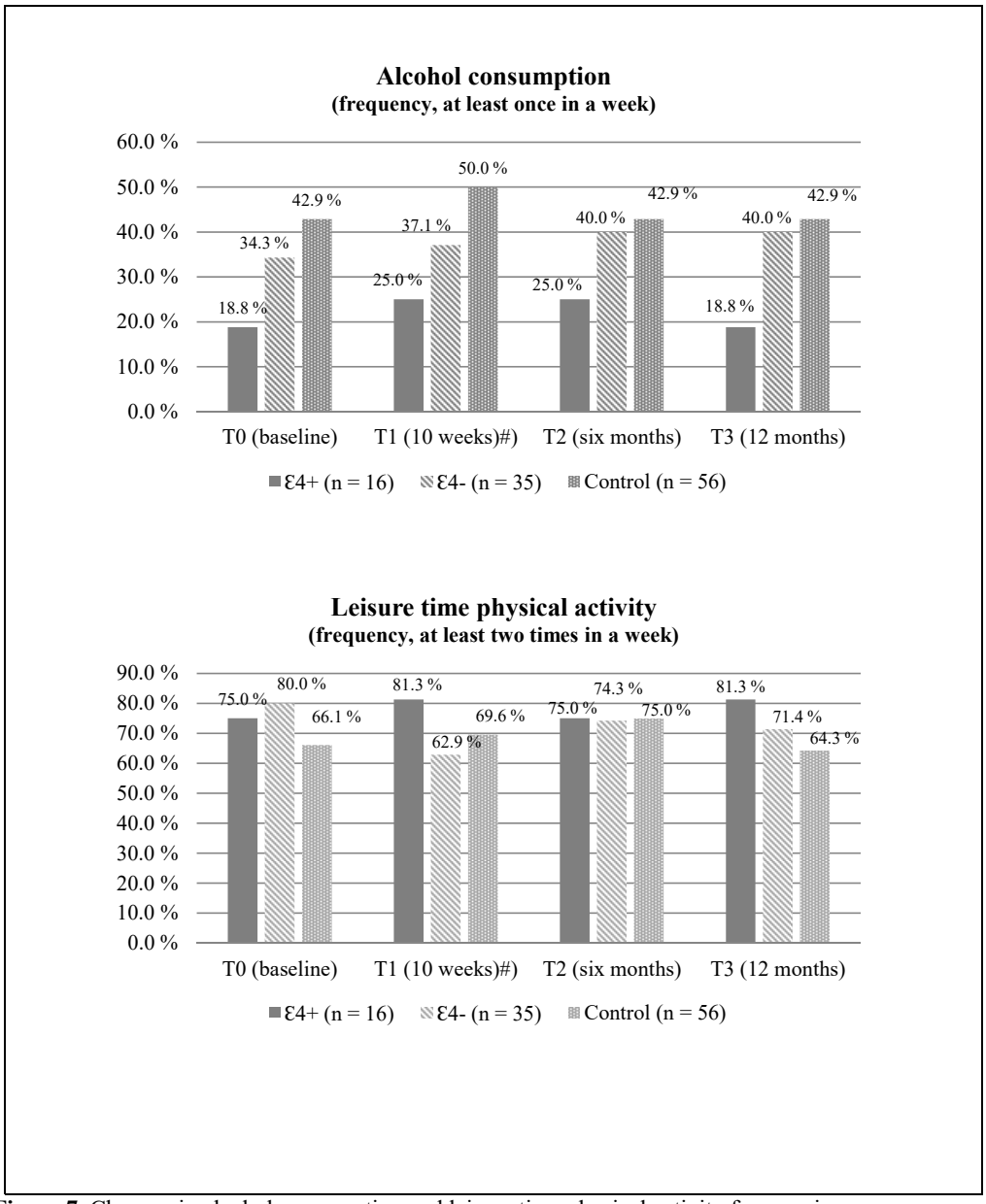

Figure 7. Changes in alcohol consumption and leisure time physical activity frequencies during the intervention.
#) two weeks after genetic feedback

5.2.3 Health and taste attitudes results (Paper II, Fig. 8)

Both health attitudes (general health interest, light product interest, and natural product interest) and taste attitudes (craving for sweet foods, using food as a reward, and pleasure) were above average (health attitudes range 20 – 160; taste attitude range 18 – 126) in the baseline in every group (health attitudes scores: 90.4 and taste scores: 73.9) (Paper II).

In every group, there was an increasing trend toward the valuation of health (T0-T1: Δ+8.3 (Ɛ4+), Δ+2.1 (Ɛ4-) and Δ+4.0 (control group) and a decreasing trend toward the valuation of taste (T0-T1: Δ-2.3 (Ɛ4+), Δ-2.3 (Ɛ4-) and Δ-1.2 (control group) after the genetic feedback (T1) (Paper II, Fig. 8). However, especially later after a six months period, the valuation of health decreased slightly in both intervention groups (T2-T3: Δ-2.2 (Ɛ4+) and Δ-1.4 (Ɛ4-) (Paper II, Fig. 8). In the control group, it stayed constant (94.4) during the later 10 months period. The taste scores decreased further during the later six months period (T2-T3) in both intervention groups, being 67.2 in Ɛ4+ group and 70.7 in Ɛ4- group after 12 months (T3). Among the control group, the valuation of taste slightly increased (Δ+1.0) and during the later six months period, was at a higher level (71.5) compared with intervention groups after 12 months (T3). (Paper II, Fig. 8) The taste attitude 'pleasure' was an exception as it increased slightly (T0-T1: Δ+0.1 (intervention groups) and Δ+0.2 (control groups) after genetic feedback (T1) (Paper II). The clearest changes were among Ɛ4+ group, although there were no statistical significant differences between the groups (Paper II).

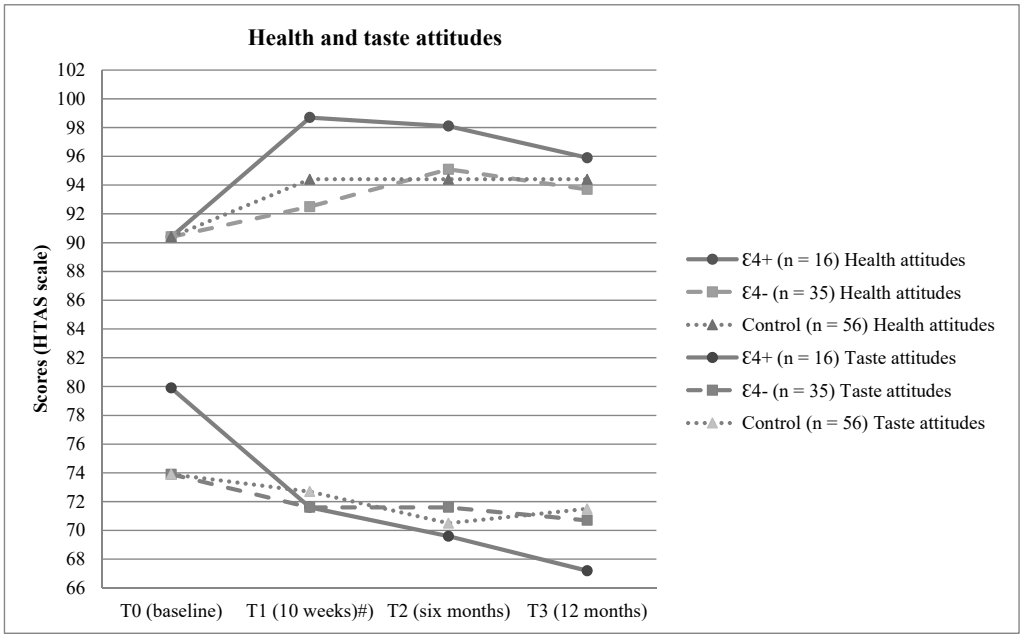

Figure 8. Changes in health and taste attitudes during the intervention.
NOTE. The health attitudes included *general health interest, light product interest* and *natural product interest.* The taste attitudes included *craving for sweet foods, using food as a reward* and *pleasure.*
Detailed scores and statistical tests are presented in Paper II. #) two weeks after genetic feedback.

5.2.4 Clinical results (Paper III, figures 9 – 11)

The intervention had a trend toward a significant effect ($p<0.05$; alpha level 0.005) on two of the CVD risk markers (triglyceride values ($p = 0.038$) and waist circumference ($p = 0.027$)) (Paper III). **The Triglyceride content** was at the recommended level (The Finnish Medical

Society Duodecim 2013) at the baseline, in every group (1.18 mmol/l). The triglyceride content decreased more in the Ɛ4+ group (Δ-0.30 mmol/l) compared with the Ɛ4- (Δ-0.09 mmol/l) and the control group (Δ-0.06 mmol/l) during the first six months (T0-T2). After a further six months (T2-T3), the triglyceride content had increased a little in the Ɛ4+ group (Δ+0.02 mmol/l), but decreased in the Ɛ4- (Δ-0.01 mmol/l) and control group (Δ-0.07 mmol/l). Despite the differences, the triglyceride values were within the normal range (The Finnish Medical Society Duodecim 2013) in every group during the intervention. The average **waist circumference** was 86.1 cm at the baseline (adjusted). During the first six months (T0-T2), waist circumference shortened 2.5 cm in the Ɛ4+ group, 0.9 cm in Ɛ4- group, while it increased in the control group (Δ+0.7 cm). In the control group, waist circumferences increased during the whole intervention period. (Paper III, Fig. 9)

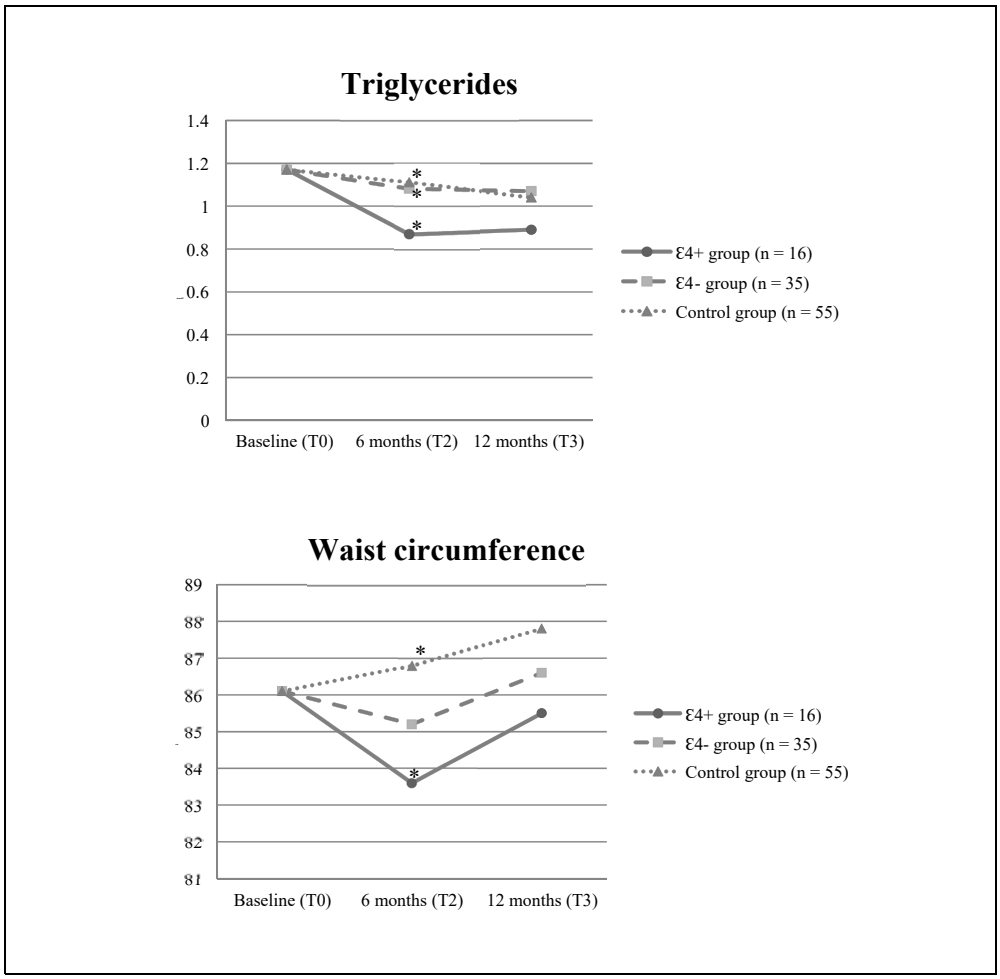

Figure 9. Changes in triglyceride content and waist circumference during the intervention.
*) p = 0.038 (alpha level 0.005) in triglycerides; *) p = 0.027 (alpha level 0.005) in waist circumference
NOTE. Detailed scores and statistical tests have presented in Paper III.

Favorable trends, but not close to a statistically significant effect were found in the **fat percentage** and **systolic blood pressure** in Ɛ4+ group. The fat percentage was 32.6 % in every group at the baseline. Among every group, fat percentage decreased during the first intensive communicating period (T0-T2). The Ɛ4+ group was the only group who improved their fat percentage during the last silent period (T2 – T3). The fat percentages were 30.1 % (Ɛ4+ group), 32.3 % (Ɛ4- group) and 32.6 % (control group) after 12 months (T3). **Systolic blood pressure** was at the recommended level (Duodecim and Suomen Verenpaineyhdistys 2009) at the baseline in every group (128.9 mmHg). It decreased in the Ɛ4+ (Δ-5.3 mmHg) and control group (Δ -4.0 mmHg) after the first intensive period. During the later six month period, the systolic blood pressure stayed almost at the same decreased level. (Paper III, Fig. 10)

A favorable, but parallel trend in every group was in the **glucose after two hours challenge (2h)**. It was 5.9 mmol/l at the baseline and it decreased slightly in every group (Ɛ4+: Δ-0.8 mmol/l; Ɛ4-: Δ-0.7 mmol/l and control: Δ-0.5 mmol/l) after 12 months (T3). (Paper III, Fig. 10)

The change in **diastolic blood pressure** was unfavorable in every group, increasing during the first six months period (T0-T2) Δ+4.9 mmHg (Ɛ4+ group), Δ+6.6 mmHg (Ɛ4- group) and Δ+4.2 mmHg (control group). In the later six months period, it decreased a little in every group, although still staying at a higher level (Ɛ4+: 78.1 mmHg, Ɛ4-: 80.5 mmHg, control: 80.6 mmHg) compared to the baseline (77.2 mmHg). (Paper III, Fig. 10)

The intervention had no effect on **total-, LDL**- and **HDL cholesterol, fasting glucose (0h)** and **BMI.** These CVD risk factors stayed almost constant during the intervention. HDL cholesterol (The Finnish Medical Society Duodecim 2013) and fasting glucose were within the normal range in every group. HDL cholesterol was 1.52 mmol/l (range during the intervention 0.00 – 0.05 mmol/l) and fasting glucose (0 h) was 5.5 mmol/l (range during the intervention -0.2 – 0.0 mmol/l). However, the total and LDL cholesterol (The Finnish Medical Society Duodecim 2013) and BMI (24.99 kg/m^2) were slightly over the recommended level in every group. Total cholesterol was 5.2 mmol/l (range during the intervention 0.0 - 0.1 mmol/l) and LDL cholesterol was 3.1 mmol/l (range during the intervention 0.1 – 0.2 mmol/l). The average body mass index was at the baseline 25.8 kg/m^2 (adjusted). Overweight participants were more common in the present study (68 % of men and 53 % of women) compared with the total Finnish average (Helldán et al. 2013). Detailed scores and statics are presented in Paper III.

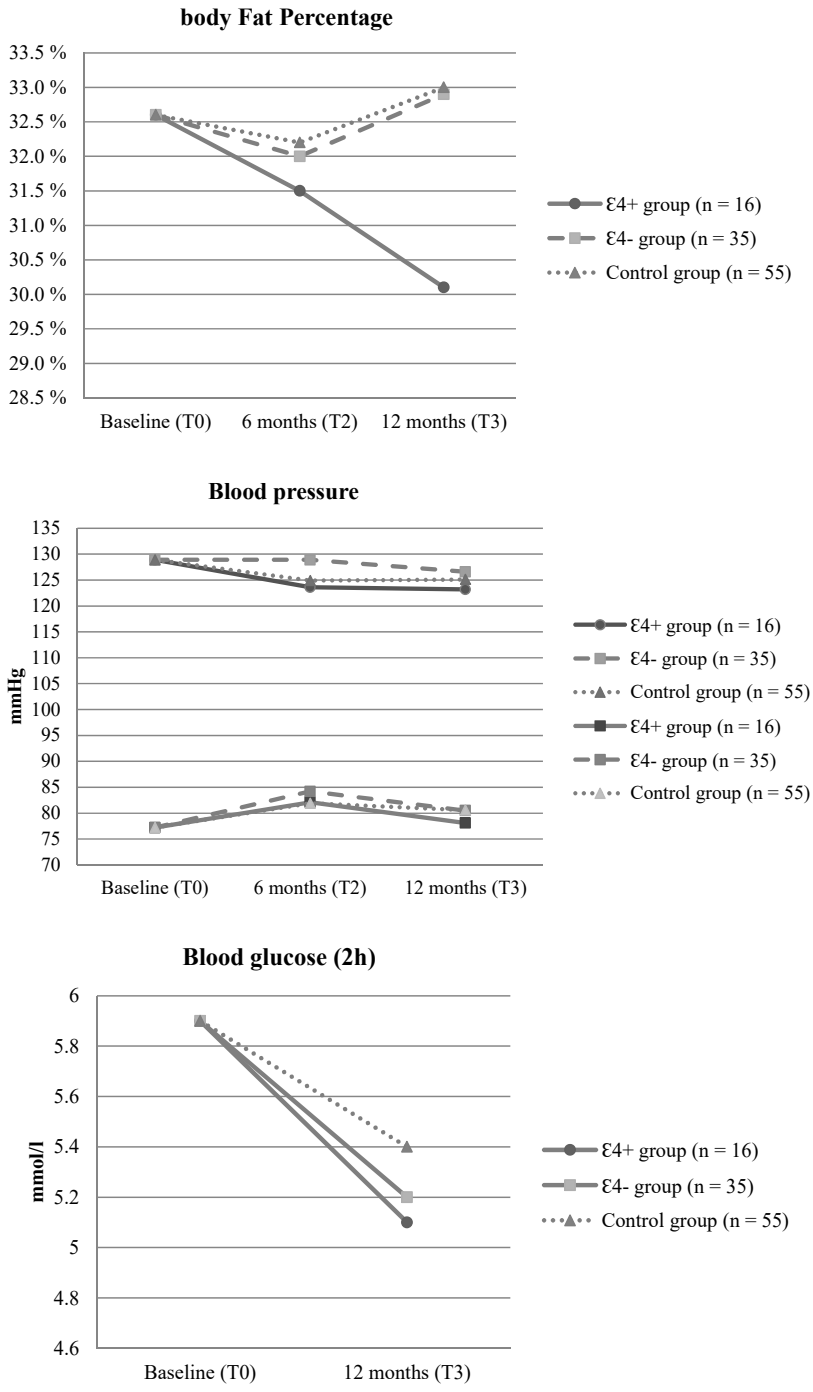

Figure 10. Changes in body Fat Percentage, blood pressure and blood glucose (2h) during the intervention.
NOTE. Detailed scores and statistical tests have presented in Paper III.

Metabolic Syndrome

In every group, the prevalence of metabolic syndrome decreased during the first intensive communicating period (T0-T2), but increased again after the later silent period (T2-T3) (Fig. 11).

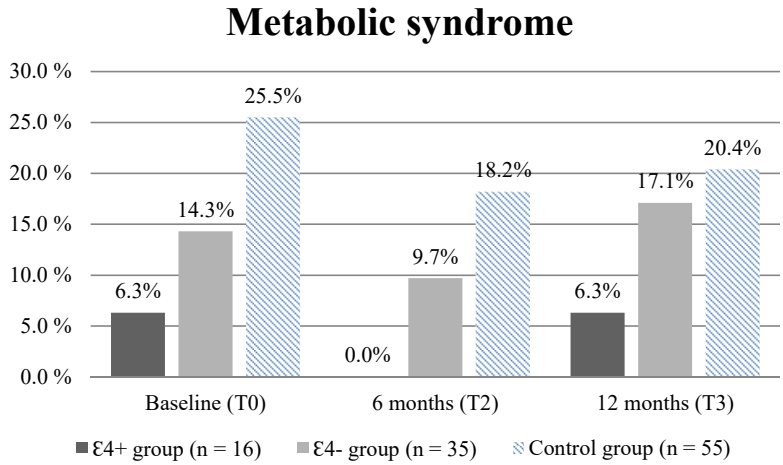

Figure 11. Frequency of Metabolic syndrome during the intervention (T0, T2, T3).
NOTE. The criterion for the Metabolic Syndrome: waist circumference ≥94 cm (men) and ≥80 cm (women) and having at least two of the following health risks: **1)** triglyceride content of serum over 1.7 mmol/l, **2)** HDL cholesterol under 1.0 mmol/l (men) or 1.3 mmol/l (women), **3)** systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg, **4)** fasting glucose (0h) over 6.0 mmol/l or glucose after 2 hours challenge (2h) ≥7.8 mmol/l.

5.3 Results of the predictors behind the significant changes (Paper IV, table 8, Fig. 12)

Change (ΔT0-T1) in **threat experience** was best explained by the model (c) (15.8 %; $p = 0.005$) which included the group, change in systolic blood pressure (T0-T2) and change in total cholesterol (T0-T2). The strongest predictor was the systolic blood pressure (T0-T2) (9.4 %; $p = 0.007$; $\beta = 0.290$)

Dietary fat quality change (ΔT0-T1) was best explained by the model (b) (16.0 %; $p = 0.002$), which included the group and body fat percentage (T0-T2). The strongest predictor was the body fat percentage (9.3 %; $p = 0.005$; $\beta = -0.307$).

Change (ΔT0-T2) in **waist circumference** was best explained by the model (b) (28.8 %; $p < 0.001$) which included the group and the BMI, the strongest predictor being the BMI (21.9 %; $p < 0.001$; $\beta = 0.471$).

Change (ΔT0-T2) in **triglycerides** was best explained by the model (c) (25.6 %; $p < 0.001$), which included the group and the changes (T0-T2) in the Body mass index (BMI) and HDL-cholesterol, the strongest predictor being the BMI (19.5 %; $p < 0.001$; $\beta = 0.464$).

The hierarchical regression analyses also revealed some statistically significant interaction-effects on change in triglyceride values (Fig. 12). Triglycerides correlated negatively with the HDL cholesterol ($r = -0.245$, $p<0.05$) and positively with the BMI ($r = 0.470$, $p<0.001$). HDL cholesterol correlated with the total cholesterol ($r = 0.422$, $p<0.001$), which correlated further with the threat experience ($r = 0.281$, $p<0.05$). The Body fat percentage correlated with the BMI ($r = 0.455$, $p<0.001$) and also waist circumference had an effect on the BMI ($r = 0.386$, $p<0.01$). The group (Ɛ4+, Ɛ4- and control) also had an effect on waist circumference ($r = 0.234$, $p<0.05$). (Fig 12)

Table11. Hierarchical multiple linear regression analysis. Predictors for changes in threat experience (T0-T1), dietary fat quality (T0-T1), triglycerides (T0-T2) and waist circumference (T0-T2).

Explained change (dependent variable)	Predictors	Model R^2	p (R^2)	R^2 Change	p (change)	β	Single predictor
Threat experience (ΔT0-T1)	**Model (a)**	0.006	0.498	0.006	0.498	0.093	group
	Model (b)	0.100	0.020	0.094	0.007	0.290	blood pressure, *systolic*
	Model (c)	0.158	0.005	0.058	0.028	-0.242	total cholesterol
Dietary fat quality (ΔT0-T1)	**Model (a)**	0.066	0.024	0.066	0.024	0.226	group
	Model (b)	0.160	0.002	0.093	0.005	-0.307	body fat percentage
Triglycerides (ΔT0-T2)	**Model (a)**	0.014	0.319	0.014	0.319	0.054	group
	Model (b)	0.209	<0.001	0.195	<0.001	0.464	BMI
	Model (c)	0.256	<0.001	0.047	0.043	-0.219	HDL-cholesterol
Waist circumference (ΔT0-T2)	**Model (a)**	0.069	0.027	0.069	0.027	0.205	group
	Model (b)	0.288	<0.001	0.219	<0.001	0.471	BMI

Stepwise method was used to analyze predictors. Exception was the group, where the method was enter.

β-value (coefficient)

Single predictor is an addition to the previous model.

NOTE: Explained change (ΔT0 - T1 / ΔT0 - T2) was not included in the model.

Threat experience (ΔT0-T1): Model (a): group (Ɛ4+, Ɛ4- and control group); model (b): group and systolic blood pressure (T0-T2); model (c): group, systolic blood pressure (T0-T2) and total cholesterol (T0-T2)

Dietary fat quality (ΔT0-T1): Model (a): group; model (b): group and body fat percentage (T0-T2)

Triglycerides (ΔT0-T2): Model (a): group; model (b): group and BMI (T0-T2); model (c): group, BMI (T0-T2) and HDL-cholesterol (T0-T2);

Waist circumference (ΔT0-T2): Model (a): group; model (b): group and BMI (T0-T2)

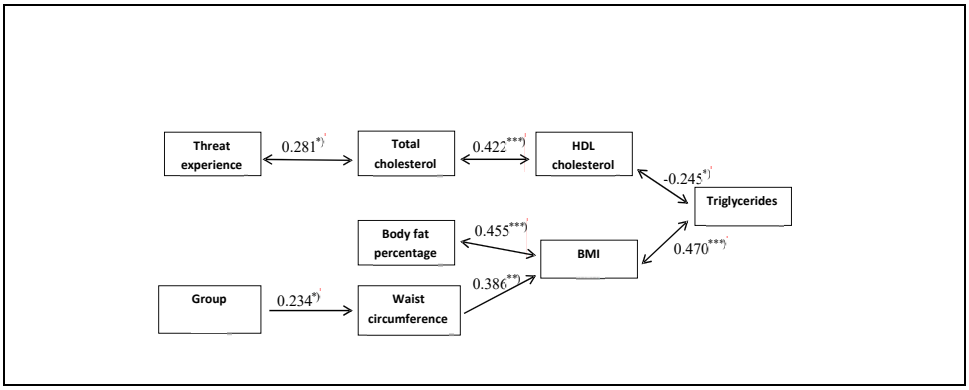

Figure 12. Partial correlations of changes (Δ), based on hierarchical regression analyses. Possible interaction-effects on triglyceride values. *) $p<0.05$,**) $p<0.01$,***) $p<0.001$

6 DISSCUSSION

6.1 Using *APOE* genotype-based health information to promote healthy lifestyles.

In this dissertation study, both short-term (10 weeks after the baseline) and long-term (6 and 12 months after the baseline) psychological, behavioral and clinical effects of hereditary genetic information were examined. Changes in state anxiety, threat experience, stage of change, dietary fat quality, the consumption of vegetables, berries and fruits, high-fat and high-sugar foods as well as alcohol consumption, exercise and health and taste attitudes were measured. Additionally, the effects on serum lipids, blood glucose, blood pressure, BMI, body fat percentage and waist circumference were analyzed.

6.1.1 Prevalence of *APOE* genotype and clinical descriptive

Approximately a quarter (26.2%) of the participants had an Ɛ4 allele (3/4, 4/4) placing them at an increased risk for CVD and the most common *APOE* genotype was *APOE* 3/3 (59.8 %). This result is nearly consistent with previous findings (Lehtimäki et al. 1990; Schiele et al. 2000). However, the prevalence of different *APOE* genotypes differs between continents and countries (Lehtimäki et al. 1990; Corbo and Scacchi 1999; Schiele et al. 2000). Among northern Europeans, for example, 30 % are *APOE* ε4 carriers, whereas in South Europe there are correspondingly less i.e. 20 % (Schiele et al. 2000).

The result of Study III indicated that body fat percentage was the only clinical marker which differed significantly at the baseline between the *APOE* 4 allele and the *APOE* 2 or 3 alleles. The trend for a higher total-, LDL- and HDL-cholesterol, but a lower level in triglycerides were found among *APOE* 4 carriers compared with the *APOE* 2 and 3 carriers. These results are in accordance with recent studies (Maxwell et al. 2013; Downer et al. 2014). In contrast to some earlier findings, however, no evidence of *APOE* genotype effects on other cardiovascular risk factors were detected (Rantala et al. 1997; Helkala et al. 2001; Saito et al. 2004; Carvalho-Wells et al. 2010). In previous studies, high blood pressure has been in some cases associated with the presence of *APOE* 4 allele (Rantala et al. 1997), but also with the *APOE* 2 allele (Couderc et al. 1993; Helkala et al. 2001; Cho et al. 2009). In addition, Helkala et al. (2001) noticed that carriers of *APOE* 2 allele had higher fasting glucose and 2 h blood glucose than *APOE* 3 and 4 carriers (Helkala et al. 2001).

6.1.2 Effects of intervention

Receiving personal genetic information, in combination with a personal health message had slight but favorable effects on dietary and cardiovascular risk markers. Both short-term and

long-term effects were found. In addition, short-term and slight long-term psychological effects, especially in threat experience were observed.

This study was planned so that the first six months were the active period with intensive health communication, while the later six months period was a non-intensive period with no active communication with the study participants. During this active period, participants attended the lectures and had an option to have a personal discussion with the doctor and received two health messages and during the silent period was no communication between the study participants and research team. The silent period was designed to simulate life with exposure only to general health information.

The results of the study indicated that the effects tend to diminish during the silent period, which has also been reported in several previous studies. Commonly, enthusiasm for life style changes decreases during interventions (Yoon et al. 2013), which was also seen in this present study, especially in the control and Ɛ4- groups. Recent studies have found that a higher intervention intensity (including frequent counseling sessions) and a longer intervention duration are more effective in achieving a permanent lifestyle change than less intensive and shorter interventions (Maderuelo-Fernandez et al. 2014; Wallace et al. 2014). Long-term and intensive health education has also been noticed to have a clearly positive effect in Finland (e.g. the North Karelia Project and FIN-D2D) (Saaristo et al. 2009; Borodulin et al. 2014), though the effect of the North Karelia Project is somewhat controversial (Ebrahim and Smith 2001). The results of this dissertation study indicated that even a very strong motivator, such as knowledge of a personal genetic risk may not be powerful enough to stimulate permanent health behavior change in the long-term without intensive repetition. There are several possible explanations for this. First, a lifestyle change demands continuous work and usually requires several changes at the same time. The second, a permanent lifestyle change occurs slowly and is gradually tailored to individualized goals (Koenigsberg et al. 2004) and third, a permanent lifestyle change may also need a change in attitude. In addition, people's values may affect the adoption of new health behavior (Schwartz 2011).

However, this dissertation has shown that it is also possible to achieve long-term changes (12 months), which was the case in the triglyceride values. There are several possible explanations (e.g. variation in responses toward dietary fat quality among *APOE* genotypes or the optimistic bias effect), why the long-term changes were detected only in triglyceride values, but not in health behaviors (e.g. dietary fat quality). These reasons discussed in detail later in this dissertation study (Chapter *Effects on health behavior and cardiovascular risk markers*).

Psychological effects

Psychological effects are one concern when studying the consequences of genetic feedback. Both results (either susceptibility to disease or not susceptibility) can be harmful. The inherited risk of a disease can cause anxiety and stress, but on the other hand negative test result can provide an explanation of an unhealthy lifestyle, if there is no recognized genetic risk of the disease (Lerman et al. 1997; McBride et al. 2002; Ito et al. 2006; Marteau and Weinman 2006; Lovegrove and Gitau 2008). There are only a limited number of studies which have concentrated on studying the psychological effects of genotyping in lifestyle-related diseases. These studies have found that genetic screening only causes short-term psychological effects (Aktan-Collan et al. 2001; Meiser et al. 2002; Ashton et al. 2002; Andrews et al. 2004; Meiser et al. 2004; Claes et al. 2005; Kinney et al. 2005; Eborall et al. 2007; Heshka et al. 2008; Park et al. 2008; Collins et al. 2011).

Results, based on Study I are mainly in line with those of previous studies, indicating that the psychological effects of personal genetic risk information were short-term, although the levels of A-State and threat experiences in the high-risk group (*Ɛ4+*) remained at a slightly higher level than at the baseline. In the case of motivation to make a lifestyle change (stage of change), every group (Ɛ4+, Ɛ4- and control group) had similar progression (from stage 2 to stage 3) during the intervention. These results indicate that receiving personal genetic information had no significant impact on motivation towards a lifestyle change.

In this present study, the opportunity was offered to have a personal discussion with a medical doctor and an elective genetic counseling lecture held by the professor of nutrigenomics. Although only a few people took these opportunities (Table 6), these sessions had some effect on the threat experience and stage of change at the end of intervention. The findings of Study I, inferred that the lecture increased the experience of threat toward CVD and those attending the personal discussion with the doctor were the more motivated participants. The participants who attended the personal discussion with the doctor, were all at stage 4 (action*, have changed their lifestyle within the last 6 months),* while the participants, who did not attended the discussion were on average at stage 3 (preparation, ready, *"have planned lifestyle change within next month").* In addition, participants, who attended the lecture, experienced threat more than the participants, who did not attend the lecture. These results further support the idea that consultation and education have a significant effect on the understanding of gene results and the experience of worry (Henneman et al. 2002).

Based on Study I, a trend for momentary anxiety existed shortly after receiving the individualized information about having a high-risk gene, *APOE* 3/4 or 4/4. This effect decreased over the subsequent months, but remained at a still higher level when compared to the baseline. Receiving individualized information about having the low-risk gene, *APOE* 2/3 or 3/3 had minor impact on the experience of A-State as it was quite stable in the Ɛ4- group during the whole intervention period. However, the control group responded contrary

to expectations, as they experienced an A-State in a very similar way to those in the Ɛ4+ group. There are few possible explanations for this outcome. There is always the possibility of an external factor, which may confound the results. Stress, for example, can increase the A-state and on the contrary, relaxation can decreases it (Spielberger C 1971). Second, there are differences in how people interpret and understand their results (Henneman et al. 2002). It is possible that the control group felt distressed because they were not provided with their genetic information at the beginning of the intervention. For instance, the delay in receiving the gene information may have caused concern and uncertainty.

The results of Study I indicated that personal genotype-based health information and also knowing their potential risk for CVD (especially the high-risk gene, *APOE* 3/4 or 4/4) clearly affects, and more specifically increases, a person's experience of the threat regarding CVD. This effect was the most intense directly after the genetic feedback. Some effects, however, also remained after 12 months. The results of Study IV also imply that the changes in cardiovascular threat experience may affected the actual changes in the participants own cardiovascular risk markers (total cholesterol and systolic blood pressure), which further had an effect on changes in triglyceride values. The results imply that when the threat experience increased, the triglyceride values decreased and our message, based on EPPM model was working correctly. The threat experience produced behavior change, which may affected the triglyceride levels. It may be possible that this outcome may be due to the nature of the CVD threat, which was strong enough to cause a sensation of danger for the Ɛ4+ group but not for the Ɛ4- group, who did not feel vulnerable to the threat of CVD. After genetic feedback (T0) participants in the Ɛ4- group could have felt relief, because they did not have a genetic susceptibility to CVD. According to Witte et al. (2001) lifestyle changes are best implemented when the threat is perceived as a danger, but not yet as a fear - and lifestyle change most often only happens when a person feels susceptible to threat, and the threat is personally large, but also when they have enough self-efficacy to observe the proposed action (Witte 1992; Witte 2001). Based on the results of Study I, none of the groups experienced fear, which means that our health message succeeded in creating danger, but not fear and therefore a lifestyle change is possible.

The stage of change was used to measure readiness and motivation for changes in lifestyle. Findings related to people's motivation for lifestyle change have been contradictory in previous studies (Marteau et al. 2010; McBride et al. 2010). Very few studies have focused on using the stage of change instrument to measure lifestyle change in the context of using genetic testing to promote a healthy lifestyles. Stage of change is commonly used to investigate smoking cessation; for example, a person's stage of readiness for smoking cessation was found to be a significant predictor of them attempting to do so (DiClemente et al. 1991; Audrain et al. 1997; Campbell et al. 2013). The results of Study I infer that genetic feedback (especially in this study genotypes *APOE* 3/4 or *APOE* 4/4) had no effect on a person's stage

of change with a similar progression (stage 2, contemplation to stage 3, preparation) in every group. There are several possible explanations for this: First, the genetic information may not be a good motivator for change, because people think that heredity is more powerful than their own behavior, and it could even have a negative impact on health behavior (Marteau & Weinman 2006) and second the fact that the *APOE* genotype is only one factor that can cause CVD, and not the only risk factor, could also affect people's perceptions of it (Song et al. 2004). In addition, the questionnaire concerning the stage of change is a very broad concept, as it asks "Have you considered lifestyle change?" It can be difficult to answer such a broad question, instead of asking "Have you changed your diet?" or even more precisely, "Have you increased your vegetables consumption?"

Effects on health behavior and cardiovascular risk markers

As stated in the literature view, cardiovascular disease is the sum of several non-modifiable (genetic, age, gender) and modifiable (obesity, dyslipidemia, high blood pressure, smoking, diabetes) risk factors, of which it is necessary to take note. Some health behavior changes may be easier to implement (e.g. changing dietary fat quality) than others (e.g. increasing vegetables consumption), depending, for example, on a very simple reason - that of seasonal variation in vegetable availability. In addition, it has shown that changing existing habits is usually more difficult than adopting new habits (Fitzgibbon et al. 2007). Partly due to these challenges, there are a limited number of studies, although they are increasing, which have focused on purely to promote healthy lifestyles (e.g. diet, physical activity, cholesterol) by genotype based health information (McBride et al. 2010). Marteau et al. (2010), for example, concluded that genetic feedback did not affect smoking or exercise habits, but it can have some favorable effects on diet and lifestyle (Marteau et al. 2010b). However, results based on Studies II and III in this dissertation, indicated that receiving personal genotype based health information can have a slight, favorable, short-term effect, but also some long-term (12 months) effects on diet and cardiovascular risk markers. The most significant effects of genetic feedback were observed in the dietary fat quality, triglyceride values and waist circumference, where the responses were greater in the Ɛ4+ group than in the Ɛ4- and control groups.

The genotype-based health information for the Ɛ4+ group highlighted the importance of genotype in the response to dietary changes (e.g., improvement of fat quality) and in increased exercise. In addition, the health information emphasis the role of dietary changes for lowering cholesterol levels and a possibly lowered CVD risk. The purpose was to give an encouraging message, based on the facts that personal lifestyle choices together the genetics can have an impact on individuals' health and risk factors. The content of the messages was based on the EPPM model and several previous studies reporting that carriers of the *APOE* ε4 allele are the most responsive to changes in dietary fat and cholesterol (Witte 2001; Masson et al. 2003;

Minihane et al. 2007). The results of Study II showed that the genotype-based health information had an effect on dietary fat quality, but not exercise or the consumption of vegetables, berries and fruits, which could be one reason why in Study III; HDL, LDL and total cholesterol level also stayed equal during the intervention. There is evidence that especially increasing exercise has favorable effects on HDL cholesterol, and a high fiber diet (e.g. vegetables, berries and fruits and whole grain cereals) on the total and LDL-cholesterol (Wood et al. 1983; Anderson 1985; Brown et al. 1999). Other possible explanations could be the seasonal variation in vegetable, berries, and fruit consumption and a low-carbohydrate diet and the use of butter, which was a popular topic in the media of Finland during the intervention.

Results of Study III indicated that the genotype-based health information had an impact on triglyceride values and waist circumference, but not cholesterol levels or other CVD risk markers. It is widely known that waist circumference differs between sexes, being higher in men. The difference in waist circumference was between Ɛ4+ group and control group and it was mainly caused by men. However, in contrast to expectations, the change in dietary fat quality did not explain the change in triglyceride values in Study IV. One possible explanation may be that the response toward dietary fat quality change indeed is different among *APOE* genotypes, which supports our EPPM based message and the previous studies (Masson et al. 2003; Minihane et al. 2007). It can be possible that change in dietary fat quality affected change in triglyceride values in Ɛ4+ group, but not in Ɛ4- group, but due to the small group sizes it was not possible to perform a separate regression analysis for different groups. The other explanation could be that there were several, slightly favorable changes in health behavior and that those together affected triglyceride values in the long-term, but alone were not to a statistically detectable degree. In addition, because the health behavior questionnaires are self-reported, there is possibility of an optimistic bias–effect, which means that in the interview people are less likely to relate negative events, and are more likely to talk about positive events) (Miles and Scaife 2003).).

When discussing genetic-dietary-interactions and nutrigenomics, there is no one right answer. Although there is evidence that the *APOE* 4 carriers are more responsive to the changes in dietary fat than other *APOE* carriers (Masson et al. 2003; Carvalho-Wells et al. 2012), several controversial or non-associations have been presented (Minihane et al. 2000; Olano-Martin et al. 2010; Egert et al. 2010; Liang et al. 2013). Liang et al. (2013), for example did not find a different response towards fish oil fatty acids eicosapentaenoic (EPA) among the *APOE* genotypes. The only significant response was seen in HDL-cholesterol among *APOE* 2 carriers (Liang et al. 2013). Further, Minihane et al. (2000) showed in their studies that *APOE* ε4 carriers' total cholesterol and LDL cholesterol increased after a fish oil supplementation, and HDL cholesterol decreased compared with *APOE* ε3 carriers. (Minihane et al. 2000). Egert et al. (2010) found that *APOE* ε3 carriers had a better response to quercetin (flavonols) supplementation than *APOE* ε4 carriers (Egert et al. 2010). These differences were

revealed in systolic blood pressure, HDL cholesterol, and ratio of LDL:HDL cholesterol (Egert et al. 2010). In this dissertation, Studies II and III found several, slight but favorable lifestyle changes (e.g. changes in fruit, berry, and vegetable consumption, in the consumption of high-fat and high-sugar foods, in health and taste attitudes and blood glucose (2h)), which were parallel in every intervention group. In these cases, a favorable lifestyle change may be explained by the *Hawthorne effect* (Noland 1959; McCarney et al. 2007), which means that progression and lifestyle changes are due rather to participating in the intervention and being examined than any impact of personal genetic risk information and thus making lifestyle changes accordingly. The other possible explanation can be the progression of a national awareness in nutrition (Helldán et al. 2013). In addition, Finns diet compliance, attitudes, and values toward general health education is fairly high attested to, for example, by the North Karelia Project, which managed to decrease CHD mortality rate by 80 % in people of working age during 1972 – 2007 (Borodulin et al. 2014). Based on Schwartz's (2011), Cultural Value Orientations Classification, Finns are more committed and dutiful compared, for example, to people in the USA or Japan, which are characterized as being audacious and detached (Schwartz 2011). It may be possible that compared to Americans or the Japanese, Finns easily accept even very generic education, as was the case in the control group in this present study (Schwartz 2011).

To best of author's knowledge, this is the first explanatory study using *APOE* genotyping to affect health behavior with the aim of lowering the risk of cardiovascular disease, which also included the effects on clinical factors (Marteau et al. 2010). The assessments of the actual cardiovascular risk markers are important to include, because people may need to see their progression in concrete terms. People, for example, may realize that exercise is one important factor in the prevention of lifestyle-related disease, but they do not understand the association between physical activity and actual metabolic risk factors (Vähäsarja et al. 2012). A previous study by Vähäsarja et al. (2012), conducted among people with a high risk of type 2 diabetes (n = 7128), found that the individual's overestimation of physical activity can be an obstacle to behavioral change (Vähäsarja et al. 2012). Increasing understanding about the connection between health behavior and metabolic risk factors and the inclusion of actual cardiovascular risk markers, may achieve better results. Lowered cholesterol levels, for example, may motivate people to extend further the changes in their health behavior. However, the effects may also be the opposite, if the desired change does not occur (Marteau and Weinman 2006), and then people can become depressed and regress back to under the baseline level. Clinical outcomes may also act as a 'control' for the self-reporting behaviour changes (e.g. diet).

6.1.3 Potential interactions and associations between the changes in different lifestyle factors

Study IV was planned to analyze associations between different lifestyle changes and it was not able to demonstrate connections between lifestyle behaviors (dietary fat quality, consumption of vegetables, berries, and fruits, consumption of high fat and sugary foods, consumption of alcohol and physical activity) and actual cardiovascular risk markers (e.g. triglyceride values and waist circumference). These results were the opposite of previous studies, which have shown that unhealthy lifestyle behaviors (e.g. physical inactivity, smoking, excessive consumption of alcohol and saturated fat and low consumption of vegetables) are closely linked to an increased risk of cardiovascular diseases (Raitakari et al. 1995; O'Neil et al. 1997; Ma et al. 2000; Schuit et al. 2002; Lukasiewicz et al. 2005; Matikainen 2009). The result was somewhat contrary to the expectations and there can be several possible explanations, which have been discussed in a previous chapter (*Effects on health behavior and cardiovascular risk markers).*

In addition, Study IV showed that changes in psychological factors (threat experience, state anxiety, stage of change) did not directly explain the changes in clinical markers (e.g. triglyceride values and waist circumference), although threat experience may have had effect on triglyceride values through total- and HDL cholesterol (Fig. 12).

Furthermore, Study IV did not find any connection between attitude changes and behavioural change. In addition, Study II showed that genetic feedback did not affect health and taste attitudes and change in dietary fat quality was short-term. These results of Study II and IV imply that behavioural changes (e.g. dietary fat quality) can occur without attitude changes, but that long-term and permanent change may also demand change in attitudes. Although there are several studies which have presented the fact that health attitudes are closely linked to health behaviour (Kearney et al. 1998; Zandstra et al. 2001; Roininen et al. 2001; Hearty et al. 2007; Talvia et al. 2011), controversial studies have also been presented (Lloyd et al. 1993). The study by Lloyd et. al (1993) found that participants, who consumed high-fat diets had similar attitudes to dietary change (to a low-fat and more healthy diet) compared with those consuming low-fat diets (Lloyd et al. 1993). The link between attitudes and health behaviour is not so unambiguous and according to Glasman et al. (2006) attitudes affect future behaviors, if they are easy to recall, stable over time, and decisive instead of ambivalent (Glasman and Albarracín 2006). In our study, the focus was the change in attitudes, therefore if the participants perhaps expressed ambivalent attitudes, this could be the one reason why the link between attitudes and health behaviour changes did not occur.

In this dissertation study, several health indicators were used to measure a change. Study IV showed that BMI was the strongest predictor for changes in the values of triglycerides and waist circumference, which indicates that, if the BMI has decreased the triglyceride values and waist circumference also decreased. In addition, other clinical markers, such as body fat

percentage, total- and HDL cholesterol had interaction-effects on the triglyceride values and waist circumference. These results are in line with those of previous studies, which have found that risk factors for cardiovascular diseases tend to accumulate (Raitakari et al. 1995; Schuit et al. 2002; Pronk et al. 2004; Lukasiewicz et al. 2005; Poortinga 2007; Artaud et al. 2013; Robinson et al. 2013).

6.1.4 Limitations

Study population and background variables

The group sizes were relatively small, which was partly due to limited resources and strict qualification for participants. The selection criteria for participants were strict and only healthy individuals were included in the study. In this study, men were in the minority and somewhat older than the women. Any long-term medication or disease was an exclusion criterion. In addition, many of the CVD risk markers (e.g., waist circumference, fat percent, and HDL cholesterol) are known to differ between sexes, but due to the small group sizes, statistical analyses between men and women were impossible to conduct. This dissertation study found statistical significant difference in the change of waist circumference between Ɛ4+ and the control group and it was produced by the men. However, the percentage of men was almost equal in those groups. Changes in body fat percentage and HDL cholesterol did not differ between the groups or sexes during the intervention. However, despite the small group sizes and the very healthy individuals included, we managed to achieve some significant differences between the different groups. It is reasonable to first carry out this kind of very sensitive, explanatory research among healthy people. It may be possible that lifestyle change with healthy people signals further clearer changes among less healthy people.

The randomization was done to divide the participants into the intervention and control groups before genotyping, and therefore the group sizes differed. This difference was purely due to the number of carries with *APOE* 3/4 and 4/4. At the baseline, 34.4% of the participants in the intervention group were *APOE* 4 carries, which is consistent with previous findings (Lehtimäki et al. 1990; Schiele et al. 2000).

Underreporting and also an optimistic bias –effect occurs when people self-report their diet (Mattisson et al. 2005; Yannakoulia et al. 2006). Women tend to underreport more than men (Mattisson et al. 2005; Yannakoulia et al. 2006). This may have had some effects on results, as women were in the majority among the participants. However, to control for an optimistic bias –effect, we also performed clinical assessments in our study.

It is also impossible to control all the external factors, although some external factors (e.g. education, marital status, family history of cardiovascular, or Alzheimer's disease) could have been considered in this dissertation. Previous studies have shown, for example, that low socioeconomic status predicts mental disorders (e.g. depression or anxiety) (McLeod and

Shanahan 1993; Rutter 2003). We had several psychological and behavioral questionnaires, so we asked only a few background questions (sex, age, A-trait) to avoid peoples' frustration in having to answer to many questionnaires.

Assessments and procedure

The motivation toward lifestyle change (stage of change) was only measured by one question based on the validated Transtheoretical Model and some non-validated dietary and physical activity questionnaires were used in the study. However, these questionnaires are widely used in Finland. The motivation toward lifestyle change –questionnaire, used in Study I, is the only validated questionnaire in Finnish, so it was justified to choose this questionnaire which is well known. Validated dietary and physical activity questionnaires, used in Study II are not available in Finnish, and international questionnaires would have had to be tailored in order to apply them to Finnish dietary and physical activity habits.

We had four different measuring times (T0, T1, T2 and T3) during the one year intervention. Health behavioral and attitude questionnaires were completed at each measuring time, but the psychological questionnaires were completed at the baseline (T0), two weeks after the genetic feedback (T1) and at the end of the intervention (T3). The clinical assessments were at the baseline (T0), after six months (T2) and the end of the intervention (T3). This variation in measuring times (T0, T1, T2 and T3) produces some challenge to analyzing the predictors in Study IV. However, it was reasonable to ask about the psychological factors immediately after the genetic feedback and in contrast the effect on the clinical markers may be reflected after several months. In addition, we did not want to burden participants by asking them to attend and answer several questionnaires and assessments at the same time.

Only one genotype (*APOE*) was analyzed in this dissertation study. This choice was relevant when the study was designed (in 2010). The *APOE* was then amongst the most widely studied genotypes in gene-diet interactions, and carriers of the *APOE* 4 allele are more common in Finland than, for example, in southern Europe (Lehtimäki et al. 1990; Schiele et al. 2000). However, nowadays the costs of genotyping have decreased and several variants in the genes of lipid metabolism are known to interact with dietary fat intake and dietary fatty acid composition, thus affecting the risk of metabolic diseases (Phillips 2013; Wetterstrand 2014). In addition, there are many gene variants that remain unknown as of yet (Phillips 2013). In this dissertation, the genotype-based health information was based on the evidence that *APOE* carriers have higher total and LDL cholesterol than carriers of other alleles (Masson et al. 2003; Minihane et al. 2007). However, there are studies that have found controversial results or no connection at all among different *APOE* genotypes and dietary fat (Minihane et al. 2000; Egert et al. 2010).

Some other factors, which could have caused bias in our study and results, are low-carbohydrate diets and the use of butter, which was a popular topic in the Finnish media, and

occurred simultaneously with the intervention. In addition, communicated increased AD risk of *APOE* 4 carriers, which was one criterion for ethical permission and very limited number of participants in voluntary lecture and personal discussion could have caused some bias in our study.

6.1.5 Further research suggestions and practical implications

In light of the limitations, and due the very explanatory nature of this dissertation study, further research will be required. There is a need for individual, genotype-based health and dietary advice, in order for genotyping in prevention of lifestyle-related diseases might increase in the future. This is why more research is needed utilizing genetic screening aimed at preventing lifestyle-related diseases. Genetic screening may be a potential tool in public health care for the early diagnosis and prevention of disease. Lifestyle diseases are multifactorial, and there are several genes that may predispose individuals to disease risk, for example, diabetes mellitus, high blood pressure, CVD, etc. in combination with the environment. This information can be used to develop tailored interventions, including health information based on genotyping that would aim at preventing lifestyle diseases. There are several factors which can affect an individual's background (e.g. socioeconomic status, attitudes toward genetic testing), therefore further studied that are more focused on the factors which affect the adoption and utilization of genetic information, are suggested.

Based on Study I, genetic testing does not have a strong effect of people's anxiety and the threat experience in the long-term. The study supports the fact that the effect of *APOE* genotype-based health information on psychological factors may not be an obstacle for using genotyping to promote healthy lifestyles (dietary, exercise) in healthy adults. According to Aatre and Day (2011), the genetic feedback may raise some apprehension in people of the potential impact of their lifestyle choices and at the same time give them hope and strengthen their will and commitment (Aatre and Day 2011). This study used the EPPM model to create a health risk messages in the context of the genotype-based health information promoting healthy lifestyles. However, as stated in literature review, this model is a fairly new and unique approach to promote healthy lifestyles in combination with the 'real' threat i.e. the inherited genotype and the 'perceived' threat. Consequently, more research is needed about how to utilize the EPPM model in the context of genotype-based health promotion studies. Nevertheless, to achieve better results, every targeted, health behavior promotion intervention should include some kind of health behavior model (Glanz et al. 2008). One future research aspect in lifestyle-related diseases field could be focused on creating targeted health risk messages, which could be based on the psychological properties of individuals, e.g. motivation, threat experience or self-efficacy. Further, comparing different kinds of models to promote healthy lifestyles (e.g. models based on health risk messages and genotype information and

models based on enhancing motivation (e.g. *motivational interviewing*)) could be an important aspect of future research.

A permanent health behavior change may depend on attitudes, and other psychological factors so further studies, including several psychological factors (e.g. motivation, stress level, depression, self-efficacy, attitudes, values and health-related meanings) are recommended. Permanent lifestyle changes occur individually and gradually, therefore future studies on the current topic should include a longer follow-up time, intensive repetition, and targeting. In addition, people usually tend to adopt one or only a few, lifestyle change at a time, so future research should put more focus on implementing only one or two precisely defined lifestyle changes.

To best of the author's knowledge, this is the first study using *APOE* genotype-based health information to affect health behavior, which also takes into account clinical risk markers and psychological factors. In Study IV it was shown that attitude, psychological- and behavioral changes did not directly explain the changes in cardiovascular risk markers (e.g. triglycerides, waist circumference), although change in threat experience may have affected changes in triglyceride-values through total- and HDL cholesterol. This may indicate some optimistic bias –effect, which is important to take note of when planning further research. Actual clinical markers can act as a 'control' for self-reporting behavioral questionnaires. In addition, one possibility could be that response in triglyceride values may indeed vary between *APOE* genotypes due to the various changes in dietary fat quality. This is also one valuable aspect for consideration in future studies.

Currently, the challenge is the direct-to-consumer genetic tests (DTC), which can be purchased from the Internet without any control. DTC tests do not offer any opportunity for genetic counseling and the given nutritional advice is very generic without any emotional support. One research aspect could combine these DTC genetic tests and an opportunity for a consultation with a doctor. Despite the fact that the cost of genotyping has decreased, genetic screening in the prevention of lifestyle-related diseases is not routine practice in public health care (Bloss et al. 2011; Voils et al. 2012). There is a lack of know-how among health care professionals and a lack of resources (Mountcastle-Shah and Holtzman 2000; Taloustutkimus Oy and The Finnish Innovation Fund 2013). In the future, more effort should be put into educating nutritionists and doctors in the field of genotyping for the prevention of lifestyle related diseases. It could be economically worthwhile to research which has the more beneficial affect: (1) individual, genotype-based health information combined with only a few meetings with a nutritionist and doctor or (2) very general dietary advice, combined with several meetings with healthcare professionals.

7 CONCLUSIONS

This dissertation study has given some indications that individualized *APOE* genotype-based health information may be one potential practical tool to be used in the future by clinical professionals in public health care for preventing lifestyle-related diseases. However, more research as well all more expertise among health care professionals is needed.

The results of the study indicate that:

1. Genetic information, based on the *APOE* genotype causes short-term and only slightly long-term anxiety and threat. Psychological factors may not be an obstacle for using CVD-related *APOE* genotyping to promote healthy lifestyles in healthy adults.

2. *APOE*-genotype based dietary and physical activity advice has positive effects on dietary and CVD-risk markers. Positive short-term effects were found in dietary fat quality and waist circumferences. A positive long-term (12 months) effect was found in triglyceride values.

3. The positive effect tended to diminish after the active communication period. Even in the case of very personal health information, to achieve permanent health behavior change, attitudes are important, as well as intensive repetition and a longer intervention duration.

4. Changes in psychological factors (anxiety- and threat experience, motivation), health and taste attitudes, and health behavioral factors (dietary, alcohol consumption, physical activity) did not directly explain the changes in triglyceride values and waist circumference. However, changes in cardiovascular threat experience may have affected changes in triglyceride values due the total- and HDL cholesterol.

ACKNOWLEDGEMENTS

This study was carried out in University Consortium of Seinäjoki (Researchers' Residence) and the main university was Turku University, Finland. All clinical analyses were conducted in the Central Hospital of Southern Ostrobothnia, department of clinical chemistry. *APOE* genotyping was conducted in Natural Resources Institute Finland and the first face-to-face interview was done in Seinäjoki University of Applied Sciences, Finland. I am very thankful to these institutes. Special thanks for the opportunity to carry out this study and the fruitful cooperation belong to Hannu Puolijoki, Professor and Medical Director of Southern Ostrobothnia and Professor of Nutrigenomics Raija Tahvonen at the Natural Resources Institute of Finland. During these years, this study was financially supported by the project – Healthier food choices, tailored models for eating and exercise (TERVAS) (University of Turku, Finland), The Finnish Cultural Foundation, the Central Hospital of Southern Ostrobothnia (EVO 1140), the Aarne and Aili Turunen Foundation, the Pihkahovi Foundation, Women's Foundation of Lapua, the European Regional Development Fund (EAKR) Project A31342 and by grant from the University of Turku. I would like to express gratitude to these organizations for making this work possible to complete.

I am deeply grateful for my supervisors, Professors Anu Hopia and Harri Luomala. They both have had firm belief in me during the entire project. This has encouraged me to continue and further improve the work. Thank you for giving me enough space to produce my own kind of work, but also giving me important, supporting and reassuring comments and advice during this project.

I sincerely thank my official reviewers Professors Anne-Marie Minihane and Atte vonWright for their valuable critique and also Elizabeth Nyman for her revision of the English language.

I also owe gratitude to my co-authors, Kari Åkerman, Terhi Iso-Touru, Leena Koivusilta, Raija Tahvonen and Hannu Puolijoki for their valuable contributions and cooperation during this research project. I also want thank the Research Group of Food Development, Seinäjoki (University of Turku). The members of this group have given me valuable comments concerning my work and we have spent many hilarious moments working together.

I am grateful to the staff of Foodwest Oy for their assistance in recruiting participants, the Department of Clinical Chemistry at the Central Hospital of Southern Ostrobothnia and all the technical assistants, who enabled this project to be carry out. I owe special thanks to Sanja Laitila for her prodigious background work for this study, nutritionist Hilpi Linjama for her nutritional lectures and valuable contribution to the planning of the dietary questionnaires and also Jouko Katajisto and Hannu Tuuri for their statistical advice. Very warm thanks go

to all the women and men in Southern Ostrobothnia, who participated in this study; without you, this study and dissertation would not exist.

I express very warm graditude also to my parents, Heleena and Reijo and my siblings. You have all supported me in your own unique ways. Special thanks belong to my mother, who has always been ready to care our children and also my dear friends, of which some have been part of my life for over 30 years. Time spent with you by relaxing and chatting has always given me new strength to continue my work. I also want to thank my mental mentor, Päivi Saranpää, who has always guided me to think what is best for me and my family.

Finally, the words are not enough to tell, how deeply thankful i am for my loving and patient husband Kari. I think every woman should have husband, like he is, because everything is possible to achieve with him. He has taken big responsibility to raising our children during these busy years. He is my best friend. My dear, wonderful children Kastanja, Vanilja and Timjami deserve biggest gratitude. With you, my life has been full of joy and happiness outside the researcher chamber. You make this achievement worth of celebrate.

Seinäjoki, February 2016

Hannamaria Hietaranta-Luoma

REFERENCES

Aatre RD, Day SM (2011) Psychological issues in genetic testing for inherited cardiovascular diseases. Circulation Cardiovascular genetics 4:81–90. doi: 10.1161/CIRCGENETICS.110.957365

Aktan-Collan K (2001) Predictive Genetic Testing and Counselling for Hereditary Non-Polyposis Colorectal Cancer (HNPCC). University of Helsinki

Aktan-Collan K, Haukkala A, Mecklin JP, et al (2001) Psychological consequences of predictive genetic testing for hereditary non-polyposis colorectal cancer (HNPCC): a prospective follow-up study. International journal of cancer Journal international du cancer 93:608–11.

Alberti KGMM, Zimmet P, Shaw J (2005) The metabolic syndrome--a new worldwide definition. Lancet 366:1059–62. doi: 10.1016/S0140-6736(05)67402-8

Almeida S, Fiegenbaum M, de Andrade FM, et al (2006) ESR1 and APOE gene polymorphisms, serum lipids, and hormonal replacement therapy. Maturitas 54:119–126. doi: 10.1016/j.maturitas.2005.09.009

American Heart Association What Your Cholesterol Levels Mean? http://www.heart.org/HEARTORG/Conditions/Cholesterol/AboutCholesterol/What-Your-Cholesterol-Levels-Mean_UCM_305562_Article.jsp.

Anderson JW (1985) Physiological and metabolic effects of dietary fiber. Federation proceedings 44:2902–6.

Andrews L, Meiser B, Apicella C, Tucker K (2004) Psychological impact of genetic testing for breast cancer susceptibility in women of Ashkenazi Jewish background: a prospective study. Genetic testing 8:240–7.

Anonymous. Finnish electronic medical book. (2009) Rasvaprosentin mittaaminen. Measure of fat percentage. http://www.tohtori.fi/?page=7481805&id=6362126.

Anonymous. The Office of Disease Prevention and Health Promotion. (2008) Physical activity guidelines for Americans. http://www.health.gov/paguidelines/guidelines/. Accessed 1 Jan 2015

Arkadianos I, Valdes AM, Marinos E, et al (2007a) Improved weight management using genetic information to personalize a calorie controlled diet. Nutrition Journal 6:29. doi: 10.1186/1475-2891-6-29

Arkadianos I, Valdes AM, Marinos E, et al (2007b) Improved weight management using genetic information to personalize a calorie controlled diet. Nutrition journal 6:29. doi: 10.1186/1475-2891-6-29

Artaud F, Dugravot A, Sabia S, et al (2013) Unhealthy behaviours and disability in older adults: Three-City Dijon cohort study. British Medical Journal 347:in press. doi: 10.1136/bmj.f4240

Ashton HA, Buxton MJ, Day NE, et al (2002) The Multicentre Aneurysm Screening Study (MASS) into the effect of abdominal aortic aneurysm screening on mortality in men: a randomised controlled trial. Lancet 360:1531–9.

Audrain J, Boyd NR, Roth J, et al (1997) Genetic susceptibility testing in smoking-cessation treatment: one-year outcomes of a randomized trial. Addictive behaviors 22:741–51.

Bandura A (1977) Social learning theory. Prentice Hall, Englewood cliffs., New York

Barker ME, Thompson KA, McClean SI (1995) Attitudinal dimensions of food choice and nutrient intake. The British journal of nutrition 74:649–659. doi: 10.1079/BJN19950168

Barrett-Connor E, Khaw KT (1989) Cigarette smoking and increased central adiposity. Annals of Internal Medicine 111:783–787.

Beilby JP, Hunt CCJ, Palmer LJ, et al (2003) Apolipoprotein E gene polymorphisms are associated with carotid plaque formation but not with intima-media wall thickening: results from the Perth Carotid Ultrasound Disease Assessment Study (CUDAS). Stroke; a journal of cerebral circulation 34:869–874. doi: 10.1161/01.STR.0000062901.54157.12

Bennet AM, Angelantonio E Di, Ahlbom A, et al (2007) Association of apolipoprotein E genotypes with lipid levels and coronary risk. JAMA : the journal of the American Medical Association 298:1300–11. doi: 10.1001/jama.298.11.1300

Benzer W, Bitschnau R, Groechenig E, et al (1998) Regular Physical Activity and Risk Factors for Coronary Heart Disease Response. Circulation 98:2356–2356.

Bercedo-Sanz A, González-Lamuño D, Málaga S, García-Fuentes M (1999) Impact of ApoE4 allele on total cholesterol levels of children in northern Spain. Clinical genetics 55:69–70.

Biltoft-Jensen A, Groth M V, Matthiessen J, et al (2009) Diet quality: associations with health messages included in the Danish Dietary Guidelines 2005, personal attitudes and social factors. Public health nutrition 12:1165–73. doi: 10.1017/S1368980008003662

Bloss CS, Schork NJ, Topol EJ (2011) Effect of direct-to-consumer genomewide profiling to assess disease risk. The New England journal of medicine 364:524–34. doi: 10.1056/NEJMoa1011893

Bloss CS, Wineinger NE, Darst BF, et al (2013) Impact of direct-to-consumer genomic testing at long term follow-up. Journal of medical genetics 50:393–400. doi: 10.1136/jmedgenet-2012-101207

Borodulin K, Vartiainen E, Peltonen M, et al (2014) Forty-year trends in cardiovascular risk factors.

Brown L, Rosner B, Willett WW, Sacks FM (1999) Cholesterol-lowering effects of dietary fiber: a meta-analysis. The American journal of clinical nutrition 69:30–42.

Campbell S, Bohanna I, Swinbourne A, et al (2013) Stages of change, smoking behaviour and readiness to quit in a large sample of indigenous Australians living in eight remote north Queensland communities. International journal of environmental research and public health 10:1562–71. doi: 10.3390/ijerph10041562

Canoy D, Wareham N, Luben R, et al (2005) Cigarette smoking and fat distribution in 21,828 British men and women: a population-based study. Obesity research 13:1466–1475. doi: 10.1038/oby.2005.177

Carvalho-Wells AL, Jackson KG, Gill R, et al (2010) Interactions between age and apoE genotype on fasting and postprandial triglycerides levels. Atherosclerosis 212:481–7. doi: 10.1016/j.atherosclerosis.2010.06.036

Carvalho-Wells AL, Jackson KG, Lockyer S, et al (2012) APOE genotype influences triglyceride and C-reactive protein responses to altered dietary fat intake in UK adults. American Journal of Clinical Nutrition 96:1447–1453. doi: 10.3945/ajcn.112.043240

Chao S, Roberts JS, Marteau TM, et al (2008) Health behavior changes after genetic risk assessment for Alzheimer disease: The REVEAL Study. Alzheimer disease and associated disorders 22:94–7. doi: 10.1097/WAD.0b013e31815a9dcc

Cho S-W, Kang J-Y, Park Y-K, et al (2009) A 12-week worksite health promotion program reduces cardiovascular risk factors in male workers with the apolipoprotein E2 and apolipoprotein E3 genotypes, but not in apolipoprotein E4 genotype. Nutrition research (New York, NY) 29:542–50. doi: 10.1016/j.nutres.2009.08.002

Claassen L, Henneman L, Janssens a CJW, et al (2010) Using family history information to promote healthy lifestyles and prevent diseases; a discussion of the evidence. BMC Public Health 10:248.

Claes E, Evers-Kiebooms G, Denayer L, et al (2005) Predictive genetic testing for hereditary breast and ovarian cancer: psychological distress and illness representations 1 year following disclosure. Journal of genetic counseling 14:349–63. doi: 10.1007/s10897-005-1371-4

Cnop M, Havel PJ, Utzschneider KM, et al (2003) Relationship of adiponectin to body fat distribution, insulin sensitivity and plasma lipoproteins: evidence for independent roles of age and sex. Diabetologia 46:459–69. doi: 10.1007/s00125-003-1074-z

Collins RE, Lopez LM, Marteau TM (2011) Emotional impact of screening: a systematic review and meta-analysis. BMC public health 11:603. doi: 10.1186/1471-2458-11-603

Collins V, Meiser B, Gaff C, et al (2005) Screening and preventive behaviors one year after predictive genetic testing for hereditary nonpolyposis colorectal carcinoma. Cancer 104:273–81. doi: 10.1002/cncr.21183

Commission E (2004) Ethical, legal and social aspects of genetic testing. Directorate-General for Research, Directorate C-Science and Society. Brussels,

Conradt M, Dierk JM, Schlumberger P, et al (2009) A consultation with genetic information about obesity decreases self-blame about eating and leads to realistic weight loss goals in obese individuals. Journal of Psychosomatic Research 66:287–295. doi: 10.1016/j.jpsychores.2008.09.003

Cooke R, Sheeran P (2004) Moderation of cognition-intention and cognition-behaviour relations: a meta-analysis of properties of variables from the theory of planned behaviour. The British journal of social psychology / the British Psychological Society 43:159–186. doi: 10.1348/0144666041501688

Corbo RM, Scacchi R (1999) Apolipoprotein E (APOE) allele distribution in the world. Is APOE*4 a "thrifty" allele? Annals of human genetics 63:301–10.

Corella D, Ordovas JM (2009) Nutrigenomics in cardiovascular medicine. Circulation: Cardiovascular Genetics 2:637–651.

Corella D, Tucker K, Lahoz C, et al (2001) Alcohol drinking determines the effect of the APOE locus on LDL-cholesterol concentrations in men: The Framingham Offspring Study. American Journal of Clinical Nutrition 73:736–745.

Couderc R, Mahieux F, Bailleul S, et al (1993) Prevalence of apolipoprotein E phenotypes in ischemic cerebrovascular disease. A case-control study. Stroke; a journal of cerebral circulation 24:661–4.

Dallongeville J, Lussier-Cacan S, Davignon J (1992) Modulation of plasma triglyceride levels by apoE phenotype: a meta-analysis. Journal of lipid research 33:447–54.

Dallongeville J, Marécaux N, Ducimetière P, et al (1998) Influence of alcohol consumption and various beverages on waist girth and waist-to-hip ratio in a sample of French men and women. International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity 22:1178–1183. doi: 10.1038/sj.ijo.0800744

DeBusk RM (2009) Nutritional Genomics. The Foundation for Personalized Nutrition, What Is Nutritional Genomics. In: Gropper SS, Smith JL, Groff JL (eds) Advanced nutritiona and human metabolism., 5th editio. Wadsworth-Cengage Learning, Belmont, USA, pp 29–32

DiClemente CC, Prochaska JO, Fairhurst SK, et al (1991) The process of smoking cessation: an analysis of precontemplation, contemplation, and preparation stages of change. Journal of consulting and clinical psychology 59:295–304.

Doll J, Ajzen I (1992) Accessibility and stability of predictors in the theory of planned behavior. Journal of Personality and Social Psychology 63:754–765.

Downer B, Estus S, Katsumata Y, Fardo D (2014) Longitudinal Trajectories of Cholesterol from Midlife through Late Life according to Apolipoprotein E Allele Status. International Journal of Environmental Research and Public Health 11:10663–10693. doi: 10.3390/ijerph111010663

Dumont J, Huybrechts I, Spinneker A, et al (2011) FADS1 genetic variability interacts with dietary α-linolenic acid intake to affect serum non-HDL-cholesterol concentrations in European adolescents. The Journal of nutrition 141:1247–1253. doi: 10.3945/jn.111.140392

Duodecim SL, Suomen Verenpaineyhdistys R (2009) Current Care Guidelines: High blood pressure. http://www.kaypahoito.fi/web/kh/suositukset/naytaartikkeli/pecks/hoi04010.

Eborall HC, Griffin SJ, Prevost AT, et al (2007) Psychological impact of screening for type 2 diabetes: controlled trial and comparative study embedded in the ADDITION (Cambridge) randomised controlled trial. BMJ (Clinical research ed) 335:486. doi: 10.1136/bmj.39303.723449.55

Ebrahim S, Smith GD (2001) Exporting failure? Coronary heart disease and stroke in developing countries. International journal of epidemiology 30:201–205. doi: 10.1093/ije/30.2.201

Egert S, Boesch-Saadatmandi C, Wolffram S, et al (2010) Serum lipid and blood pressure responses to quercetin vary in overweight patients by apolipoprotein E genotype. The Journal of nutrition 140:278–84. doi: 10.3945/jn.109.117655

Egglestone C, Morris A, O'Brien A (2013) Effect of direct-to-consumer genetic tests on health behaviour and anxiety: A survey of consumers and potential consumers. Journal of Genetic Counseling 22:565–575. doi: 10.1007/s10897-013-9582-6

Ehnholm C, Lukka M, Kuusi T, et al (1986) Apolipoprotein E polymorphism in the Finnish population: gene frequencies and relation to lipoprotein concentrations. Journal of lipid research 27:227–35.

Ervin RB (2009) Prevalence of metabolic syndrome among adults 20 years of age and over, by sex, age, race and ethnicity, and body mass index: United States, 2003-2006. National health statistics reports 1–7.

Evans JP, Skrzynia C, Burke W (2001) The complexities of predictive genetic testing. BMJ (Clinical research ed) 322:1052–1056. doi: 10.1136/bmj.322.7293.1052

Farhud DD, Yeganeh MZ, Yeganeh MZ (2010) Nutrigenomics and nutrigenetics. Iranian Journal of Public Health 39:1–14. doi: 10.1016/B978-012088393-6/50058-0

Faul F, Erdfelder E, Lang A-G, Buchner A (2007) G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behavior research methods 39:175–91.

Ferguson LR (2009) Nutrigenomics Approaches to Functional Foods. Journal of the American Dietetic Association 109:452–458. doi: 10.1016/j.jada.2008.11.024

Ferguson LR et al. (2014) Nutrigenomics and Nutrigenetics in Functional Foods and Personalized Nutrition. Taylor & Francis group

Ferrara CM, Goldberg AP, Nicklas BJ, et al (2008) Sex differences in insulin action and body fat distribution in overweight and obese middle-aged and older men and women. Applied physiology, nutrition, and metabolism = Physiologie appliquée, nutrition et métabolisme 33:784–90. doi: 10.1139/H08-062

Finnish Heart Association (2015) Nutrition Recommendations for Patients of Cardiovascular Diseases. In: Nutrition Recommendations for Patients of Cardiovascular Diseases. http://www.sydan.fi/ravitsemussuositus/sydansairaudet. Accessed 1 Jan 2015

Finnish Heart Association (2010) Finnish Hearth Association. In: fat quality of dietary. http://www.sydanliitto.fi/rasvat1.

Fishbein M, Cappella JN (2006) The Role of Theory in Developing Effective Health Communications. Journal of Communication 56:S1–S17. doi: 10.1111/j.1460-2466.2006.00280.x

Fitzgibbon M, Gans KM, Evans WD, et al (2007) Communicating healthy eating: lessons learned and future directions. Journal of nutrition education and behavior 39:S63–71. doi: 10.1016/j.jneb.2006.08.017

Flegal K, Carroll M (2010) Prevalence and Trends in Obesity Among US Adults. JAMA. doi: 10.1001/jama.2009.2014

Fogelholm M, Hakala P, Kara R, et al (2014) Terveyttä ruoasta. Suomalaiset ravitsemussuositukset 2014. Valtion ravitsemusneuvottelukunta., Tampere

Freimuth VS, Quinn SC (2004) The contributions of health communication to eliminating health disparities. American Journal of Public Health 94:2053–2055.

Frosch DL, Mello P, Lerman C (2005) Behavioral consequences of testing for obesity risk. Cancer epidemiology biomarkers prevention a publication of the American Association for Cancer Research cosponsored by the American Society of Preventive Oncology 14:1485–1489.

Gefenas E, Cekanauskaite A, Tuzaite E, et al (2011) Does the “new philosophy” in predictive, preventive and personalised medicine require new ethics? EPMA Journal 2:141–147.

Glanz K, Brug J, van Assema P (1997) Are awareness of dietary fat intake and actual fat consumption associated?--a Dutch-American comparison. European journal of clinical nutrition 51:542–547. doi: 10.1038/sj.ejcn.1600442

Glanz K, Rimer BK, Viswanath K (2008) Health education. Theory, research and practice., 4th edn. Jossey-Bass Wiley Imprint, San Francisco

Glasman LR, Albarracín D (2006) Forming attitudes that predict future behavior: a meta-analysis of the attitude-behavior relation. Psychological bulletin 132:778–822. doi: 10.1037/0033-2909.132.5.778

Goei R, Boyson AR, Lyon-Callo SK, et al (2010) An examination of EPPM predictions when threat is perceived externally: an asthma intervention with school workers. Health Communication 25:333–344. doi: 10.1080/10410231003775164

Gohman D. (1997) Personal and social determinants. Handbook of Health Behavior Research. Plenum Press, New York, p Vol.1

Gramling R, Nash J, Siren K, Culpepper L (2003) Predictive genetics in primary care: expectations for the motivational impact of genetic testing affects the importance family physicians place on screening for familial

cancer risk. Genetics in medicine : official journal of the American College of Medical Genetics 5:172–5. doi: 10.1097/01.GIM.0000068986.03217.BB

Grammer TB, Hoffmann MM, Scharnagl H, et al (2013) Smoking, apolipoprotein E genotypes, and mortality (the Ludwigshafen RIsk and Cardiovascular Health study). Eur Heart J 34:1298–1305. doi: 10.1093/eurheartj/eht001

Grant RW, O'Brien KE, Waxler JL, et al (2013) Personalized genetic risk counseling to motivate diabetes prevention: a randomized trial. Diabetes care 36:13–9. doi: 10.2337/dc12-0884

Gustavsson J, Mehlig K, Leander K, et al (2012) Interaction of apolipoprotein E genotype with smoking and physical inactivity on coronary heart disease risk in men and women. Atherosclerosis 220:486–92. doi: 10.1016/j.atherosclerosis.2011.10.011

Haddy N, De Bacquer D, Chemaly MM, et al (2002) The importance of plasma apolipoprotein E concentration in addition to its common polymorphism on inter-individual variation in lipid levels: results from Apo Europe. European journal of human genetics : EJHG 10:841–50. doi: 10.1038/sj.ejhg.5200864

Haffner SM, Stern MP, Miettinen H, et al (1996) Apolipoprotein E polymorphism and LDL size in a biethnic population. Arteriosclerosis, thrombosis, and vascular biology 16:1184–8.

Halbert CH, Lynch H, Lynch J, et al (2004) Colon cancer screening practices following genetic testing for hereditary nonpolyposis colon cancer (HNPCC) mutations. Archives of internal medicine 164:1881–7. doi: 10.1001/archinte.164.17.1881

Harvey-Berino J, Gold EC, West DS, et al (2001) Does genetic testing for obesity influence confidence in the ability to lose weight? A pilot investigation. Journal of the American Dietetic Association 101:1351–3. doi: 10.1016/S0002-8223(01)00323-6

Haslam DW, James WPT (2005) Obesity. Lancet. pp 1197–1209

Hearty AP, McCarthy SN, Kearney JM, Gibney MJ (2007) Relationship between attitudes towards healthy eating and dietary behaviour, lifestyle and demographic factors in a representative sample of Irish adults. Appetite 48:1–11. doi: 10.1016/j.appet.2006.03.329

Helakorpi S, Pajunen T, Jallinoja P, et al (2011) Suomalaisen aikuisväestön terveyskäyttäytyminen ja terveys, kevät 2010 Health Behaviour and Health among the Finnish Adult Population,.

Helakorpi S, Prättälä R, Uutela A (2008) Suomalaisen aikuisväestön terveyskäyttäytyminen ja terveys, kevät 2007 Health Behaviour and Health among the Finnish Adult Population, Spring 2007. Helsinki

Helkala EL, Lakka T, Vanhanen M, et al (2001) Associations between apolipoprotein E phenotype, glucose metabolism and cognitive function in men. An explorative study in a population sample. Diabetic medicine : a journal of the British Diabetic Association 18:991–7.

Helldán A, Helakorpi S, Virtanen S, Uutela A (2013) Suomalaisen aikuisväestön terveyskäyttäytyminen ja terveys, kevät 2012 Health Behaviour and Health among the Finnish Adult Population, Spring 2012. Helsinki, Finland

Hendershot CS, Otto JM, Collins SE, et al (2010) Evaluation of a brief web-based genetic feedback intervention for reducing alcohol-related health risks associated with ALDH2. Annals of Behavioral Medicine 40:77–88. doi: 10.1007/s12160-010-9207-3

Henneman L, Bramsen I, van der Ploeg HM, ten Kate LP (2002) Preconception cystic fibrosis carrier couple screening: impact, understanding, and satisfaction. Genetic testing 6:195–202. doi: 10.1089/109065702761403351

Herron KL, McGrane MM, Waters D, et al (2006) The ABCG5 polymorphism contributes to individual responses to dietary cholesterol and carotenoids in eggs. The Journal of nutrition 136:1161–1165.

Heshka JT, Palleschi C, Howley H, et al (2008) A systematic review of perceived risks, psychological and behavioral impacts of genetic testing. Genetics in medicine : official journal of the American College of Medical Genetics 10:19–32. doi: 10.1097/GIM.0b013e31815f524f

Hietaranta-Luoma H-L, Hopia A, Luomala H, Puolijoki H (2014) Using ApoE genotyping to Promote Healthy Lifestyles in Finland - Psychological Impacts: Randomized Controlled Trial. Journal of genetic counseling 1 – 39. doi: 10.1007/s10897-015-9826-8

Hietaranta-Luoma H-L, Karhu H, Eromäki H, et al (2011) Lifestyles of South Ostrobothnians - what arte they like and where are we now? Analysis based on identification of consumer groups with varying meanings of health. Seinäjoki

Hietaranta-Luoma H-L, Luomala H, Tahvonen R, et al (2015a) Using Individual, ApoE Genotype-Based Dietary and Physical Activity Advice to Promote Healthy Lifestyle: Associations between Psychological-, Behavioral- and Clinical Factors. Journal of Nutritional Health and Food Sciences 3:1–7. doi: 10.15226/jnhfs.2015.00151

Hietaranta-Luoma H-L, Tahvonen R, Iso-Touru T, et al (2015b) An Intervention Study of Individual, apoE Genotype-Based Dietary and Physical-Activity Advice: Impact on Health Behavior. Journal of Nutrigenetics and Nutrigenomics 161–174. doi: 10.1159/000371743

Hietaranta-Luoma H-L, Åkerman K, Tahvonen R, et al (2015c) Using Individual, ApoE Genotype-Based Dietary and Physical Activity Advice to Promote Healthy Lifestyles in Finland—Impacts on Cardiovascular Risk Markers. Open Journal of Preventive Medicine 05:206–217. doi: 10.4236/ojpm.2015.55024

Holmes M V., Frikke-Schmidt R, Melis D, et al (2014) A systematic review and meta-analysis of 130,000 individuals shows smoking does not modify the association of APOE genotype on risk of coronary heart disease. Atherosclerosis 237:5–12. doi: 10.1016/j.atherosclerosis.2014.07.038

Hornik R, Kelly B (2007) Communication and Diet: An Overview of Experience and Principles. Journal of Nutrition Education and Behavior. doi: 10.1016/j.jneb.2006.08.020

Hubert HB, Feinleib M, McNamara PM, Castelli WP (1983) Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. Circulation 67:968–977. doi: 10.1161/01.CIR.67.5.968

Huebbe P, Lodge JK, Rimbach G (2010) Implications of apolipoprotein E genotype on inflammation and vitamin E status. Molecular nutrition & food research 54:623–30. doi: 10.1002/mnfr.200900398

Huebbe P, Nebel A, Siegert S, et al (2011) APOE ε4 is associated with higher vitamin D levels in targeted replacement mice and humans. FASEB journal : official publication of the Federation of American Societies for Experimental Biology 25:3262–70. doi: 10.1096/fj.11-180935

Humphries SE, Talmud PJ, Hawe E, et al (2001) Apolipoprotein E4 and coronary heart disease in middle-aged men who smoke: a prospective study. Lancet 358:115–9. doi: 10.1016/S0140-6736(01)05330-2

Ito H, Matsuo K, Wakai K, et al (2006) An intervention study of smoking cessation with feedback on genetic cancer susceptibility in Japan. Preventive medicine 42:102–8. doi: 10.1016/j.ypmed.2005.10.006

Janz NK, Becker MH (1984) The Health Belief Model: a decade later. Health education quarterly 11:1–47. doi: 10.1177/109019818401100101

Jonsson S, Hedblad B, Engström G, et al (2002) Influence of obesity on cardiovascular risk. Twenty-three-year follow-up of 22,025 men from an urban Swedish population. International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity 26:1046–1053. doi: 10.1038/sj.ijo.0802060

Juma S, Imrhan V, Vijayagopal P, Prasad C (2014) Prescribing Personalized Nutrition for Cardiovascula Health: Are We Ready? Journal of nutrigenetics and nutrigenomics 7:153–160. doi: 10.1159/000370213

Juonala M, Viikari JS a, Hutri-Kähönen N, et al (2004) The 21-year follow-up of the Cardiovascular Risk in Young Finns Study: risk factor levels, secular trends and east-west difference. Journal of Internal Medicine 255:457–468.

Kannel WB (1995) Blood pressure as a cardiovascular risk factor: prevention and treatment. JAMA : the journal of the American Medical Association 275:1571–1576.

Kaput J (2008) Nutrigenomics research for personalized nutrition and medicine. Current Opinion in Biotechnology 19:110–120.

Kasl S V, Cobb S (1966a) Health behavior, illness behavior, and sick role behavior. I. Health and illness behavior. Archives of environmental health 12:246–266. doi: 10.1080/00039896.1966.10664365

Kasl S V, Cobb S (1966b) Health behavior, illness behavior, and sick-role behavior. II. Sick-role behavior. Archives of environmental health 12:531–541. doi: NEED

Kearney M, Kelly A, Gibney M. (1998) Attitudes toward and beliefs about nutrition and health among a random sample of adults in the Republic of Ireland and Northern Ireland: Application of logistic regression modelling. Journal of Nutrition Education 30:139–148.

Keller KL, Liang LCH, Sakimura J, et al (2012) Common Variants in the CD36 Gene Are Associated With Oral Fat Perception, Fat Preferences, and Obesity in African Americans. Obesity 20:1066–1073.

Keller PA, Lipkus IM, Rimer BK (2002) Depressive Realism and Health Risk Accuracy: The Negative Consequences of Positive Mood. Journal of Consumer Research 29:57–69.

Keller PA, Lipkus IM, Rimer BK (2003) Affect, Framing, and Persuasion. Journal of Marketing Research 40:54–64.

Kim SH, Reaven G (2013) Sex differences in insulin resistance and cardiovascular disease risk. The Journal of clinical endocrinology and metabolism 98:E1716–21. doi: 10.1210/jc.2013-1166

Kinney AY, Bloor LE, Mandal D, et al (2005) The impact of receiving genetic test results on general and cancer-specific psychologic distress among members of an African-American kindred with a BRCA1 mutation. Cancer 104:2508–2516. doi: 10.1002/cncr.21479

Koenigsberg MR, Bartlett D, Cramer JS (2004) Facilitating treatment adherence with lifestyle changes in diabetes. American family physician 69:309–16.

Koh-Banerjee P, Chu NF, Spiegelman D, et al (2003) Prospective study of the association of changes in dietary intake, physical activity, alcohol consumption, and smoking with 9-y gain in waist circumference among 16 587 US men. American Journal of Clinical Nutrition 78:719–727.

Kohlmeier M, Saupe J, Schaefer K, Asmus G (1998) Bone fracture history and prospective bone fracture risk of hemodialysis patients are related to apolipoprotein E genotype. Calcified tissue international 62:278–281. doi: 10.1007/s002239900430

Kohlmeir M (2013) Nutrigenetics. Applying the Science of Personal Nutrition., First edit. Academic Press Inc Elsevier Science

Koriyama H, Nakagami H, Katsuya T, Morishita R (2012) Dyslipidemia - From Prevention to Treatment.

Kraus SJ (1995) Attitudes and the Prediction of Behavior: A Meta-Analysis of the Empirical Literature. Personality and Social Psychology Bulletin 21:58–75.

Kreuter MW, Strecher VJ, Glassman B (1999) One size does not fit all: the case for tailoring print materials. Annals of behavioral medicine : a publication of the Society of Behavioral Medicine 21:276–83.

Krieger JL, Sarge M a (2013) A serial mediation model of message framing on intentions to receive the human papillomavirus (HPV) vaccine: revisiting the role of threat and efficacy perceptions. Health communication 28:5–19. doi: 10.1080/10410236.2012.734914

Kuusisto J, Mykkänen L, Kervinen K, et al (1995) Apolipoprotein E4 phenotype is not an important risk factor for coronary heart disease or stroke in elderly subjects. Arteriosclerosis, thrombosis, and vascular biology 15:1280–1286.

Lehtimäki T, Moilanen T, Viikari J, et al (1990) Apolipoprotein E phenotypes in Finnish youths: a cross-sectional and 6-year follow-up study. Journal of lipid research 31:487–95.

Lemieux S, Després JP, Moorjani S, et al (1994) Are gender differences in cardiovascular disease risk factors explained by the level of visceral adipose tissue? Diabetologia 37:757–764. doi: 10.1007/BF00404332

Lerman C, Gold K, Audrain J, et al (1997) Incorporating biomarkers of exposure and genetic susceptibility into smoking cessation treatment: effects on smoking-related cognitions, emotions, and behavior change. Health psychology : official journal of the Division of Health Psychology, American Psychological Association 16:87–99.

Liang S, Steffen LM, Steffen BT, et al (2013) APOE genotype modifies the association between plasma omega-3 fatty acids and plasma lipids in the Multi-Ethnic Study of Atherosclerosis (MESA). Atherosclerosis 228:181–187. doi: 10.1016/j.atherosclerosis.2013.02.004

Lillie SE, Brewer NT, O'Neill SC, et al (2007) Retention and use of breast cancer recurrence risk information from genomic tests: the role of health literacy. Cancer epidemiology, biomarkers & prevention : a publication of the

American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 16:249–55. doi: 10.1158/1055-9965.EPI-06-0525

Lindström J (2006) Prevention of Type 2 Diabetes with lifestyle intervention - Emphasis on Dietary composition and identification of high-risk individuals. University of Helsinki

Lloyd HM, Paisley CM, Mela DJ (1993) Changing to a low fat diet: attitudes and beliefs of UK consumers. European journal of clinical nutrition 47:361–373.

Lovegrove J a, Gitau R (2008) Personalized nutrition for the prevention of cardiovascular disease: a future perspective. Journal of human nutrition and dietetics the official journal of the British Dietetic Association 21:306–316.

Luc G, Bard JM, Arveiler D, et al (1994) Impact of apolipoprotein E polymorphism on lipoproteins and risk of myocardial infarction. The ECTIM Study. Arteriosclerosis and thrombosis : a journal of vascular biology / American Heart Association 14:1412–9.

Ludwig DS, Pereira MA, Kroenke CH, et al (1999) Dietary fiber, weight gain, and cardiovascular disease risk factors in young adults. JAMA : the journal of the American Medical Association 282:1539–1546. doi: 10.1001/jama.282.16.1539

Lukasiewicz E, Mennen LI, Bertrais S, et al (2005) Alcohol intake in relation to body mass index and waist-to-hip ratio: the importance of type of alcoholic beverage.

Lusis AJ (2000) Atherosclerosis. Nature 407:233–41. doi: 10.1038/35025203

Ma J, Betts NM, Hampl JS (2000) Clustering of lifestyle behaviors: the relationship between cigarette smoking, alcohol consumption, and dietary intake. American journal of health promotion : AJHP 15:107–17.

Maderuelo-Fernandez JA, Recio-Rodríguez JI, Patino-Alonso MC, et al (2014) Effectiveness of interventions applicable to primary health care settings to promote Mediterranean diet or healthy eating adherence in adults: A systematic review. Preventive medicine. doi: 10.1016/j.ypmed.2014.12.011

Markowitz SM, Park ER, Delahanty LM, et al (2011) Perceived impact of diabetes genetic risk testing among patients at high phenotypic risk for type 2 diabetes. Diabetes Care 34:568–573. doi: 10.2337/dc10-1960

Marques-Vidal P, Bongard V, Ruidavets J-B, et al (2003) Obesity and alcohol modulate the effect of apolipoprotein E polymorphism on lipids and insulin. Obesity research 11:1200–1206. doi: 10.1038/oby.2003.165

Marteau T, French D, Griffin S, et al (2010a) Effects of communicating DNA-based disease risk estimates on risk-reducing behaviours (Review).

Marteau T, Senior V, Humphries SE, et al (2004) Psychological impact of genetic testing for familial hypercholesterolemia within a previously aware population: a randomized controlled trial. American journal of medical genetics Part A 128A:285–93. doi: 10.1002/ajmg.a.30102

Marteau TM, French DP, Griffin SJ, et al (2010b) Effects of communicating DNA-based disease risk estimates on risk-reducing behaviours. Cochrane database of systematic reviews (Online) CD007275. doi: 10.1002/14651858.CD007275.pub2

Marteau TM, Weinman J (2006) Self-regulation and the behavioural response to DNA risk information: a theoretical analysis and framework for future research. Social science medicine 62:1360–1368. doi: 10.1016/j.socscimed.2005.08.005

Marti B, Tuomilehto J, Salomaa V, et al (1991) Body fat distribution in the Finnish population: environmental determinants and predictive power for cardiovascular risk factor levels. Journal of epidemiology and community health 45:131–137.

Martinez-Hervas S, Mansego ML, de Marco G, et al (2012) Polymorphisms of the UCP2 gene are associated with body fat distribution and risk of abdominal obesity in Spanish population. European Journal of Clinical Investigation 42:171–178. doi: 10.1111/j.1365-2362.2011.02570.x

Mason OJ, Holt R (2012) Mental health and physical activity interventions: A review of the qualitative literature. Journal of Mental Health 21:274–284.

Masson LF, McNeill G, Avenell A (2003) Genetic variation and the lipid response to dietary intervention: a systematic review. The American journal of clinical nutrition 77:1098–111.

Matikainen N (2009) [Elevated triglyceride level]. Duodecim; lääketieteellinen aikakauskirja 125:371–80.

Mattisson I, Wirfält E, Aronsson CA, et al (2005) Misreporting of energy: prevalence, characteristics of misreporters and influence on observed risk estimates in the Malmö Diet and Cancer cohort. The British journal of nutrition 94:832–42.

Maxwell TJ, Ballantyne CM, Cheverud JM, et al (2013) APOE modulates the correlation between triglycerides, cholesterol, and CHD through pleiotropy, and gene-by-gene interactions. Genetics 195:1397–1405. doi: 10.1534/genetics.113.157719

McBride CM, Bepler G, Lipkus IM, et al (2002) Incorporating genetic susceptibility feedback into a smoking cessation program for African-American smokers with low income. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 11:521–8.

McBride CM, Koehly LM, Sanderson SC, Kaphingst KA (2010) The behavioral response to personalized genetic information: will genetic risk profiles motivate individuals and families to choose more healthful behaviors? Annual review of public health 31:89–103. doi: 10.1146/annurev.publhealth.012809.103532

McCarney R, Warner J, Iliffe S, et al (2007) The Hawthorne Effect: a randomised, controlled trial. BMC medical research methodology 7:30. doi: 10.1186/1471-2288-7-30

McKay DL, Berkowitz JM, Blumberg JB, Goldberg JP (2004) Communicating cardiovascular disease risk due to elevated homocysteine levels: using the EPPM to develop print materials. Health education behavior the official publication of the Society for Public Health Education 31:355–371. doi: 10.1177/1090198104263353

McLeod J, Shanahan M (1993) Poverty, parenting and children's mental health. American Sociological Review 58:351–366.

Meisel SF, Beeken RJ, van Jaarsveld CHM, Wardle J (2012) Genetic test feedback with weight control advice: study protocol for a randomized controlled trial. Trials 13:235. doi: 10.1186/1745-6215-13-235

Meisel SF, Beeken RJ, van Jaarsveld CHM, Wardle J (2015) Genetic susceptibility testing and readiness to control weight: Results from a randomized controlled trial. Obesity 23:305–312. doi: 10.1002/oby.20958

Meisel SF, Wardle J (2014) "Battling my biology": Psychological effects of genetic testing for risk of weight gain. Journal of Genetic Counseling 23:179–186. doi: 10.1007/s10897-013-9628-9

Meiser B, Butow P, Friedlander M, et al (2002) Psychological impact of genetic testing in women from high-risk breast cancer families. European Journal of Cancer 38:2025–2031.

Meiser B, Collins V, Warren R, et al (2004) Psychological impact of genetic testing for hereditary non-polyposis colorectal cancer. Journal of Clinical Oncology 66:502–511. doi: 10.1200/JCO.2005.07.102

Mente A, de Koning L, Shannon HS, Anand SS (2009) A systematic review of the evidence supporting a causal link between dietary factors and coronary heart disease. Archives of internal medicine 169:659–669. doi: 10.1001/archinternmed.2009.38

Mihovilovic M, Robinette JB, DeKroon RM, et al (2007) High-fat/high-cholesterol diet promotes a S1P receptor-mediated antiapoptotic activity for VLDL. Journal of lipid research 48:806–815. doi: 10.1194/jlr.M600201-JLR200

Mikkilä V, Räsänen L, Raitakari OT, et al (2005) Consistent dietary patterns identified from childhood to adulthood: the cardiovascular risk in Young Finns Study. The British journal of nutrition 93:923–31.

Miles S, Scaife V (2003) Optimistic bias and food. Nutrition research reviews 16:3–19. doi: 10.1079/NRR200249

Miller SA, Dykes DD, Polesky HF (1988) A simple salting out procedure for extracting DNA from human nucleated cells. Nucleic acids research 16:1215.

Minich DM, Bland JS (2013) Personalized lifestyle medicine: relevance for nutrition and lifestyle recommendations. TheScientificWorldJournal 2013:129841. doi: 10.1155/2013/129841

Minihane a M, Jofre-Monseny L, Olano-Martin E, Rimbach G (2007) ApoE genotype, cardiovascular risk and responsiveness to dietary fat manipulation. The Proceedings of the Nutrition Society 66:183–197. doi: 10.1017/S0029665107005435

Minihane AM, Khan S, Leigh-Firbank EC, et al (2000) ApoE Polymorphism and Fish Oil Supplementation in Subjects With an Atherogenic Lipoprotein Phenotype. Arteriosclerosis, Thrombosis, and Vascular Biology 20:1990–1997. doi: 10.1161/01.ATV.20.8.1990

Misra A, Vikram NK (2003) Clinical and pathophysiological consequences of abdominal adiposity and abdominal adipose tissue depots. Nutrition 19:457–466.

Moleres A, Ochoa MC, Rendo-Urteaga T, et al (2012) Dietary fatty acid distribution modifies obesity risk linked to the rs9939609 polymorphism of the fat mass and obesity-associated gene in a Spanish case–control study of children. British Journal of Nutrition 107:533–538.

Moran A, Jacobs DR, Steinberger J, et al (2008) Changes in insulin resistance and cardiovascular risk during adolescence: establishment of differential risk in males and females. Circulation 117:2361–8. doi: 10.1161/CIRCULATIONAHA.107.704569

Mountcastle-Shah E, Holtzman NA (2000) Primary care physicians' perceptions of barriers to genetic testing and their willingness to participate in research. American journal of medical genetics 94:409–16.

National Institute for Health and Welfare Kansallinen lihavuusohjelma. http://www.thl.fi/fi_FI/web/fi/tutkimus/ohjelmat/kansallinen_lihavuusohjelma_2012_2015/luvut/yleisyys_suomessa.

National Institute of Health Cholesterol Levels: What You Need to Know. http://www.nih.gov/.

Ng N, Johnson O, Lindahl B, Norberg M (2012) A reversal of decreasing trends in population cholesterol levels in V?? sterbotten County, Sweden. Global Health Action. doi: 10.3402/gha.v5i0.10367

Nielsen D., Shih S, El-Sohemy A (2014) Perceptions of Genetic Testing for Personalized Nutrition: A Randomized Trial of DNA-Based Dietary Advice. Journal of nutrigenetics and nutrigenomics 7:94–104. doi: 10.1159/000365508

Nielsen DE, El-Sohemy A (2012) A randomized trial of genetic information for personalized nutrition. Genes and Nutrition 7:559–566. doi: 10.1007/s12263-012-0290-x

Noar SM, Benac CN, Harris MS (2007) Does tailoring matter? Meta-analytic review of tailored print health behavior change interventions. Psychological bulletin 133:673–693. doi: 10.1037/0033-2909.133.4.673

Noland EW (1959) HAWTHORNE REVISITED. By Henry A. Landsberger. Ithaca, New York: The New York State School of Industrial and Labor Relations, 1958, 132 pp. $3.50. Social Forces 37:361–364. doi: 10.2307/2574186

Nuutila P, Knuuti MJ, Mäki M, et al (1995) Gender and insulin sensitivity in the heart and in skeletal muscles. Studies using positron emission tomography. Diabetes 44:31–6.

Nyrhinen T (2007) Ethics in diagnostic genetic testing. University of Turku

O'Neil CE, Nicklas TA, Myers L, et al (1997) Cardiovascular risk factors and behavior lifestyles of young women: implications from findings of the Bogalusa Heart Study. The American journal of the medical sciences 314:385–95.

O'Neill SC, Kaufman E, DeMarco T, et al (2008) Changes in diet and physical activity following BRCA1/2 testing. Journal of psychosocial oncology 26:63–80. doi: 10.1080/07347330802116051

Ogden CL, Carroll MD, Kit BK, Flegal KM (2014) Prevalence of Childhood and Adult Obesity in the United States, 2011-2012. JAMA 311:806. doi: 10.1001/jama.2014.732

Olano-Martin E, Anil E, Caslake MJ, et al (2010) Contribution of apolipoprotein E genotype and docosahexaenoic acid to the LDL-cholesterol response to fish oil. Atherosclerosis 209:104–110. doi: 10.1016/j.atherosclerosis.2009.08.024

Olsen SO (2003) Understanding the relationship between age and seafood consumption: the mediating role of attitude, health involvement and convenience. Food Quality and Preference 14:199–209.

Ong TP, Pérusse L (2011) Impact of nutritional epigenomics on disease risk and prevention: introduction. Journal of nutrigenetics and nutrigenomics 4:245–7. doi: 10.1159/000334813

Ordovas JM (2002) Gene-diet interaction and plasma lipid responses to dietary intervention. Biochemical Society transactions 30:68–73. doi: 10.1042/BST0300068

Ordovas JM, Corella D (2004) Nutritional genomics. Annual review of genomics and human genetics 5:71–118. doi: 10.1146/annurev.genom.5.061903.180008

Ordovas JM, Corella D, Cupples LA, et al (2002) Polyunsaturated fatty acids modulate the effects of the APOA1 G-A polymorphism on HDL-cholesterol concentrations in a sex-specific manner: The Framingham study. American Journal of Clinical Nutrition 75:38–46.

Ordovas JM, Kaput J, Corella D (2007) Nutrition in the genomics era: cardiovascular disease risk and the Mediterranean diet. Molecular nutrition & food research 51:1293–9. doi: 10.1002/mnfr.200700041

Ordovas JM, Lopez-Miranda J, Mata P, et al (1995) Gene-diet interaction in determining plasma lipid response to dietary intervention. Atherosclerosis 118 Suppl:S11–S27. doi: 10.1016/0021-9150(95)90069-1

Ordovás JM, Smith CE (2010) Epigenetics and cardiovascular disease. Nature reviews Cardiology 7:510–519. doi: 10.1038/nrcardio.2010.104

Pablos-Méndez A, Mayeux R, Ngai C, et al (1997) Association of apo E polymorphism with plasma lipid levels in a multiethnic elderly population. Arteriosclerosis, thrombosis, and vascular biology 17:3534–3541. doi: 10.1161/01.ATV.17.12.3534

Park P, Simmons RK, Prevost AT, Griffin SJ (2008) Screening for type 2 diabetes is feasible, acceptable, but associated with increased short-term anxiety: a randomised controlled trial in British general practice. BMC public health 8:350. doi: 10.1186/1471-2458-8-350

Patja K, Jousilahti P, Hu G, et al (2005) Effects of smoking, obesity and physical activity on the risk of type 2 diabetes in middle-aged Finnish men and women. Journal of internal medicine 258:356–362. doi: 10.1111/j.1365-2796.2005.01545.x

Peltonen M, Harald K, Männistö S, et al (2008) Finriski 2007. Helsinki, Finland

Peterson SK (2005) The role of the family in genetic testing: theoretical perspectives, current knowledge, and future directions. Health education & behavior : the official publication of the Society for Public Health Education 32:627–39. doi: 10.1177/1090198105278751

Phillips CM (2013) Nutrigenetics and metabolic disease: current status and implications for personalised nutrition. Nutrients 5:32–57. doi: 10.3390/nu5010032

Phillips CM, Kesse-Guyot E, McManus R, et al (2012) High Dietary Saturated Fat Intake Accentuates Obesity Risk Associated with the Fat Mass and Obesity-Associated Gene in Adults. Journal of Nutrition 142:824–831.

Pogribna M, Melnyk S, Pogribny I, et al (2001) Homocysteine metabolism in children with Down syndrome: in vitro modulation. American journal of human genetics 69:88–95. doi: 10.1086/321262

Poortinga W (2007) The prevalence and clustering of four major lifestyle risk factors in an English adult population. Preventive Medicine 44:124–128. doi: 10.1016/j.ypmed.2006.10.006

Prati G, Pietrantoni L, Zani B (2012) Influenza vaccination: the persuasiveness of messages among people aged 65 years and older. Health Communication 27:413–20. doi: 10.1080/10410236.2011.606523

Prochaska JO DC (2005) The transtheoretical approach. In: Norcross, JC; Goldfried, MR. Handbook of psychotherapy integration., 2nd edn. Oxford University Press; 2005, New York

Pronk NP, Anderson LH, Crain AL, et al (2004) Meeting recommendations for multiple healthy lifestyle factors: Prevalence, clustering, and predictors among adolescent, adult, and senior health plan members. American Journal of Preventive Medicine 27:25–33. doi: 10.1016/j.amepre.2004.04.022

Quach J, Porter K, Leventhal H, Kelly KM (2009) Health behaviors among Ashkenazi Jewish individuals receiving counseling for BRCA1 and BRCA2 mutations. Familial Cancer 8:241–250. doi: 10.1007/s10689-009-9235-y

Rahman B, Meiser B, Sachdev P, et al (2012) To Know or Not to Know: An Update of the Literature on the Psychological and Behavioral Impact of Genetic Testing for Alzheimer Disease Risk. Genetic Testing and Molecular Biomarkers 16:935–942.

Raitakari OT, Leino M, Räkkönen K, et al (1995) Clustering of risk habits in young adults. The Cardiovascular Risk in Young Finns Study. American journal of epidemiology 142:36–44.

Ranjith N, Pegoraro RJ, Rom L, et al (2004) Lp(a) and apoE polymorphisms in young South African Indians with myocardial infarction. Cardiovascular journal of South Africa : official journal for Southern Africa Cardiac Society [and] South African Society of Cardiac Practitioners 15:111–117.

Rantala M, Savolainen MJ, Kervinen K, Kesäniemi YA (1997) Apolipoprotein E phenotype and diet-induced alteration in blood pressure. The American journal of clinical nutrition 65:543–50.

Rastas S, Mattila K, Verkkoniemi A, et al (2004) Association of apolipoprotein E genotypes, blood pressure, blood lipids and ECG abnormalities in a general population aged 85+. BMC geriatrics 4:1. doi: 10.1186/1471-2318-4-1

Resta R, Biesecker BB, Bennett RL, et al (2006) A new definition of genetic counseling: National Society of Genetic Counselors' Task Force report. Journal of Genetic Counseling 15:77–83.

Rief W, Conradt M, Dierk JM, et al (2007) Is information on genetic determinants of obesity helpful or harmful for obese people? - A randomized clinical trial. Journal of General Internal Medicine 22:1553–1559. doi: 10.1007/s11606-007-0353-7

Roberts JS, Cupples LA, Relkin NR, et al (2005) Genetic risk assessment for adult children of people with Alzheimer's disease: the Risk Evaluation and Education for Alzheimer's Disease (REVEAL) study. Journal of Geriatric Psychiatry and Neurology 18:250–255. doi: 10.1177/0891988705281883

Robinson SM, Jameson KA, Syddall HE, et al (2013) Clustering of lifestyle risk factors and poor physical function in older adults: The hertfordshire cohort study. Journal of the American Geriatrics Society 61:1684–1691. doi: 10.1111/jgs.12457

Rogers R, Cacioppo J (toim. ., Petty R (toim. . (1983) Cognitive and physiological processes in fear appeals and attitude change: A revised theory of protection motivation. Social psychophysiology. Guilford, New York

Roininen K, Tuorila H, Zandstra EH, et al (2001) Differences in health and taste attitudes and reported behaviour among Finnish, Dutch and British consumers: a cross-national validation of the Health and Taste Attitude Scales (HTAS). Appetite 37:33–45. doi: 10.1006/appe.2001.0414

Ronksley PE, Brien SE, Turner BJ, et al (2011) Association of alcohol consumption with selected cardiovascular disease outcomes: a systematic review and meta-analysis. BMJ (Clinical research ed) 342:d671. doi: 10.1136/bmj.d671

Rosenstock I (1974) The health belief model and preventive health behavior. Health education monographs 2:354–86.

Rozin P, Fischler C, Imada S, et al (1999) Attitudes to food and the role of food in life in the U.S.A., Japan, Flemish Belgium and France: possible implications for the diet-health debate. Appetite 33:163–180. doi: 10.1006/appe.1999.0244

Ruiter RAC, Kok G, Verplanken B, van Eersel G (2003) Strengthening the persuasive impact of fear appeals: the role of action framing. The Journal of social psychology 143:397–400. doi: 10.1080/00224540309598452

Rutter M (2003) Poverty and child mental health: natural experiments and social caution. JAMA 290:2063–64.

Saaristo T, Etu-Seppälä L, Oksa H, Peltonen M (2009) FIN-D2D report.

Saito M, Eto M, Nitta H, et al (2004) Effect of apolipoprotein E4 allele on plasma LDL cholesterol response to diet therapy in type 2 diabetic patients. Diabetes care 27:1276–80.

Salmela SM, Kettunen T, Poskiparta M (2010) Vaikuttavan elintapaohjausintervention suunnittelu – helpommin sanottu kuin tehty ? 208–218.

Sanderson S, O'Neill S, Bepler G (2009) Responses to online GSTM1 genetic test results among smokers related to patients with lung cancer: a pilot study. Cancer Epidemiology … 18:1953–1961. doi: 10.1158/1055-9965.EPI-08-0620

Schiele F, De Bacquer D, Vincent-Viry M, et al (2000) Apolipoprotein E serum concentration and polymorphism in six European countries: the ApoEurope Project. Atherosclerosis 152:475–88.

Schuit AJ, van Loon AJM, Tijhuis M, Ocké MC (2002) Clustering of Lifestyle Risk Factors in a General Adult Population. Preventive Medicine 35:219–224. doi: 10.1006/pmed.2002.1064

Schwartz SH (2011) Culture Value Orientations: Nature & Implications of National Differences., 1. painos. Publishing House of SU HSE, Moscow

Sharma AM (2003) Obesity and cardiovascular risk. Growth Hormone & IGF Research 13:S10–S17.

Sheehan D, Bennett T, Cashman K (2000) Apolipoprotein E gene polymorphisms and serum cholesterol in healthy Irish adults: a proposed genetic marker for coronary artery disease risk. Irish journal of medical science 169:50–54. doi: 10.1007/BF03170486

Shin M-H, Kim H-N, Cui L-H, et al (2005) The effect of apolipoprotein E polymorphism on lipid levels in Korean adults. Journal of Korean medical science 20:361–366.

Silventoinen K, Sans S, Tolonen H, et al (2004) Trends in obesity and energy supply in the WHO MONICA Project. International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity 28:710–718. doi: 10.1038/sj.ijo.0802614

Simopoulos AP (2010) Nutrigenetics/Nutrigenomics. Annual review of public health 31:53–68. doi: 10.1146/annurev.publhealth.031809.130844

Singh PP, Singh M, Mastana SS (2006) APOE distribution in world populations with new data from India and the UK. Annals of human biology 33:279–308. doi: 10.1080/03014460600594513

Smerecnik CMR, Mesters I, van Keulen H, et al (2007) Should individuals be informed about their salt sensitivity status? First indications of the value of testing for genetic predisposition to low-risk conditions. Genetic testing 11:307–314. doi: 10.1089/gte.2007.0008

Smith CE, Ordovás JM, Sánchez-Moreno C, et al (2012) Apolipoprotein A-II polymorphism: relationships to behavioural and hormonal mediators of obesity. International Journal of Obesity 36:130–136.

Smith JR, Terry DJ, Manstead ASR, et al (2008) The attitude-behavior relationship in consumer conduct: the role of norms, past behavior, and self-identity. The Journal of social psychology 148:311–333. doi: 10.3200/SOCP.148.3.311-334

Smith TW, Orleans CT, Jenkins CD (2004) Prevention and health promotion: decades of progress, new challenges, and an emerging agenda. Health psychology : official journal of the Division of Health Psychology, American Psychological Association 23:126–31. doi: 10.1037/0278-6133.23.2.126

Song Y, Stampfer MJ, Liu S (2004) Meta-analysis: apolipoprotein E genotypes and risk for coronary heart disease. Annals of internal medicine 141:137–47.

Spielberger C (1971) Trait-State Anxiety and Motor Behavior. J Mot Behav 3:265–79.

Spielberger C, Gorsuch RL LP (1970) STAI manual for the STATE-TRAIT ANXIETY INVENTORY. ("Self-Evaluation Questionnaire"). Consulting Psychologists Press, Inc.

Spielberger C, Gorsuch RL, Lushene PR, Vagg Pra jacobs G (1983) State-Trait anxiety inventory for adults. Mind garden, Palo Alto

Srinivasan SR, Ehnholm C, Elkasabany A, Berenson G (1999) Influence of apolipoprotein e polymorphism on serum lipids and lipoprotein changes from childhood to adulthood: The Bogalusa Heart Study. Atherosclerosis 143:435–443. doi: 10.1016/S0021-9150(98)00304-9

Stamler J, Wentworth D, Neaton JD (1986) Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). JAMA : the journal of the American Medical Association 256:2823–2828. doi: 10.1001/jama.256.20.2823

Stewart-Knox BJ, Bunting BP, Gilpin S, et al (2009) Attitudes toward genetic testing and personalised nutrition in a representative sample of European consumers. The British journal of nutrition 101:982–9. doi: 10.1017/S0007114508055657

Sullivan PM, Mezdour H, Quarfordt SH, Maeda N (1998) Type III hyperlipoproteinemia and spontaneous atherosclerosis in mice resulting from gene replacement of mouse Apoe with human APOE*2. Journal of Clinical Investigation 102:130–135. doi: 10.1172/JCI2673

Suomalaisen Lääkäriseuran Duodecimin asettama työryhmä. (2012) Liikunta - käypähoito suositus. http://www.kaypahoito.fi/web/kh/suositukset/suositus;jsessionid=50891B0A59FBA9B324C24B7CC583DF9E?id=hoi50075. Accessed 1 Jan 2015

Taloustutkimus Oy F, The Finnish Innovation Fund S (2013) Genomitieto, asenneselvitys - lääkärit. Physicians: genetic testing is becoming more and more common, so where are the guidelines? Helsinki, Finland

Talvia S, Räsänen L, Lagström H, et al (2011) Parental eating attitudes and indicators of healthy eating in a longitudinal randomized dietary intervention trial (the STRIP study). Public health nutrition 14:2065–73. doi: 10.1017/S1368980011000905

Tammi A, Rönnemaa T, Viikari J, et al (2000) Apolipoprotein E4 phenotype increases non-fasting serum triglyceride concentration in infants - the STRIP study. Atherosclerosis 152:135–41.

Tarnanen K, Pietiläinen K, Hakala P, et al (2011) Käypähoitosuositukset. Lihavuus. In: Duodecim; lääketieteellinen aikakauskirja.

Tarnanen K, Tikkanen M., Syvänne M, Kukkonen-Harjula K (2013) Käypähoitosuositukset Suomessa: Dyslipidemiat (veren poikkeavat rasva-arvot, mm. kolesteroli) kuriin potilaan ja lääkärin yhteistyöllä. http://www.kaypahoito.fi/web/kh/suositukset/naytaartikkeli/tunnus/khp00047.

Taylor JY, Wu CY (2009) Effects of genetic counseling for hypertension on changes in lifestyle behaviors among African-American women. Journal of National Black Nurses' Association : JNBNA 20:1–10.

Teicher-Zallen D (2009) To Test or Not to Test: A Guide to Genetic Screening and Risk (Thorndike Health, Home & Learning). Virginia, United States

The Finnish Medical Society Duodecim (2013) Current Care Guidelines: Dyslipidemias. http://www.kaypahoito.fi/web/english/kaypa-hoito.

Tiret L, de Knijff P, Menzel HJ, et al (1994) ApoE polymorphism and predisposition to coronary heart disease in youths of different European populations. The EARS Study. European Atherosclerosis Research Study. Arteriosclerosis and thrombosis : a journal of vascular biology / American Heart Association 14:1617–24.

Torkkola S (2002) Terveysviestintä. Kustannus Oy Tammi., Helsinki, Finland

Trujillo E, Davis C, Milner J (2006) Nutrigenomics, proteomics, metabolomics, and the practice of dietetics. Journal of the American Dietetic Association 106:403–413.

Ulrik Gerdes L (2003) The common polymorphism of apolipoprotein E: Geographical aspects and new pathophysiological relations. Clinical Chemistry and Laboratory Medicine 41:628–631. doi: 10.1515/CCLM.2003.094

Wallace LM, Brown KE, Hilton S (2014) Planning for, implementing and assessing the impact of health promotion and behaviour change interventions: a way forward for health psychologists. Health psychology review 8:8–33. doi: 10.1080/17437199.2013.775629

van den Hoogen PC, Feskens EJ, Nagelkerke NJ, et al (2000) The relation between blood pressure and mortality due to coronary heart disease among men in different parts of the world. Seven Countries Study Research Group. The New England journal of medicine 342:1–8. doi: 10.1056/NEJM200001063420101

Wang C, Gordon ES, Stack CB, et al (2014) A randomized trial of the clinical utility of genetic testing for obesity: design and implementation considerations. Clinical trials (London, England) 11:102–13. doi: 10.1177/1740774513508029

Varga O, Soini S, Kääriäinen H, et al (2012) Definitions of genetic testing in European legal documents. Journal of Community Genetics 3:125–141. doi: 10.1007/s12687-012-0077-1

Vartiainen E, Laatikainen T, Peltonen M, et al (2010) Thirty-five-year trends in cardiovascular risk factors in Finland. International Journal of Epidemiology 39:504–518. doi: 10.1093/ije/dyp330

Watson M, Foster C, Eeles R, et al (2004) Psychosocial impact of breast/ovarian (BRCA1/2) cancer-predictive genetic testing in a UK multi-centre clinical cohort. British journal of cancer 91:1787–94. doi: 10.1038/sj.bjc.6602207

Vermeer C (2012) Vitamin K: The effect on health beyond coagulation - An overview. Food and Nutrition Research.

Vernarelli JA, Roberts JS, Hiraki S, et al (2010) Effect of Alzheimer disease genetic risk disclosure on dietary supplement use. American Journal of Clinical Nutrition 91:1402–1407. doi: 10.3945/ajcn.2009.28981

Wetterstrand K (2014) DNA Sequencing Costs. Data from the NHGRI Genome Sequencing Program (GSP). In: National Human Genome Research Institute. https://www.genome.gov/sequencingcosts/.

Willeit J, Kiechl S, Egger G, et al (1997) The role of insulin in age-related sex differences of cardiovascular risk profile and morbidity. Atherosclerosis 130:183–9.

Witte K (1992) Putting the fear back into fear appeals - the extended parallel process model. Communication Monographs 59:329–49.

Witte K (1991) The role of threat and efficacy in AIDS prevention. International quarterly of community health education 12:225–49. doi: 10.2190/U43P-9QLX-HJ5P-U2J5

Witte K, Allen M (2000) A meta-analysis of fear appeals: implications for effective public health campaigns. Health education & behavior : the official publication of the Society for Public Health Education 27:591–615.

Witte K, Berkowitz JM, Cameron KA, McKeon JK (1998) Preventing the spread of genital warts: using fear appeals to promote self-protective behaviors. Health education & behavior : the official publication of the Society for Public Health Education 25:571–85.

Witte KMGMD (2001) Effective health risk message: a step-by-step guide. Sage Publications, California

Voils CI, Coffman CJ, Edelman D, et al (2012) Examining the impact of genetic testing for type 2 diabetes on health behaviors: study protocol for a randomized controlled trial. Trials 13:121. doi: 10.1186/1745-6215-13-121

Wong NCH, Cappella JN (2009) Antismoking Threat and Efficacy Appeals: Effects on Smoking Cessation Intentions for Smokers with Low and High Readiness to Quit. Journal of Applied Communication Research 37:1–20.

Wood PD, Haskell WL, Blair SN, et al (1983) Increased exercise level and plasma lipoprotein concentrations: A one-year, randomized, controlled study in sedentary, middle-aged men. Metabolism 32:31–39. doi: 10.1016/0026-0495(83)90152-X

Vähäsarja K, Salmela S, Villberg J, et al (2012) Perceived need to increase physical activity levels among adults at high risk of type 2 diabetes: a cross-sectional analysis within a community-based diabetes prevention project FIN-D2D. BMC public health 12:514. doi: 10.1186/1471-2458-12-514

Yannakoulia M, Panagiotakos DB, Pitsavos C, Stefanadis C (2006) Correlates of BMI misreporting among apparently healthy individuals: the ATTICA study. Obesity (Silver Spring, Md) 14:894–901. doi: 10.1038/oby.2006.103

Yoon U, Kwok LL, Magkidis A (2013) Efficacy of lifestyle interventions in reducing diabetes incidence in patients with impaired glucose tolerance: a systematic review of randomized controlled trials. Metabolism: clinical and experimental 62:303–14. doi: 10.1016/j.metabol.2012.07.009

Zandstra E., de Graaf C, Van Staveren W. (2001) Influence of health and taste attitudes on consumption of low- and high-fat foods. Food Quality and Preference 75–82.

Zhang Y, Lee ET, Devereux RB, et al (2006) Prehypertension, diabetes, and cardiovascular disease risk in a population-based sample: The strong heart study. Hypertension 47:410–414. doi: 10.1161/01.HYP.0000205119.19804.08

APPENDIX 1. Comparison of messages' content

	Message 1 (high real threat and high experience threat)	**Message 2** (high real threat and low experience threat)	**Message 3** (low real threat and high experience threat)	**Message 4** (low real threat and low experience threat)	**Control message**
Perceived susceptibility	*APOE* 4/4 or 3/4	*APOE* 4/4 or 3/4 an increased risk for high cholesterol level and cardiovascular diseases	…although you do not have the inherited gene, which predisposes a person to a higher cholesterol level…	…although you do not have the inherited gene, which predisposes a person to a higher cholesterol level… …cardiovascular diseases are largest health problem and most common cause of death in Finland…	…cardiovascular diseases are most common cause of death in Finland… …the *APOE* gene is only one gene marker…
Perceived severity	…increased risk for high cholesterol level and cardiovascular diseases…	…high blood cholesterol increases…	…there are also several other factors, which affect a high cholesterol level, not only heredity… unhealthy lifestyle…	…there are also several other factors, which affect a high cholesterol level, not only heredity… unhealthy lifestyle… …high blood cholesterol increases the risk of contracting a cardiovascular diseases…	…there are also several other factors, which affect to high cholesterol level, not only heredity… unhealthy lifestyle… …high blood cholesterol increases the risk to get cardiovascular diseases…
Response efficacy	…decreasing saturated fat and increasing physical activity…	…decreasing saturated fat and increasing physical activity…	…decreasing saturated fat and increasing physical activity…	…decreasing saturated fat and increasing physical activity…	…unhealthy lifestyle…
Self-efficacy	…however, it is positive that especially your cholesterol will have good response to dietary changes…good luck for with your lifestyle change!	…it is possible to achieve a lifestyle… especially with your cholesterol… good luck with your lifestyle change!	…even with small lifestyle changes, it is possible to achieve…good luck with your lifestyle change!	…it is possible to achieve changes… good luck with your lifestyle change!	… the effect of changing dietary to healthier has individual, but always effective and profitable…

APPENDIX 2. Message 1

Tervehdys!

Vieläkö muistat ravitsemus, geenit ja elämäntapa tutkimuksemme, jonka alkututkimuksiin osallistuitte **syyskuussa 2010?** Miltä päivä sinusta tuntui ja saitteko mielestänne tarpeellista tietoa itsestänne ja ravitsemuksesta?

Kiitos,

että osallistutte tutkimukseen, koska teidän ansiosta saamme harvinaislaatuista tutkimustietoa eteläpohjalaisten elintavoista ja APO E geeniperimästä. Myös teillä on erinomainen mahdollisuus seurata omien henkilökohtaisten elämäntapamuutosten vaikutusta mittaustuloksiinne. Seuraavat tutkimuspäivät ovat maaliskuussa 2011 ja syyskuussa 2011.

Alkututkimuspäivänä teiltä otettiin erilaisia mittauksia (verikokeet, pituus, paino, vyötärönympärys, rasvaprosentti), joiden tulokset saitte samana päivänä. Lisäksi täytitte lukuisan joukon erilaisia kyselyitä. Merkittävistä poikkeamista on tiedotettu asianosaisille ja heitä pyydetty ottamaan yhteyttä lääkärille. Yleistä tietoa tutkimuksiin osallistuneiden tutkimustuloksista sekä muista tiedotettavista asioista on kerrottu seuraavilla sivuilla.

Edellä mainittujen mittausten jälkeen sinulta otettiin myös geenitesti. Testin perusteella sinulla on perimässäsi **APO E 4/4 tai 3/4 –alleeli**, mikä tarkoittaa, että sinulla kolesterolin imeytyminen ruoasta on erittäin tehokasta. Tämän takia sinulla on hieman suurentunut riski korkeaan kolesteroliin ja sitä kautta sydän- ja verisuonitauteihin. Suomalaisista noin kolmannes kuuluu tähän ryhmään.

Positiivista kuitenkin on, että tutkitusti jo pienillä elintapojen muuttamisilla pystyt saamaan tuloksia aikaan. Erityisesti sinulla kolesteroli reagoi herkästi elintapojen muutokseen ja voit ehkäistä sydän- ja verisuonisairauksia. Kovan rasvan vähentäminen ja pehmeiden rasvojen lisääminen ruokavalioon, säännöllinen liikunnan harrastaminen, alkoholin ja sokeripitoisten ruokien vähentäminen ruokavaliosta ja normaalipainon säilyttäminen vähentävät selvästi riskiä sairastua sydän- ja verisuonitauteihin. Ruokaremontin avulla voit vaikuttaa keskimäärin 10 - 15 %, mutta jopa 40 % veren kolesterolipitoisuuteen. Vaikutus on yksilöllinen, mutta aina tehokas ja kannattava. Ruokavalion muutos on aina ensisijainen toimenpide, kun halutaan ehkäistä veren kolesterolipitoisuuden nousua tai laskea jo kohonnutta kolesterolia.

TSEMPPIÄ elämäntapamuutokseen, koska erityisesti sinulla jo pienetkin muutokset ovat tehokkaita☺!

APPENDIX 3. Message 2

Tervehdys!

Vieläkö muistat ravitsemus, geenit ja elämäntapa tutkimuksemme, jonka alkututkimuksiin osallistuitte **syyskuussa 2010?** Miltä päivä sinusta tuntui ja saitteko mielestänne tarpeellista tietoa itsestänne ja ravitsemuksesta?

Kiitos,

että osallistutte tutkimukseen, koska teidän ansiosta saamme harvinaislaatuista tutkimustietoa eteläpohjalaisten elintavoista ja APO E geeniperimästä. Myös teillä on erinomainen mahdollisuus seurata omien henkilökohtaisten elämäntapamuutosten vaikutusta mittaustuloksiinne. Seuraavat tutkimuspäivät ovat maaliskuussa 2011 ja syyskuussa 2011.

Alkututkimuspäivänähän teiltä otettiin erilaisia mittauksia (verikokeet, pituus, paino, vyötärönympärys, rasvaprosentti), joiden tulokset saitte samana päivänä. Lisäksi täytitte lukuisan joukon erilaisia kyselyitä. Merkittävistä poikkeamista on tiedotettu asianosaisille ja pyydetty ottamaan yhteyttä lääkärille. Yleistä tietoa tutkimuksiin osallistuneiden tutkimustuloksista ja tiedotettavista asioista on kerrottu seuraavalla sivulla.

Edellä mainittujen mittausten jälkeen sinulta otettiin myös geenitesti. Testin perusteella sinulla on perimässäsi **APO E 4/4 tai 3/4 –alleeli**, mikä tarkoittaa, että sinulla kolesterolin imeytyminen ruoasta on erittäin tehokasta. Tämän takia sinulla on hieman suurentunut riski korkeaan kolesteroliin ja sitä kautta sydän- ja verisuonitauteihin. Suomalaisista noin kolmannes kuuluu tähän ryhmään.

Korkea veren kolesteroli lisää vaaraa sairastua sepelvaltimotautiin. Sepelvaltimotaudin syynä on yleensä ateroskleroosi eli verisuonten kalkkeutuminen. Ateroskleroosi syntyy, kun kolesterolia kertyy valtimoiden seinämään. Ajan myötä nämä kertymät ahtauttavat valtimoita ja haittaavat veren virtausta. Lopulta veren virtaus saattaa tyrehtyä lähes kokonaan, jolloin tuloksena on infarkti.

Muutoksia on mahdollista saada kuitenkin aikaan. **Erityisesti sinulla kolesteroli reagoi herkästi elintapojen muutokseen ja voit ehkäistä sydän- ja verisuonisairauksia.** Kovan rasvan vähentäminen ja pehmeiden rasvojen lisääminen ruokavalioon, säännöllinen liikunnan harrastaminen, alkoholin ja sokeripitoisten ruokien vähentäminen ruokavaliosta ja normaalipainon säilyttäminen vähentävät selvästi riskiä sairastua sydän- ja verisuonitauteihin. Ruokaremontin avulla voit vaikuttaa keskimäärin 10 - 15 %, mutta jopa 40 % veren kolesterolipitoisuuteen. Vaikutus on yksilöllinen, mutta aina tehokas ja kannattava. Ruokavalion muutos on aina ensisijainen toimenpide, kun halutaan ehkäistä veren kolesterolipitoisuuden nousua tai laskea jo kohonnutta kolesterolia.

TSEMPPIÄ elämäntapamuutokseen, koska jo pienet muutokset ovat tehokkaita☺!

APPENDIX 4. Message 3

Tervehdys!

Vieläkö muistat ravitsemus, geenit ja elämäntapa tutkimuksemme, jonka alkututkimuksiin osallistuitte **syyskuussa 2010?** Miltä päivä sinusta tuntui ja saitteko mielestänne tarpeellista tietoa itsestänne ja ravitsemuksesta?

Kiitos,
että osallistutte tutkimukseen, koska teidän ansiosta saamme harvinaislaatuista tutkimustietoa eteläpohjalaisten elintavoista ja APO E geeniperimästä. Myös teillä on erinomainen mahdollisuus seurata omien henkilökohtaisten elämäntapamuutosten vaikutusta mittaustuloksiinne. Seuraavat tutkimuspäivät ovat maaliskuussa 2011 ja syyskuussa 2011.

Alkututkimuspäivänähän teiltä otettiin erilaisia mittauksia (verikokeet, pituus, paino, vyötärönympärys, rasvaprosentti), joiden tulokset saitte samana päivänä. Lisäksi täytitte lukuisan joukon erilaisia kyselyitä. Merkittävistä poikkeamista on tiedotettu asianosaisille ja heitä on pyydetty ottamaan yhteyttä lääkärille. Yleistä tietoa tutkimuksiin osallistuneiden tutkimustuloksista ja muista tiedotettavista asioista on kerrottu seuraavilla sivuilla.

VIESTI

Edellä mainittujen mittausten jälkeen sinulta otettiin myös geenitesti. Testin perusteella sinulla on perimässäsi **APO E 2/3 tai 3/3 –alleeli**, joten sinulla kolesterolin imeytyminen on tavanomaisella tasolla. Tämä tarkoittaa, että sinulla *APOE* geeni perimässäsi ei lisää riskiä korkeaan kolesteroliin ja sitä kautta sydän- ja verisuonitauteihin. Suomalaisista noin 64 % kuuluu tähän ryhmään.

Vaikka perimässäsi ei olekaan korkeaan kolesteroliin altistavaa geeniä, niin elämäntapojen tarkistaminen saattaa silti olla paikallaan, varsinkin, jos omien mittaustulosten perusteella on parantamisen varaa. Tutkimuksessa selvitettävä geeni, APO E on vain yksi sairastumisriskiä kuvaava geeni. Korkeaan kolesteroliin ja sydän- ja verisuonitautien kehittymiseen vaikuttavat suurelta osin myös muutkin tekijät kuin perinnöllisyys. Epäterveelliset elämäntavat (mm. runsas kovan rasvan ja alkoholin käyttö, ylipaino, liikkumattomuus ja tupakointi) lisäävät selvästi riskiä sairastua sydän- ja verisuonitauteihin.

Jo pienillä muutoksilla on kuitenkin mahdollista saada tuloksia aikaan. Kovan rasvan vähentäminen ja pehmeiden rasvojen lisääminen ruokavalioon, säännöllinen liikunnan harrastaminen, alkoholin ja sokeripitoisten ruokien vähentäminen ruokavaliosta ja normaalipainon säilyttäminen vähentävät selvästi riskiä sairastua sydän- ja verisuonitauteihin. Ruokaremontin avulla voit vaikuttaa keskimäärin 10 - 15 %, mutta jopa 40 % veren kolesterolipitoisuuteen. Vaikutus on yksilöllinen, mutta aina tehokas ja kannattava. Ruokavalion muutos on aina ensisijainen toimenpide, kun halutaan ehkäistä veren kolesterolipitoisuuden nousua tai laskea jo kohonnutta kolesterolia.

TSEMPPIÄ elämäntapamuutokseen, koska pienetkin muutokset ovat kannattavia☺!

APPENDIX 5. Message 4

Tervehdys!

Vieläkö muistat ravitsemus, geenit ja elämäntapa tutkimuksemme, jonka alkututkimuksiin osallistuitte **syyskuussa 2010?** Miltä päivä sinusta tuntui ja saitteko mielestänne tarpeellista tietoa itsestänne ja ravitsemuksesta?

Kiitos,

että osallistutte tutkimukseen, koska teidän ansiosta saamme harvinaislaatuista tutkimustietoa eteläpohjalaisten elintavoista ja APO E geeniperimästä. Myös teillä on erinomainen mahdollisuus seurata omien henkilökohtaisten elämäntapamuutosten vaikutusta mittaustuloksiinne. Seuraavat tutkimuspäivät ovat maaliskuussa 2011 ja syyskuussa 2011.

Alkututkimuspäivänä teiltä otettiin erilaisia mittauksia (verikokeet, pituus, paino, vyötärönympärys, rasvaprosentti), joiden tulokset saitte samana päivänä. Lisäksi täytitte lukuisan joukon erilaisia kyselyitä. Merkittävistä poikkeamista on tiedotettu asianosaisille ja heitä on pyydetty ottamaan yhteyttä omalle lääkärille. Yleistä tietoa tutkimuksiin osallistuneiden tutkimustuloksista ja muista tiedotettavista asioista on kerrottu seuraavalla sivulla.

VIESTI

Edellä mainittujen mittausten jälkeen sinulta otettiin myös geenitesti. Testin perusteella sinulla on perimässäsi **APO E 2/3 tai 3/3 –alleeli**, joten sinulla kolesterolin imeytyminen on tavanomaisella tasolla. Tämä tarkoittaa, että sinulla *APOE* geeni perimässäsi ei lisää riskiä korkeaan kolesteroliin ja sitä kautta sydän- ja verisuonitauteihin. Suomalaisista noin 64 % kuuluu tähän ryhmään.

Vaikka perimässäsi ei olekaan korkeaan kolesteroliin altistavaa geeniä, niin elämäntapojen tarkistaminen saattaa silti olla paikallaan varsinkin, jos omien mittaustulosten perusteella on parantamisen varaa. Tutkimuksessa selvitettävä geeni, APO E on vain yksi sairastumisriskiä kuvaava geeni. Korkeaan kolesteroliin ja sydän- ja verisuonitautien kehittymiseen vaikuttavat suurelta osin myös muutkin tekijät kuin perinnöllisyys. Epäterveelliset elämäntavat (mm. runsas kovan rasvan ja alkoholin käyttö, ylipaino, liikkumattomuus ja tupakointi) lisäävät selvästi riskiä sairastua sydän- ja verisuonitauteihin. Korkea veren kolesteroli lisää vaaraa sairastua sepelvaltimotautiin. Sepelvaltimotaudin syynä on yleensä ateroskleroosi eli verisuonten kalkkeutuminen. Ateroskleroosi syntyy, kun kolesterolia kertyy valtimoiden seinämään. Ajan myötä nämä kertymät ahtauttavat valtimoita ja haittaavat veren virtausta. Lopulta veren virtaus saattaa tyrehtyä lähes kokonaan, jolloin tuloksena on infarkti. (Sydän- ja verisuonisairaudet ovat kansantautimme. Suomessa yleisin kuolinsyy on sepelvaltimotauti, johon kuolee noin 13 000 ihmistä vuosittain.)

Muutoksia on kuitenkin mahdollista saada aikaan. Kovan rasvan vähentäminen ja pehmeiden rasvojen lisääminen ruokavalioon, säännöllinen liikunnan harrastaminen, alkoholin ja sokeripitoisten ruokien vähentäminen ruokavaliosta ja normaalipainon säilyttäminen vähentävät selvästi riskiä sairastua sydän- ja verisuonitauteihin. Ruokaremontin avulla voit vaikuttaa keskimäärin 10-15 %, mutta jopa 40 % veren kolesterolipitoisuuteen. Vaikutus on yksilöllinen, mutta aina tehokas ja kannattava. Ruokavalion muutos on aina ensisijainen toimenpide, kun halutaan ehkäistä veren kolesterolipitoisuuden nousua tai laskea jo kohonnutta kolesterolia.

TSEMPPIÄ elämäntapamuutokseen!

APPENDIX 6. Message for control group

Tervehdys!

Vieläkö muistat ravitsemus, geenit ja elämäntapa tutkimuksemme, jonka alkututkimuksiin osallistuitte **syyskuussa 2010?** Miltä päivä sinusta tuntui ja saitteko mielestänne tarpeellista tietoa itsestänne ja ravitsemuksesta?

Kiitos,

että osallistutte tutkimukseen, koska teidän ansiosta saamme harvinaislaatuista tutkimustietoa eteläpohjalaisten elintavoista ja APO E geeniperimästä. Myös teillä on erinomainen mahdollisuus seurata omien henkilökohtaisten elämäntapamuutosten vaikutusta mittaustuloksiinne. Seuraavat tutkimuspäivät ovat maaliskuussa 2011 ja syyskuussa 2011.

Alkututkimuspäivänä teiltä otettiin erilaisia mittauksia (verikokeet, pituus, paino, vyötärönympärys, rasvaprosentti), joiden tulokset saitte samana päivänä. Lisäksi täytitte lukuisan joukon erilaisia kyselyitä. Merkittävistä poikkeamista on tiedotettu asianosaisille ja pyydetty ottamaan yhteyttä lääkärille. Yleistä tietoa tutkimuksiin osallistuneiden tutkimustuloksista ja muista tiedotettavista asioista on kerrottu seuraavilla sivuilla.

VIESTI

Edellä mainittujen mittausten lisäksi teiltä otettiin myös APO E geenitesti. Geenitestin tulokset saatte niin halutessanne loppumittausten yhteydessä, syyskuussa 2011.

Tutkimuksessa selvitettävä geeni, APO E on vain yksi sairastumisriskiä kuvaava geeni. Korkeaan kolesteroliin ja sydän- ja verisuonitautien kehittymiseen vaikuttavat suurelta osin myös muutkin tekijät kuin perinnöllisyys. Epäterveelliset elämäntavat (mm. runsas kovan rasvan ja alkoholin käyttö, ylipaino, liikkumattomuus ja tupakointi) lisäävät selvästi riskiä sairastua sydän- ja verisuonitauteihin. Korkea veren kolesteroli lisää vaaraa sairastua sepelvaltimotautiin. Sepelvaltimotaudin syynä on yleensä ateroskleroosi eli verisuonten kalkkeutuminen. Ateroskleroosi syntyy, kun kolesterolia kertyy valtimoiden seinämään. Ajan myötä nämä kertymät ahtauttavat valtimoita ja haittaavat veren virtausta. Lopulta veren virtaus saattaa tyrehtyä lähes kokonaan, jolloin tuloksena on infarkti. (Sydän- ja verisuonisairaudet ovat kansantautimme. Suomessa yleisin kuolinsyy on sepelvaltimotauti, johon kuolee noin 13 000 ihmistä vuosittain.)

Sydän- ja verisuonitaudeille altistaa perimä, mutta terveelliset ruokailutottumukset (kovan rasvan vähentäminen ja pehmeiden rasvojen lisääminen ruokavalioon), säännöllinen liikunnan harrastaminen, alkoholin ja sokeripitoisten ruokien vähentäminen ruokavaliosta ja normaalipainon säilyttäminen vähentävät selvästi riskiä sairastua sydän- ja verisuonitauteihin. Ruokaremontin avulla voit vaikuttaa keskimäärin 10 - 15 %, mutta jopa 40 % veren kolesterolipitoisuuteen. Vaikutus on yksilöllinen, mutta aina tehokas ja kannattava. Ruokavalion muutos on aina ensisijainen toimenpide, kun halutaan ehkäistä veren kolesterolipitoisuuden nousua tai laskea jo kohonnutta kolesterolia.

APPENDIX 7. Information message for intervention group

TIEDOTETTAVIA ASIOITA TUTKIMUKSEN JATKOSTA

Noin viikon kuluessa teille lähetetään sähköpostitse täytettäviä kyselyitä, jotka ovat myös tärkeä osa tutkimusta. Tämän takia toivomme niihin pikaista vastausta. Heihin, joilla sähköpostia ei ole käytössä, otetaan yhteyttä puhelimitse.

Kaikille vapaaehtoinen perinnöllisyysneuvonta –tilaisuus järjestetään 9.12.2010 klo 17 – 19, Seinäjoen keskussairaalan (Hanneksenrinne 7) **auditoriossa** (= pääovesta sisään ja aulasta raput yksi kerros ylöspäin (raput ovat neuvontaa vastapäätä)). Ravitsemuksesta ja APO E:n vaikutuksesta kolesteroliin luennoi kliininen ravitsemustieteilijä, maa- ja elintarviketalouden tutkimuskeskuksen (MTT) professori Raija Tahvonen. Paikalla on myös Etelä-Pohjanmaan sairaanhoitopiirin johtajaylilääkäri, Hannu Puolijoki, jonka kanssa on mahdollisuus henkilökohtaiseen 5 – 10 minuutin keskusteluun geeniperimän (APO E) vaikutuksesta elämäntapoihin ja sairastumisriskiin. Tilaisuudessa on tarjolla pieni iltapala.

Tarjoilun vuoksi perinnöllisyysneuvonta –tapahtumaan on ilmoittauduttava viimeistään 1.12.2010 joko sähköpostitse hlhieta@utu.fi **tai puhelimitse 040-4444084. Ilmoittautumisen yhteydessä on myös mainittava, mikäli haluatte varata ajan henkilökohtaiseen keskusteluun asiantuntijan kanssa.**

APPENDIX 8. Information message for control group.

TIEDOTETTAVIA ASIOITA TUTKIMUKSEN JATKOSTA

Noin viikon kuluessa teille lähetetään sähköpostitse täytettäviä kyselyitä, jotka ovat myös tärkeä osa tutkimusta. Tämän takia toivomme niihin pikaista vastausta. Heihin, joilla sähköpostia ei ole käytössä, otetaan yhteyttä puhelimitse.

Kaikille vapaaehtoinen perinnöllisyysneuvonta –tilaisuus järjestetään 9.12.2010 klo 17 – 19, Seinäjoen keskussairaalan (Hanneksenrinne 7) **auditoriossa** (= pääovesta sisään ja aulasta raput yksi kerros ylöspäin (raput ovat neuvontaa vastapäätä)). Ravitsemuksesta ja APO E:n vaikutuksesta kolesteroliin luennoi kliininen ravitsemustieteilijä, maa- ja elintarviketalouden tutkimuskeskuksen (MTT) professori Raija Tahvonen. Paikalla on myös Etelä-Pohjanmaan sairaanhoitopiirin johtajaylilääkäri Hannu Puolijoki. Tilaisuudessa on tarjolla pieni iltapala.

Tarjoilun vuoksi perinnöllisyysneuvonta –tapahtumaan on ilmoittauduttava viimeistään 1.12.2010 joko sähköpostitse hlhieta@utu.fi **tai puhelimitse 040-4444084.**

Turun yliopisto
University of Turku