

Using Individual, ApoE Genotype-Based Dietary and Physical Activity Advice to Promote Healthy Lifestyles in Finland—Impacts on Cardiovascular Risk Markers

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Abstract

Aim: There is increasing demand for individualized health advice. The aim of this study was to assess the effects on cardiovascular risk markers of receiving personal genetic health information, using apoE genotypes as a tool for promoting lifestyle changes. ApoE was chosen because it had a significant impact on lipid metabolism and cholesterol absorption, all factors for CVD. **Methods:** This study was a one-year explanatory intervention study for healthy adults, aged between 20 - 67 years old (n = 106). Their clinical markers (serum lipids, blood glucose, blood pressure, Body Mass Index, body fat percentage and waist circumference) were measured three times during the intervention. The clinical effects were assessed for three groups: a high risk group (E4+, n = 16); a low-risk group (E4-, n = 35); and a control group (n = 55). **Results:** The triglyceride values and waist circumference lowered more in E4+ compared with the control group (p < 0.05; alpha value 0.005) during the intervention. **Conclusion:** The personal genetic information, based on apoE, may have positive effects on cardiovascular risk markers (e.g., improvement in triglyceride values). The individual health information, based on genotyping could be a potential option in the prevention of CVD. More research is required on how to utilize genotype-based health information in the prevention of lifestyle-related diseases.

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Keywords

Genetic Information, ApoE, Intervention, Healthy Lifestyle, Cardiovascular Risk Markers

1. Introduction

Genetic profiling has increasingly become a potential option for preventing lifestyle related diseases [1]-[3]. The general population-based dietary recommendations do not always motivate healthy people to change their lifestyle, and thus there is a need for individualized information and new tools to promote healthy lifestyle changes [4]-[7]. Currently, several commercial companies offer genetic testing to the public, but genetic screening in the prevention of lifestyle-related diseases is not routine practice in public health care [1] [2]. Some reasons for this are the lack of know-how among health care professionals, the lack of resources, and the expense of the tests [8] [9]. In addition, a lack of clear guidelines and uniform policy is an obstacle to using genetic screening in public health care in Finland [8].

Cardiovascular diseases (CVD) and the apoE genotype is an ideal combination for examining this issue for several reasons. First, CVD are the main cause of mortality and morbidity in Finland as well as worldwide [10] [11] and 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 [12] [13]. Second, the most widely-studied gene related to CVD is the apoE having three common alleles/isoforms ($\epsilon 2$, $\epsilon 3$, $\epsilon 4$) [14]. Meta-analysis of Song *et al.* (2004) showed that individuals with the apoE $\epsilon 4$ allele may even have 42 % higher risk for CVD than carriers of the apoE 3/3 genotype [15]. In addition, carriers of apoE 4 allele have 3 - 4 fold (genotype 3/4) and 12 - 16 fold (genotype 4/4) increased risk of Alzheimer's disease [16]. ApoE affects cholesterol absorption, lipid metabolism and have function in vitamin E metabolism and the immune system [17]. It has been demonstrated that carriers of at least one apoE $\epsilon 4$ allele have a higher cholesterol count, but better response to dietary changes (e.g. fat quality) and exercise than apoE $\epsilon 3$ or $\epsilon 2$ carriers [14] [18] [19]. However, controversial outcomes have also been observed, for example after flavonoid or fish oil supplementation [20] [21]. Third, because of the multifactorial nature of lifestyle related diseases, there are only a few studies that have been done in this field. Some favorable effects on diet and lifestyle have been found [22]. However, no results of health behavior effects on clinical factors in the context of using individualized genotype information, exist [22].

Some studies have aimed to affect the motivation to decrease the risk factors of lifestyle diseases [23] [24]. Marteau *et al.* (2004) studied how information about inherited familial hypercholesterolemia (FH) affects people's motivation to lower their serum's cholesterol content and Harvey-Berino *et al.* (2001) studied how information about the obesity-predisposing gene affects motivation to lose weight. Both studies found that individualized information does not motivate participants to decrease the risk factors of lifestyle diseases [23] [24]. Furthermore, in the study of Arkadianos *et al.* (2007), receiving nutrigenetic test did not affect BMI reduction, fasting glucose, or serum lipids during the first 300 days, but had an effect on BMI reduction in the longer-term (>300 days) [25].

The purpose of this study was to examine how people respond to knowledge on personal genetic information in combination with a tailored health message. In our previous papers, we have reported psychological [26] and behavioral [27] effects. In the current paper, we focus on the effect of the specific risk factors of CVD. The genetic risk information and health message was focused on the apoE gene. The intervention included both an intensive communication period (first 6 months), as well as a follow-up period (last 6 months), during which the participants received no health communication from the research group. In this paper, we report the clinical effects (changes in serum lipids, blood glucose, blood pressure, Body Mass Index, body fat percentage and waist circumference). The hypothesis of this study was that a personalized health message based on an individual's genetic risk would motivate people to change their lifestyle, which would also have a favorable effect on the specific risk factors of CVD. To our knowledge, there have been no controlled studies on the effect of a personalized health message based on apoE genotype as regards lowering the risk factors of CVD.

2. Methods

2.1. Study Design and Participants

Altogether, 122 adults, aged between 20 - 67 years of age participated in this one-year, single-blinded, explana-

tory intervention study. The participants included in the study were healthy, had no long-term medication (e.g., diabetes, cholesterol, blood pressure, psychiatric medication) or chronic conditions (e.g., diabetes or mental disorders). 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/m²), 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.

The participants were randomized into a control (n = 61) and an intervention group (n = 61) before the genetic results were available. There were 40 participants in $\mathcal{E}4-$ group (included apoE genotypes 3/4 and 4/4) and 21 participants in the $\mathcal{E}4+$ group (included apoE genotypes 2/3 and 3/3). The control group included 61 participants (included apoE genotypes 3/4, 4/4, 2/3, 3/3 and 2/2).

The baseline and follow-up assessments included detailed measurements of psychological (threat and anxiety experience, stage of change), [26] and behavioral (dietary fat quality, consumption of vegetables—high fat/sugar foods and—alcohol, physical activity and health and taste attitudes) [27] and clinical factors (Table 1). 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 ($\mathcal{E}4+$ and $\mathcal{E}4-$) received their apoE genotype information and health message at the beginning of the intervention. The message for the $\mathcal{E}4+$ group stressed the importance of the genotype in the response to dietary changes (e.g.

Table 1. Clinical measurements.

Measurement	Method of analyses	Recommended level	Note
Serum's lipids ¹⁾			
Total cholesterol	Enzymatic photometry, The Architect c8200 analyzer (Abbott Diagnostics, Abbot Park, IL, USA)	<5.0 mmol/l (200 mg/dL)	
HDL cholesterol		>1.0 mmol/l (men) and >1.3 (women)	
Triglyceride content		<1.7 mmol/l (151 mg/dL)	
LDL cholesterol	By computationally formula of Friedewalds with total and HDL-cholesterol content	<3.0 mmol/l (100 mg/dL)	
Blood glucose ¹⁾			
Fasting glucose (0 h)	Entzymatic photometry (regulatory enzyme as hexokinase), the Architect c8200 analyzer (Abbot Diagnostics, Abbot Park, IL, USA)	≤6.0 mmol/l (<i>normal</i>); 6.1 - 6.9 mmol/l (<i>increased fasting glucose (IFG)</i>); ≥7.0 mmol/l (<i>diabetes</i>)	Measurements at baseline (T0) and the end of the intervention (T3)
2 hours after challenge (2 h)		<7.8 mmol/l (<i>normal</i>); 7.8 - 11.0 mmol/l (<i>impaired glucose tolerance (IGT)</i>); >11.0 mmol/l (<i>diabetes</i>)	
Blood pressure (<i>systolic/diastolic</i>) ¹⁾	Oscillometric, Omron M3 and Microlite BP A100: in a sitting position, right arm, after 15 minutes of rest and two measures at each time, which of better one remained in force.	≤130/85 mmHg (<i>normal</i>); 130/85 mmHg - 140/90 mmHg (<i>satisfactory, but needs checking once in a year</i>); >140/90 mmHg (<i>at raised level</i>).	
Body Mass Index (BMI) ¹⁾		18.5 - 24.99 kg/m ² (<i>normal</i>)	
Fat percentage ²⁾	Body composition meter (Omron BF 500). Weight was measured with light indoor clothes and height without the shoes.	8 - 21.9 % (men, 18 - 59 y); 21 - 33.9 (women, 18 - 59 y)	Based on electrical conductivity. Muscle tissue conducts electricity better and faste tahn adiposity tissue. Omron BF-500 meter takes note the total body fat content.
Waist circumference ³⁾	Tape measure from midway between the lowest rib and iliac crest.	≤94 cm (men) and ≤80 cm (women) (<i>normal</i>); >102 cm (men) and >88 cm (women) (<i>significant health risk</i>)	Reveals on amount of visceral fat and fat in area of abdominal cavity.

¹⁾Current Care Guidelines in Finland developed by the Finnish Medical Society Duodecim. Available from: <http://www.kaypahoito.fi/web/english/home>;

²⁾Measure of body fat percentage. 2009. Available from: <http://www.tohtori.fi/?page=7481805&id=6362126>; ³⁾Alberti KGMM, Zimmet P, Shaw J. The metabolic syndrome—a new worldwide definition. *Lancet*. 366(9491):1059-1062. Available from:

<http://www.ncbi.nlm.nih.gov/pubmed/16182882>.

improvement of fat quality) and increasing exercise to lower the cholesterol level and prevent CVD. The message for the $\epsilon 4-$ group emphasized the interaction between environmental factors and the genotype and highlighted the significance of their own lifestyle. At the beginning of the intervention, the control group received only general information about the present study and general health message based on the basic health and nutrition recommendations and studies of the National Institute for Health and Welfare. The control group received their apoE genotype information after the intervention.

Of all 122 participants, five people dropped out and four participants who had started cholesterol, blood pressure, or diabetes medication during the intervention; seven participants who had missing values in their answers or turned out to be outliers were excluded. Effects on cardiovascular risk markers were assessed for the three groups ($n = 106$): the intervention high-risk group ($\epsilon 4+$, $n = 16$); the intervention low-risk group ($\epsilon 4-$, $n = 35$); and the control group ($n = 56$). A detailed procedure of this intervention has been described in our previous papers [26] [27].

2.2. Clinical Measurements

Table 1 describes the qualities of clinical measurements. All clinical measurements were done three times (except two hours after the blood glucose challenge test two times (T_0 , T_3)) during the intervention: at the baseline (T_0), after six months (T_2) and at the end of the intervention (T_3). Measurements were done in the Department of Clinical Chemistry, 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 [28].

2.3. 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. Variables (*BMI* and *waist circumference*) which were not normally distributed were transformed and modified to a “Square root”. The main variables were adjusted for their own baseline scores (T_0) by covariance analyses (ANCOVA).

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 model (repeated measures)). T-test and a Chi-Square-test was used to analyze background variables (study population characteristics) and the frequency of MeS. Pairwise comparisons were conducted using the Bonferroni method. The family wise error (a Type 1 error) was controlled by setting the alpha value 0.005. Statistical power analysis was conducted by a G*Power program [29].

3. Results

3.1. Study Population Characteristics (Table 2 and Table 3)

The characteristics of the study population have been described in detail in **Table 2** and **Table 3**. There were statistically significant differences ($p < 0.001$, partial eta squared = 0.124) in the age between women and men who participated in the study (women 44.1 (S.D. 11.5) years versus men 53.3 (S.D. 11.4) years). There were no statistical differences in genotypes between the test group and the control group.

Clinical measurements were analyzed also at the baseline between the different apoE genotypes. The total population ($n = 106$) was divided into two groups: apoE4+ ($n = 28$), including participants with the apoE 3/4 and 4/4 genotypes and apoE4- ($n = 78$), including apoE 2/2, 2/3 and 3/3 genotypes. There were minor differences in clinical outcomes between the groups. ApoE4+ group had a higher total, LDL and HDL cholesterol than the apoE4- group and correspondingly the apoE4- group had higher triglyceride content, blood glucose (0 h and 2 h), blood pressure (systolic and diastolic), BMI, fat percent, and waist circumference than the apoE4+ group. The only significant difference was in body fat percentage ($p < 0.01$, partial eta squared = 0.084).

3.2. Primary Outcomes

Effects of Intervention (Table 4)

The intervention had a trend towards a significant effect ($p < 0.05$; alpha level 0.005) on two of the CVD risk

Table 2. Demographics and background variables of included (106) participants.

	Total	£4+ group	£4- group	Control group	p-value	Partial Eta Squared
Number of participants (n)	106	16	35	55	NA	NA
Age (years, mean ± SD)	47.0 ± 12.2	47.8 ± 12.3	47.3 ± 11.2	46.6 ± 13.0	NS	NA
Men (years, mean ± SD)	53.3 ± 11.4				<0.001	0.124
Women (years, mean ± SD)	44.1 ± 11.5					
Female, sex %, (n)	68.9	62.5	85.7 ^{a)}	60.0 ^{a)}	0.031	0.066
ApoE genotype %, (n)					NS ^{#)}	NA
E3/E3	59.4 (63)	0 (0)	77.1 (27)	65.5 (36)		
E3/E4	24.5 (26)	93.8 (15)	0 (0)	20.0 (11)		
E2/E3	13.2 (14)	0 (0)	22.9 (8)	10.9 (6)		
E4/E4	1.9 (2)	6.3 (1)	0 (0)	1.8 (1)		
E2/E2	0.9 (1)	0 (0)	0 (0)	1.8 (1)		

Analysed by t-test (mean) and Chi-Square-test. If statistical significance difference was found, pairwise comparison was done by Bonferroni. NA (not analysed); NS (not significant); ^{a)}Statistical significance (p < 0.05) difference between these groups. ^{#)}distribution of apoE genotypes was compared between intervention and control groups.

Table 3. Comparison of baseline clinical measurements between the apoE4+ (3/4, 4/4) and apoE4- group (2/2, 2/3, 3/3).

Measurement	Total	ApoE4+ group (n = 28)	ApoE4- group (n = 78)
	Mean (SD) (baseline)	Mean (SD) (baseline)	Mean (SD) (baseline)
Total cholesterol (mmol/l)	5.2 (0.95)	5.26 (0.90)	5.15 (0.96)
LDL cholesterol (mmol/l)	3.1 (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 (mmol/l)	1.18 (0.60)	1.06 (0.55)	1.22 (0.61)
Blood glucose (0 h) (mmol/l)	5.5 (0.43)	5.48 (0.45)	5.53 (0.42)
Blood glucose (2 h) (mmol/l)	5.9 (1.32)	5.52 (1.33)	5.98 (1.30)
Blood pressure, <i>systolic</i> (mmHg)	129.3 (16.6)	127.0 (17.4)	130.1 (16.4)
Blood pressure, <i>diastolic</i> (mmHg)	77.1 (9.0)	75.8 (9.2)	77.6 (8.9)
Body Mass Index (BMI) (kg/m ²)	32.5 (8.2)	24.7 (3.0)	26.1 (4.0)
body Fat Percentage (%)	25.8 (3.8)	28.5 (6.8) ^{*)}	33.9 (8.3) ^{*)}
Waist circumference (cm)	85.9 (11.2)	84.2 (10.6)	86.6 (11.4)

Analysed by t-test (one-way Anova). ^{*)}p = 0.003, Partial Eta Squared = 0.084.

markers (triglyceride values and waist circumference). The Triglyceride content decreased more in the £4+ group compared with the £4- and control group during the first six months (T0 - T2). After a further six months (T2 - T3), the triglyceride content had increased a little in the £4+ group, but decreased in the £4- and control group. Despite the differences, the triglyceride values were within the normal range [30] in every group during the intervention. Waist circumference reduced more in the £4+ group compared with the control group. This change was clearest during the first six months (T0 - T2). In the control group, waist circumference increased during the whole intervention period.

Favorable trends, but not close to statistically significant effects were also found in the fat percentage and systolic blood pressure in £4+ group. Every group decreased their fat percentage during the first intensive communicating period (T0 - T2). The £4+ group was the only group who improved their fat percentage during the last silent period (T2 - T3).

Table 4. Comparison of clinical outcomes (cardiovascular risk markers) between E4+, E4- and control group in the baseline (T0), after six months (T2) and after 12 months (T3).

Measure	Group	Baseline (T0)			6 months (T2)			12 months (T3)			Main effects		Interaction effect	
		Mean	99.5% CI	Mean (change T0 - T2)	99.5% CI	Mean (change T0 - T3)	99.5% CI	p-value (F-value)	Group	p-value (F-value)	Time	p-value (F-value)	Time*group	
Total cholesterol (mmol/l)	E4+ group (n = 16)	5.2	5.2 - 5.2	0.0	4.8 - 5.7	0.0	4.8 - 5.6							
	E4- group (n = 35)	5.2	5.2 - 5.2	0.1	5.0 - 5.6	0.0	4.9 - 5.5		0.961 (0.039)	<0.001 (8.218)		0.994 (0.054)		
LDL cholesterol (mmol/l)	Control group (n = 55)	5.2	5.2 - 5.2	0.0	5.0 - 5.4	0.0	5.0 - 5.4							
	E4+ group (n = 16)	3.1	3.1 - 3.1	0.1	2.8 - 3.6	0.1	2.9 - 3.6		0.907 (0.098)	0.100 (2.327)		0.612 (0.672)		
HDL cholesterol (mmol/l)	E4- group (n = 35)	3.1	3.1 - 3.1	0.2	3.0 - 3.6	0.1	2.9 - 3.4							
	Control group (n = 55)	3.1	3.1 - 3.1	0.1	3.0 - 3.4	0.1	3.0 - 3.4							
Triglycerides (mmol/l)	E4+ group (n = 16)	1.52	1.52 - 1.52	0.05	1.45 - 1.70	0.03	1.42 - 1.65							
	E4- group (n = 35)	1.52	1.52 - 1.52	0.02	1.46 - 1.63	0.03	1.46 - 1.63		0.684 (0.382)	0.015 (4.278)		0.847 (0.345)		
Blood glucose (0 h) (mmol/l)	Control group (n = 55)	1.52	1.52 - 1.52	0.00	1.46 - 1.60	0.01	1.46 - 1.58							
	E4+ group (n = 16)	1.17	1.17 - 1.17	-0.30	0.65 - 1.09	-0.28	0.65 - 1.15		0.035 (3.457); 0.038 ^{b)}	<0.001 (8.243); <0.001 ^{b)}		0.194 (1.533)		
Blood glucose (2 h) (mmol/l)	E4- group (n = 35)	1.17	1.17 - 1.17	-0.09	0.92 - 1.23	-0.10	0.89 - 1.24							
	Control group (n = 55)	1.17	1.17 - 1.17	-0.06	0.98 - 1.22	-0.13	0.92 - 1.19							
Blood pressure, systolic (mmHg)	E4+ group (n = 16)	5.5	5.5 - 5.5	-0.1	5.2 - 5.6	-0.1	5.2 - 5.7							
	E4- group (n = 35)	5.5	5.5 - 5.5	-0.1	5.2 - 5.5	-0.2	5.1 - 5.5		0.306 (1.197)	<0.001 (13.474); 0.002 ^{c)}		0.440 (0.943)		
Blood pressure, diastolic (mmHg)	Control group (n = 55)	5.5	5.5 - 5.5	0.0	5.3 - 5.6	-0.1	5.3 - 5.5							
	E4+ group (n = 16)	5.9	5.9 - 5.9	NM	NM	-0.8	4.3 - 5.9							
Body Mass Index (BMI) (kg/m ²)	E4- group (n = 35)	5.9	5.9 - 5.9	NM	NM	-0.7	4.6 - 5.8		0.475 (0.750)	<0.001 ^{d)} (20.094)		0.475 (0.750)		
	Control group (n = 55)	5.9	5.9 - 5.9	NM	NM	-0.5	5.0 - 5.9							
body Fat Percentage (%)	E4+ group (n = 16)	128.9	128.9 - 128.9	-5.3	115.8 - 131.6	-5.7	116.0 - 132.2							
	E4- group (n = 35)	128.9	128.9 - 128.9	0.0	123.3 - 134.8	-2.2	122.4 - 133.4		0.135 (2.045)	0.011 (4.584)		0.516 (0.816)		
Waist circumference (cm)	Control group (n = 55)	128.9	128.9 - 128.9	-4.0	120.9 - 130.0	-4.2	120.9 - 129.3							
	E4+ group (n = 16)	77.2	77.2 - 77.2	4.9	76.1 - 87.7	0.9	73.5 - 82.6							
body Fat Percentage (%)	E4- group (n = 35)	77.2	77.2 - 77.2	6.6	79.5 - 87.9	3.3	76.7 - 83.3		0.572 (0.563)	0.001 (7.825) 0.005 ^{e)} , <0.001 ^{d)}		0.294 (1.244)		
	Control group (n = 55)	77.2	77.2 - 77.2	4.2	78.0 - 84.4	3.4	78.1 - 83.1							
Waist circumference (cm)	E4+ group (n = 16)	25.8	25.8 - 25.8	-0.3	24.9 - 26.1	-0.3	24.9 - 26.2							
	E4- group (n = 35)	25.8	25.8 - 25.8	-0.2	25.2 - 26.0	-0.1	25.3 - 26.2		0.446 (0.813)	0.423 (0.863)		0.690 (0.562)		
Waist circumference (cm)	Control group (n = 55)	25.8	25.8 - 25.8	0.0	25.4 - 26.1	0.0	25.5 - 26.2							
	E4+ group (n = 16)	32.6	32.6 - 32.6	-1.1	29.8 - 33.2	-2.5	30.1 - 33.6		0.473 (0.754)	0.868 (0.142)		0.513 (0.822)		
Waist circumference (cm)	E4- group (n = 35)	32.6	32.6 - 32.6	-0.6	30.7 - 33.1	0.3	31.7 - 34.2							
	Control group (n = 55)	32.6	32.6 - 32.6	-0.4	31.2 - 33.0	0.4	31.5 - 33.4							
Waist circumference (cm)	E4+ group (n = 16)	86.1	86.1 - 86.1	-2.5	80.4 - 86.1	-0.6	82.7 - 88.5		0.020 (4.066); 0.027 ^{e)}	0.056 (2.924)		0.045 (2.491)		
	E4- group (n = 35)	86.1	86.1 - 86.1	-0.9	82.8 - 87.0	0.5	84.5 - 88.8							
Waist circumference (cm)	Control group (n = 55)	86.1	86.1 - 86.1	0.7	84.8 - 87.9	1.7	86.4 - 89.5							

General linear model (repeated measures; alpha = 0.005) was used to analyze the effects of group, time and time*group during the intervention. If statistically significant difference was found, pairwise comparison was done by the Bonferroni method. NOTE. Variables, which are not normally distributed, have tested from modified scores. BMI and waist circumference scores have transformed to square roots. NOTE. Results were adjusted (controlled) for the baseline (T0) scores and presented as not modified. CI, 99.5% confidence interval. NM (not measured) a, g) Trend toward statistically significant effect (alpha level 0.005) between E4+ and control group. b) SSD (statistically significant difference) between T0 and T2 measuring points and also between T0 and T3 measuring points; c, d, e) SSD between T0 and T3 measuring points; f) SSD between T0 and T2 measuring points.

Systolic blood pressure decreased in the $\epsilon 4+$ and control group after the first intensive period. During the later six months, the systolic blood pressure stayed almost at the same decreased level. A favorable, but parallel trend in every group was in the glucose after two hours challenge (2 h).

The intervention had no effect on the total-, LDL- and HDL cholesterol, fasting glucose (0 h), and BMI. These CVD risk factors stayed almost constant during the intervention. Both LDL and HDL cholesterol [30] and fasting glucose were within the normal range in every group. However, the total cholesterol [30] and BMI (24.99 kg/m^2) was slightly over the recommended level in every group. Overweight participants were more common in the present study (68% of men and 53% of women) compared with the total Finnish average [31].

The change in diastolic blood pressure was unfavorable in every group.

3.3. 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) (Figure 1).

4. Discussion

In this study, the effects on cardiovascular risk markers of hereditary genetic information were examined in an intensive period (first six months) and a silent period (last six months). The hypothesis of this study was that a personalized health message based on the individual’s genetic risk would motivate people to change their lifestyle, which would also have a favorable effect on the specific risk factors of CVD.

Receiving personal genetic information in combination with the personal health message had favorable effects (trend toward significant effect) in the high-risk group ($\epsilon 4+$) on some cardiovascular disease risk factors. The most substantial effect of the genetic feedback was observed in the triglyceride values and waist circumference. In the high-risk group ($\epsilon 4+$) the triglyceride values and waist circumference lowered during the intervention. The effect on triglyceride values was also nearly permanent after the later silent period (12 months), but on the waist circumference it was only short-term (six months). However, both CVD risk markers remained at an improved level among the high risk group compared with the baseline.

In addition, some favorable changes in the high-risk group ($\epsilon 4+$) were observed in fat percentage and systolic blood pressure. Favorable, but parallel effects were observed in blood glucose (2 h). In every group the blood glucose (2 h) lowered during the intervention, which indicates that this favorable impact was, consequently, due to the intervention and not the personal genetic information.

To our 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 [22]. We

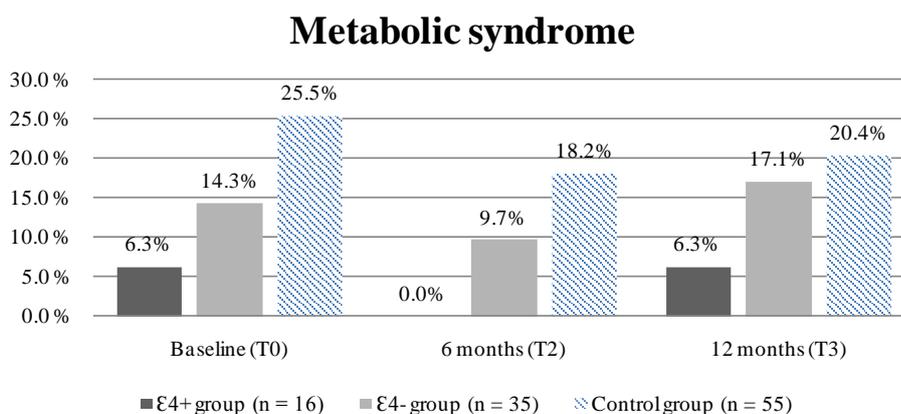


Figure 1. Frequency of Metabolic syndrome during the intervention (T0, T2, T3). NOTE. The criterion for the Metabolic Syndrome: waist circumference ≥ 94 cm (men) and ≥ 80 cm (women) and having at least two of the following health risks: 1) triglyceride content of serum over 1.7 mmol/l, 2) HDL cholesterol 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 (0 h) over 6.0 mmol/l or glucose after 2 hours challenge (2 h) ≥ 7.8 mmol/l.

regarded clinical measurements as an important perspective, because people may need to see their progression in concrete terms. People, for example, may perceive that they need to increase physical activity, but they are not aware of the association between physical activity and actual metabolic risk factors [32]. A previous study by Vähäsarja *et al.* (2012) conducted among people with a high risk of type 2 diabetes ($n = 7128$), found that individual's overestimation of physical activity can be an obstacle to behavioral change [32]. Increasing understanding about the connection between health behavior and metabolic risk factors and the inclusion of clinical markers, such as physical factors, may also achieve better results. Clinical outcomes may also act as a "control" for the self-reporting behavioral changes (e.g. diet). Lowered cholesterol levels, for example, may motivate people to extend further the changes in their health behavior. However, the effects may also be the opposites, if the desired change does not occur [33], and then people can become depressed and regress back under the baseline level. Furthermore, as the *apoE* genotype is only one factor that can cause CVD [15] and as we are not able to predict the outcome with certainty [34], these could be some of the reasons why change did not occur in every clinical marker (e.g. BMI). In the case of the $\epsilon 4^-$ and control group, they may have thought that they had no reason to change, because they either did not know their genotype, or they thought that they were not at risk. Genetic testing could undermine current dietary advice because people might believe that only those with the risk gene need to change their health behavior to lower cardiovascular disease risk [35].

The health message, with the genotype information, highlighted the importance of genotype response to dietary fat quality changes and increased exercise, lowering cholesterol levels, and lowering the CVD risk. We reported previously that response to the change of fat quality was significantly greater in the $\epsilon 4^+$ group ($\Delta +3.8$) than the control ($\Delta +1.8$) group, but there were no differences in the exercises [27]. The participants may have embraced the role of fat quality and its impact on reducing the risk for CVD. In this present study, triglyceride values lowered more in the $\epsilon 4^+$ group than the $\epsilon 4^-$ and control groups during the intervention. However, the health message together with the genotype information did not affect cholesterol levels or other CVD risk factors. This finding is in agreement with Carvalho-Wells *et al.* (2012) who found genotype-diet interaction in plasma triglycerides but not in cholesterol values in their dietary fat intervention [36]. Minihane *et al.* (2000) showed in their studies that apoE $\epsilon 4$ carriers' total cholesterol and LDL cholesterol increased after a fish oil supplementation, and HDL cholesterol decreased compared with apoE $\epsilon 3$ carriers [20]. Further, Egert *et al.* (2010) found that apoE $\epsilon 3$ carriers had a better response to quercetin (flavonols) supplementation than apoE $\epsilon 4$ carriers [21]. The differences were revealed in systolic blood pressure, HDL cholesterol, and ratio of LDL:HDL cholesterol [21].

In this present study, the reason for the cholesterol levels not being affected is not clear, but it may have something to do with the differences in dietary changes. It may be possible that some dietary changes (e.g., increase of unsaturated fat) or health behavioral changes are easier to implement and maintain as a routine than others (e.g. increasing consumption of vegetables). There is evidence that especially increasing exercise has favorable effects on HDL cholesterol, and a high fiber diet (e.g. vegetables, berries and fruits + whole grain cereals) on the total and LDL-cholesterol [37]-[39]. However, our previous paper [27] did not find any significant changes in exercise or the consumption of vegetables, which could be one reason why HDL, LDL and total cholesterol level also stayed equal during the intervention. 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.

The current study found 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. ApoE 4 carriers had a slightly higher total, LDL and HDL cholesterol, but a lower level in triglycerides compared with apoE 2 and 3 carriers. These results are in line with those of most recent studies [40] [41]. However, on the contrary to the present study, some previous studies have suggested that apoE genotype also affects other cardiovascular risk factors [42]-[45]. High blood pressure has been associated with the presence of apoE 4 allele [44], but also with the apoE 2 allele [13] [43] [46] and Helkala *et al.* (2001) found that carriers of apoE 2 allele had higher fasting glucose and 2 h blood glucose than apoE 3 and 4 carriers [43].

In the current study, the first six months were deemed the intensive period, where participants attended a lecture and received two health messages, while the later six months were a silent period, which was designed to simulate normal life. The effect tended to tail away during the silent period, which is clearly seen in the trend of the Metabolic Syndrome (Figure 1). This "tailing away effect" has also been reported previously [47]. In the case of waist circumference, the results indicated that even a very strong motivator, such as knowledge of personal genetic risk may not be powerful enough to stimulate a permanent life style change for preventing lifestyle diseases. The

lifestyle change demands continuous work and usually requires several changes at the same time. Permanent lifestyle change occurs slowly and is gradually tailored to individualized goals [48]. However, this study showed that it is also possible to achieve long-term changes, which was the case in the triglyceride values. The higher intervention intensity (including frequent counseling sessions) and longer intervention duration have been found to be more effective than less intensive and shorter interventions to achieve a permanent lifestyle change [49] [50].

Some common limitations of our study (e.g. group sizes, only one biomarker, randomization and lack of background variables) have been reported in our previous studies [26] [27].

Many of the CVD risk markers (e.g., waist circumference, fat percent, and HDL cholesterol) are known to differ between sexes. However, due to the small group sizes, we were not able to do statistical analyses between men and women. We adjusted the baseline to the same level in each group and analyzed only the change between the different groups.

In the present study, genetic screening was combined with the genotype-specified health information and it produced favorable changes in some CVD risk markers. A further study with more focus on CVD risk markers in the context of genotype based health information, aimed at lowering CVD risk, is therefore suggested. 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 is also recommended.

5. Conclusion

To conclude, this explanatory study has demonstrated for the first time that personal health information, based on genetic screening, may have positive effects on CVD risk markers (e.g. improvement in triglyceride values). This paper also indicates the importance of the intensive repetition of health information, a longer intervention duration, and inclusion of clinical factors. This research will serve as a basis for future studies, and the study in addition suggests that further research might also explore the impact of genotype-based health information on clinical factors, not only on health behavior (e.g. diet). This is because clinical outcomes may work as a motivator and control for self-reporting. Overall, it can be concluded that genetic screening as a part of the prevention of CVD will become more common and therefore more research is required as to how to make genetic screening a practical tool in public health care.

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Conflict of Interests

The authors confirm that they have no conflict of interest. Finnish Cultural Foundation, Central Hospital of Southern Ostrobothnia (EVO 1140) and European Regional Development Fund (EAKR) Project A31342 have funded the work. Hanna-Leena Hietaranta-Luoma MSc. prepared the manuscript. All authors critically reviewed the manuscript and approved the final version submitted for publication.

Human Studies and Informed Consent

All procedures followed were in accordance with the ethical standards of the responsible committees on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all patients for being included in the study.

Animal Studies

No animal studies were carried out by the authors for this article.

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