A Long-Term Follow-Up Study on Disclosing Genetic Risk Information \textit{(APOE)} to Promote Healthy Lifestyles in Finland

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\textbf{Keywords} \\
\textit{APOE} · Nutrigenetics · Disclosing genetic information · Motivation for lifestyle change · Genotyping · Public health and preventive medicine · Lipid metabolism

\textbf{Abstract} \\
\textbf{Aim:} This observational follow-up study was designed to assess the long-term behavioural and clinical effects of receiving personal genetic risk information. The information disclosed was the carrier status of the apolipoprotein E (\textit{APOE}) alleles, which differentially contribute to the genetic risk for cardiovascular disease (CVD) and Alzheimer’s disease. \textbf{Methods:} This study forms a continuum with a previous 1-year intervention (2010–2011) monitoring the effects of disclosing the carrier status of the \textit{APOE}\textit{ε}4 risk allele. The follow-up measurements, performed 5.5 years post-intervention, included clinical measurements (blood values and anthropomorphic parameters) and questionnaires (psychological and behavioural factors). The participants were healthy adult volunteers, aged 26–73 years (\textit{n} = 70) who had participated in the previous intervention, and received their \textit{APOE} allele status either at the beginning (former test group) or the end of the intervention (former control group). \textbf{Results:} Personal genetic risk information resulted in a moderate health-conscious change in diet and had a slight positive long-term effect on clinical factors, particularly the serum lipids. These improvements were subsequent to the disclosure of genetic information and occurred mainly in the \textit{APOE}\textit{ε}4-positive members of the former control group, that is, those who were at increased genetic risk for CVD but had not been informed of their status before the end of the intervention. In contrast, changes in the values and health behaviour of the \textit{APOE}\textit{ε}4-positive individuals in the former test group, who had already changed their health behaviour during the previous intervention as a result of being informed of their carrier status, varied more: some continued to improve, some remained at their previously improved level, and some relapsed slightly. Both groups had nonetheless displayed an improvement immediately subsequent to the disclosure of their personal genetic risk. \textbf{Conclusion:} Receiving information on increased personal genetic risk (carrier status of \textit{APOE}\textit{ε}4) for CVD provided the motivation for improvements in health behaviour. The resulting changes, while modest, in most cases remained visible even after a number of years.

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Introduction

Cardiovascular diseases (CVD) are among the leading causes of death for adults in Finland and have been the target of prevention programmes for decades [1]. Typically, these conditions are contributed to by a complex array of genetic and epigenetic risk factors [2, 3]. The most prominent epigenetic risk factor is the modern Western lifestyle, combining immobility with a calorie-dense diet containing a large proportion of saturated fats. Modifying this lifestyle can improve an individual’s prospects dramatically, but executing the change requires motivation and persistence [4, 5].

Phenotypic, health-related risk information (such as raised blood pressure or blood glucose values) has been routinely used for decades to provide a wake-up call for individuals at risk for lifestyle-related diseases, such as coronary heart disease [6]. Recently, as genetic information has become more mainstream, the question has arisen of whether genetic risk information, such as susceptibility gene carrier status, could be used for similar purposes. The debate is still ongoing: on the one hand, knowledge regarding one’s genes provides the empowerment necessary to take preventative action and promote one’s health and well-being. On the other hand, due to heredity, disclosing genetic information automatically involves the person’s relatives, complicating the picture [7].

Apolipoprotein E (APOE) is a plasma lipoprotein that regulates lipid homeostasis in the brain, redistributing cholesterol and phospholipids [8, 9]. Recently, it has been discovered to be involved in neuroprotection, oxidative stress, and inflammation, and to function as a transcription factor [10, 11]. Due to its role in cholesterol metabolism, APOE is the most studied gene in dietary fat response [12, 13]. The human APOE gene exists in three different alleles, ε2, ε3, and ε4. The alleles have different, allele-specific properties [12, 14]: ε4 is associated with hyperlipidaemia and hypercholesterolaemia (predisposing to atherosclerosis, CVD, stroke, and Alzheimer’s disease; AD), whereas ε2 has been reported to have protective effects [8, 15–18]. The disease risk is highest for the ε4 homozygotes and lowest for the ε2 homozygotes [8]. However, the actual risk is greatly contributed to by modifiable, lifestyle-related risk factors (such as high blood pressure, high plasma cholesterol, smoking, and physical inertia), particularly for ε4 carriers. Moreover, the ε4 allele carriers respond particularly well to lifestyle changes, such as dietary improvements and increased physical activity [14, 19, 20].

This study examines the long-term effects of the disclosure of genetic risk information (APOE) on health. It follows up on a group of individuals from the Finnish region of Ostrobothnia who received their APOE genotype and health advice (focussing mainly on the fat quality and sugar and vegetable content of the diet) in our previous intervention (2010–2011 [21–24]). Half of the participants, the test group, were disclosed their APOE alleles at the beginning of the study, whereas the control group received this information 1 year later, at the end of the study. During the 2010–2011 intervention, improvements were observed particularly in the APOE ε4-positive participants’ dietary fat quality, waist circumference, and CVD markers, but the effects started to fade in the absence of health message repetition [22–24]. Here, we report the long-term (5.5/6.5 years) behavioural and clinical effects following this APOE genotype disclosure, indicating the utility of individual genetic risk information as a motivator for maintaining a lifestyle change. To our knowledge, no such longitudinal follow-up studies of lifestyle interventions have been published previously.

Materials and Methods

Study Design

This follow-up study is a part of the “Genetic Information as a Lifestyle Change Motivator” (ApoE4mot) project in Southern Ostrobothnia, Finland, a collaborative project between the University of Turku, the University of Eastern Finland, the Seinäjoki Central Hospital, and the Natural Resources Institute, Finland (Luke). The measurements were carried out during spring 2017.

The basis of this study is formed by the behavioural and clinical results of our previous 2010–2011 intervention that have been published previously in three parts [22–24]. These results were obtained by comparing the test group (APOE information disclosed at the beginning of the intervention) to the control group (APOE information disclosed at the end of the intervention). In the current study, the same factors were re-analysed and the results compared with those from the final time point of the previous study to establish the long-term behavioural and clinical effects. The time points during the two studies have been named and took place as follows: T0 at the beginning of the 2010–2011 study, T1 at 8 weeks, T2 at 6 months, and T3 at 12 months (the end of the intervention) of the 2010–2011 study [22–24]. T4 refers to spring 2017, 6.5 or 5.5 years after APOE genotype disclosure.

The participants (described below) were examined as groups based on their APOE alleles, ε4 versus non-ε4 (referred to as E4+ and E4−, respectively) and the time they received this information during the previous intervention (T0 vs. T3) [22]. This yielded four different groups: E4+ T0 (n = 13) and E4− T0 (n = 25; those informed at the beginning of the previous intervention, T0), and E4+ T3 (n = 4) and E4− T3 (n = 28; those informed at the end of the intervention, T3, the former control group). The long-term behavioural and clinical effects of genetic risk information were analysed.
The 107 study subjects from our 2010–2011 intervention study were re-recruited with personal invitation letters and 83 opted to enter the new study. These individuals were healthy adult volunteers, aged 26–73 years, who had received their APOE genotypes 6.5 or 5.5 years previously (the former test and control group, respectively) and completed the intervention [22–24].

Of the 83 volunteers, 70 participated in the laboratory tests and 63 completed the food behaviour questionnaires. The mean age was 54.5 years (n = 70, SD 12.2, range 26–73 years), and the majority (65.7%) were women. There was a significant difference (p = 0.005, partial h² = 0.144) in age between the men and women: on average, the men were older than the women (women: 51.5 years, SD 11.8; men: 61.3 years, SD 9.9; Table 1). We also observed a statistically significant difference (p = 70, SD 12.2, range 26–73 years), and the majority (65.7%) were women. There was a significant difference (p = 0.005, partial h² = 0.144) in age between the men and women: on average, the men were older than the women (women: 51.5 years, SD 11.8; men: 61.3 years, SD 9.9; Table 1). We also observed a statistically significant difference (p < 0.05) in the ages of those who joined the new study and those who declined, with the re-recruits being on average about 5 years older. No statistically significant difference could be detected in the gender or genotype division. All volunteers were ethnically Finnish and originated from the Finnish hospital district of Southern Ostrobothnia. All participants knew their APOE ε4 carrier status from T3; 17 were ε4 positive and 53 were ε4 negative. Slightly less than a quarter (24.3%) had at least one APOE ε4 allele, and 12.6% carried an ε2 allele.

Written informed consent was obtained from all participants. Before consenting to enter this new study, the participants were required to attend a lecture on genetics by a clinical geneticist and were offered genetic counselling. The investigation corresponds to the principles outlined in the Declaration of Helsinki and was approved by the Ethics Committee of the Pirkanmaa Hospital District, Finland (12/2016; December 14, 2016).

### Table 1. The distribution of age, gender, and APOE genotype by participant group

| Variable | E4+ T0 | E4+ T3 | E4– T0 | E4– T3 | Total |
|----------|--------|--------|--------|--------|-------|
| Participants | 13     | 4      | 25     | 28     | 70    |
| Age, years | 52.5±13.1 | 48.8±17.8 | 56.2±10.4 | 55.6±12.5 | 54.5±12.2 |
| Men       | 57.2±15.2 | 61.0±17.0 | 65.6±5.9  | 61.4±7.0  | 61.3±9.9a |
| Women     | 50.1±10.9 | 36.5±7.8  | 53.3±10.0 | 51.9±13.9 | 51.5±11.8a |
| Female sex | 53.8 (7) | 50.0 (2)  | 80.0 (20) | 60.7 (17) | 65.7 (46) |
| APOE genotype |        |        |        |        |       |
| ε2/ε2     | 0.0 (0) | 0.0 (0)  | 0.0 (0)  | 3.6 (1)  | 1.4 (1) |
| ε2/ε3     | 0.0 (0) | 0.0 (0)  | 24.0 (6) | 7.1 (2)  | 11.4 (8) |
| ε3/ε3     | 0.0 (0) | 0.0 (0)  | 76.0 (19) | 89.3 (25) | 62.9 (44) |
| ε2/ε4     | 0.0 (0) | 0.0 (0)  | 0.0 (0)  | 0.0 (0)  | 0.0 (0) |
| ε3/ε4     | 92.3 (12) | 100.0 (4) | 0.0 (0)  | 0.0 (0)  | 22.9 (16) |
| ε4/ε4     | 7.7 (1)  | 0.0 (0)  | 0.0 (0)  | 0.0 (0)  | 1.4 (1) |

Data are presented as n, mean ± SD, or % (n). E4+, individuals with at least one APOE ε4 allele; E4–, individuals with no APOE ε4 allele; T0, APOE allele information disclosed at the beginning of the previous intervention; T3, APOE allele information disclosed at the end of the previous intervention.

a Statistically significant difference (p = 0.005, partial h² = 0.144) in age between the men and women.

by comparing their results at T4 to those at T3 (the time point by which everybody’s APOE carrier status had been disclosed).

**Participants**

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### Measurements and Questionnaires

The T4 assessments included measurements of behavioural and clinical factors identical to those in the 2010–2011 intervention study [22–24]. In addition, we also measured other factors, such as blood glucose levels 30 min after a glucose challenge and visceral fat values, and asked about the participants’ eating habits. Behavioural factors were enquired into using secure Webropol questionnaires.

The clinical values reported in this paper included the blood glucose levels (fasting value, and 30 min and 2 h after a glucose challenge) and serum lipids (total, low-density lipoprotein [LDL] and high-density lipoprotein [HDL] cholesterol, and triglycerides), which were analysed at the Central Hospital of Southern Ostrobothnia, Finland (Department of Clinical Chemistry) with enzymatic photometry using the Cobas 8000 Analyser (Roche Diagnostics, Risch-Rotkreuz, Switzerland) according to standard guidelines. We also measured the blood pressure, and some anthropometric parameters such as the BMI, body fat percentage, and waist circumference (Table 2). The BMI and body fat percentage (the biological impedance method) were calculated using the OMRON BF511 Body Composition Monitor (OMRON Healthcare, Hoofdorp, The Netherlands), and waist circumference with a measuring tape.

The participants reported on their diets, including dietary fat quality, consumption of vegetables, berries, and fruits, high-fat/high-sugar foods, and alcohol. The consumption of different food stuffs was reported per day (vegetables, fruits, and berries) or per week (sweet and savoury delicacies, alcohol). The consumption questionnaires were created by the National Institute for Health and Welfare, Finland [25], and were also used in our previous intervention [22]. In the dietary fat quality assessment, created for self-monitoring purposes by the Finnish Heart Association [26], the greater the score, the greater the proportion of unsaturated fats in the diet (a score of 27–33 points equals a sufficient proportion of unsaturated fats, whereas <15 points equals mostly saturated fats).
**Data Analysis**

The preliminary analyses (exploring the reliability, normality, missing values, and outliers) were performed before the final analyses. Normality was assessed using the Kolmogorov-Smirnov method and histograms. By analysing changes between the groups, the main variables were adjusted for their own baseline scores by covariance analyses.

The main effects of the baseline-adjusted scores were analysed 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 χ² test was used to analyse the frequencies. Pairwise comparisons were conducted using the Bonferroni method. Effect sizes (partial η²) and observed power were also analysed. The data management and analysis were performed using SPSS (IBM SPSS Statistics for Windows, version 24.0, 2012; IBM Corporation, Armonk, NY, USA).

**Results**

**Clinical Changes**

A slight general trend for improvement was detected in the laboratory markers studied. For the most part, the changes were only subtle and did not reach statistical significance. The clearest change was the reduction in triglyceride values: the E4+ T3 group’s values improved the most, decreasing from 1.1 mmol/L at T3 to 0.8 mmol/L at T4 (Fig. 1; Table 2), whereas the values of the other groups remained closer to the T3 level (the recommended value for plasma triglycerides is <2 mmol/L). This effect was of near statistical significance (p = 0.057) and continued the trend witnessed in the previous intervention [24]. The total cholesterol and LDL cholesterol values decreased, and HDL cholesterol values increased in every group. The changes in the total and HDL cholesterol (p < 0.05) were statistically significant, although the differences between the groups were not (Fig. 1; Table 2).

The blood glucose values also showed improvement in every group. The average fasting glucose values at T3/T4 were 5.5/5.1 mmol/L for the E4+ T0 group, 5.2/5.1 mmol/L for the E4– T0 group, 5.5/4.8 mmol/L for the E4+ T3 group, and 5.4/5.1 mmol/L for the E4– T3 group (normal range being 4.0–6.0 mmol/L). Time had a statistically significant effect (p < 0.001 for 0 h and p = 0.001 for

| Parameters measured                              | Main effects group p value (F value) | time p value (F value) | Interaction effect time × group p value (F value) |
|--------------------------------------------------|-------------------------------------|-----------------------|-------------------------------------------------|
| Serum lipids, mmol/L                             |                                     |                       |                                                 |
| Triglycerides                                    | 0.057* (2.643)                      | <0.001*** (10.987)    | 0.177 (1.432)                                   |
| LDL cholesterol                                  | 0.900 (0.195)                       | 0.296 (1.259)         | 0.506 (0.924)                                   |
| HDL cholesterol                                  | 0.488 (0.819)                       | 0.049* (2.772)        | 0.840 (0.545)                                   |
| Total cholesterol                                | 0.789 (0.350)                       | 0.021* (3.501)        | 0.283 (1.223)                                   |
| Blood glucose, mmol/L                            |                                     |                       |                                                 |
| Fasting glucose (0 h)                            | 0.705 (0.469)                       | <0.001*** (18.402)    | 0.350 (1.121)                                   |
| 2 h after glucose challenge                      | 0.862 (0.248)                       | 0.001*** (8.267)      | 0.577 (0.793)                                   |
| Blood pressure, mm Hg                            |                                     |                       |                                                 |
| Systolic                                         | 0.218 (1.521)                       | 0.050* (2.764)        | 0.536 (0.890)                                   |
| Diastolic                                        | 0.331 (1.162)                       | <0.001*** (7.380)     | 0.292 (1.208)                                   |
| Anthropometric analyses                          |                                     |                       |                                                 |
| BMI                                              | 0.362 (1.086)                       | 0.271 (1.337)         | 0.789 (0.608)                                   |
| Body fat percentage, %                           | 0.606 (0.617)                       | 0.106 (2.131)         | 0.722 (0.685)                                   |
| Waist circumference, cm                          | 0.067* (2.503)                      | 0.137 (1.913)         | 0.379 (1.081)                                   |
| Diet                                             |                                     |                       |                                                 |
| Dietary fat quality (scale 0–33)                 | 0.552 (0.707)                       | <0.001*** (10.657)    | 0.775 (0.674)                                   |
| Vegetable, fruit and berry consumption, portions/day | 0.348 (1.121)                  | <0.001*** (23.191)    | 0.196 (1.348)                                   |
| Consumption of foods containing excessive fat and sugar, times/week | 0.162 (1.796)                  | <0.001*** (6.642)    | 0.037* (1.923)                                   |
| Alcohol consumption, doses/week                  | 0.809 (0.323)                       | 0.017* (3.259)        | 0.231 (1.283)                                   |

The results were adjusted (controlled) for the baseline (T0) scores. * Near statistical significance.

*p ≤ 0.05; ***p ≤ 0.001.
Long-Term Effects of Receiving the APOE Gene Results

Blood pressure decreased particularly in the Ε4+ T3 group, the average systolic/diastolic values being 130/83 and 127/77 mm Hg for T3 and T4, respectively (statistically significant change; Table 2).

The development of some indices, however, was less positive: the averages for the BMI, waist circumference, and body fat percentage increased clearly in every group from T3 to T4. The average BMI increase by group was 0.9 (Ε4+ T0), 1.0 (Ε4– T0), 1.2 (Ε4+ T3), and 1.3 (Ε4– T3), and the trend was similar for the body fat percentage and waist circumference. These changes, however, did not reach statistical significance (Table 2).

Changes in Food Behaviour

There were changes in the participants’ diets (Fig. 1). The intake of saturated fat increased and that of unsaturated fat decreased in all groups except Ε4+ T3. The dietary fat scores (out of 33) at T3/T4 were 17.2/16.6 for the
The consumption of vegetables, berries, and fruits increased during the 5.5 years (T3–T4). This change was statistically significant (p < 0.001). At T4, the average consumption for all groups was 3.5 portions per day, while at T3 it was 2.4 portions per day (Fig. 1; Table 2). The consumption of excessively fatty and sugary food products increased for the E4+ T0 and E4– T0 groups, but decreased for the E4+ T3 and E4– T3 groups (Fig. 1; Table 2).

The average alcohol consumption decreased slightly from 1.8 units/week at T3 to 1.5 units/week at T4. Alcohol consumption actually increased slightly during the 5.5 years from T3 to T4 in all the other groups but E4+ T3, in which it more than halved (from 2.8 units/week at T3 to 1.3 units/week at T4), reducing the average consumption. Time had a statistically significant effect on the change (p < 0.05; Table 2).

Discussion

This study examined the long-term (6.5 years for the T0 groups and 5.5 years for the T3 groups) behavioural and clinical effects of receiving personal genetic risk information (APOE genotype). Changes in the participants’ dietary fat quality, vegetable, fruit, and berry consumption, sugary and fatty food, and alcohol consumption were measured. The clinical factors analysed and reported here are the serum lipids and blood glucose.

According to our results, receiving personal genetic risk information had a small but clear beneficial effect on the participants’ health, documented by a number of minor improvements in the parameters analysed. The largest improvements were observed in plasma lipid values, the triglycerides in the E4+ T3 group, and the LDL cholesterol values in both of the high-risk groups, particularly in the E4+ T0 group, when compared to the low-risk groups. Improvements were also observed in the blood pressure values for the E4+ T3 group. These changes were contributed to by the increase in vegetable, fruit, and berry consumption in both groups, an improvement of dietary fat quality in the E4+ T3 group and the reduction in the consumption of sugary and fatty foodstuffs in the E4+ T3 group. However, despite the improvements, the dietary fat quality remained poor in every group (the average score being 15.9 out of 33 points, indicating a large proportion of saturated fats in the diet), as did the BMI and waist circumference, which increased in every group.

There was a sharp increase in the self-reported consumption of vegetables, fruits, and berries in each group, potentially reflected in the slight improvement in blood glucose values in every group. It is possible that this increase is also contributed to by a natural seasonal variation in the participants’ diets: T4 occurred in the spring, whereas T3 was in the autumn. In the previous intervention, a similar increase in vegetable, fruit, and berry consumption was seen at T2, which took place in the spring. This outcome is in line with previous literature regarding the seasonality of vegetable consumption [27]. Alternatively, since all the groups increased their vegetable, fruit, and berry intake, it may also be explained by the Hawthorne effect [28] and be the consequence of participating in the intervention in the first place.

We based our genetic risk information on the APOE gene as it is one of the most widely studied genes in gene-diet interactions and the relative risk it poses is documented as being modifiable by lifestyle factors. It is also relevant to the population as the frequency of the APOE ε4 allele is greater in Finland (approximately 30%) compared to the global average (13.4%) [8, 29]. The most significant limitation of our study is the small size of the participant groups, particularly E4+ T3, which contained only 4 people. Therefore, repeating the study with larger sample sizes would be needed to draw final conclusions.

When predicting the outcome of a complex condition for an individual, the effect of one risk allele may be small; a more complete picture can be achieved by calculating a genetic risk score that combines the effect of several associated risk genes [2, 3, 30]. Implementing these polygenic risk scores has improved the accuracy of risk prediction in health care compared to conventional clinical risk markers [30], whereas in health promotion its utility has been modest. To date, few studies have been carried out on the efficacy of genetic risk information in health promotion, and the results have been contradictory. In some interventions, providing genetic risk information has made no difference to the effect of personal nutritional advice (for example the Food4Me trial [31]), whereas in others [32, 33], similarly to ours, a clear benefit has been observed (e.g., the REVEAL study [32]). Predicting the outcome of a health promotion scheme is difficult as individuals are motivated by different things. What motivates one may stress another, and receiving a non-risk result may give the recipient a false all-clear
message, having an adverse effect on their health. In this study, for example, the triglyceride values of the E4– T3 group increased after the disclosure of their non-risk genotype.

The most interesting result of this study is that the values of the E4+ T3 group improved from 2011 to 2017 in nearly every category studied. In the previous intervention, the members of this group belonged to the control group and only received their genetic risk information at the end of that intervention, at T3. We suggest that the disclosure of the APOE risk genotype has contributed to the improvements (although, due to the small size of the group the evidence is not conclusive). We further suggest that the reason that the values of the E4+ T0 group had not improved equally during the T3–T4 period is that their corresponding improvements already occurred during the previous intervention as a response to receiving their genetic risk information at T0. Naturally, the improvements in the participants’ diets and other habits may also be due to their increasing health consciousness with increasing age, or other unmeasured personal factors, as participating in such intervention studies in the first place demonstrates interest in health issues. However, we argue that the timing of the improvement of the E4+ T3 group’s participants’ values likely demonstrates the impact of genetic risk information as an additional motivator for a healthy life. Genetic risk information may thus have the potential to provide the motivation for the permanent lifestyle change required for the prevention of lifestyle-related diseases, which is normally challenging to carry out and maintain.

To our knowledge, this study is the first longitudinal follow-up study focusing on the APOE gene as a risk information marker utilised to promote health. We discovered that during the 5.5-year period between our previous intervention and the present one, modest positive lifestyle changes had been carried out, particularly by the APOE ε4-positive members of the former control group, who were informed about their risk genotype only at the end of the previous intervention (E4+ T3). These improvements corresponded to those already carried out by the APOE ε4-positive members of the former test group (E4+ T0) during the previous intervention, suggesting that these changes were triggered by the disclosure of the risk genotype. Some of the beneficial changes carried out during the previous intervention by the at-risk members of the former test group (E4+ T0) had also been maintained.

In conclusion, the results of this study suggest that disclosing genetic risk information has positive effects on individuals’ health, particularly with those at risk for CVD, and may therefore prove useful in CVD prevention and general health promotion.

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Statement of Ethics

The participants all gave their written informed consent (after attending an obligatory lecture on genetics by a clinical geneticist, and being offered genetic counselling). The investigation corresponds to the principles outlined in the Declaration of Helsinki, and the study protocol was approved by the Ethics Committee of the Pirkkamo Hospital District, Finland (12/2016). No animal experiments were performed in this study.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

H.-L.H.-L. prepared the data for the manuscript and M.T. prepared the manuscript. H.-L.H.-L, M.T., H.K., K.V., A.-M.P., H.P., R.T., and A.H. were involved in planning the work, and H.-L.H.-L., M.T., H.K., and A.H. in its execution. L.T. prepared and gave the lectures on genetics to the participants. K.Å. was responsible for the collection of laboratory data. All authors critically reviewed the manuscript and approved the final version submitted for publication.
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