

Is There an Association between Temperament and Apolipoprotein E? A Replication of a 1993 Young Finns Study

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ABSTRACT

Background: An association between *apolipoprotein E (apoE)* gene polymorphism and temperament has been found in the Young Finns cohort. Motor activity in childhood and mental vitality, sociability and positive emotionality in adolescence were associated with *apoE*. Two research groups have attempted to replicate these findings but no associations have been found. **Purpose:** The purpose of the present study was to confirm the original findings with new and more reliable genotyping from a larger sample derived from the same Young Finns Study as the original finding. **Methods:** The study included 2808 participants aged 3 - 18 years in 1980. The same methods in assessing temperament were used as in the original study. Temperament was operationalized as motor activity, cooperativeness, negative emotionality, mental vitality, sociability and positive emotionality. Temperament was assessed by participants' mothers in 1980 and 1983 and self-rated in 1983 by adolescent participants. **Results:** Motor activity was not associated with *apoE* polymorphisms. All other previous results were replicated. Adolescents' positive emotionality, mental vitality and sociability were associated with *apoE*. **Conclusions:** The results indicated that there is an association between temperament and *apoE*. The previous absence of association between temperament and *apoE* in the replication studies may be due to the fact that researchers used different dimensions of temperament and thus probably studied different phenomena. Cultural differences in personality assessment might also explain the contradictory findings.

Keywords: Temperament; Personality; Behavioral Genetics; Biological Psychology; *apoE*

1. Introduction

Apolipoprotein E (apoE) is a gene linked with coronary heart disease (CHD). A high prevalence of genotypes $\epsilon 4/3$ and $\epsilon 4/4$ has been meta-analytically associated with diagnosed CHD cases [1]. An association between *apoE* polymorphism and temperament was first found in a Young Finns cohort [2]. In a population-based sample of 1577 participants, motor activity in childhood and mental vitality, sociability and positive emotionality in adolescence were associated with the *apoE* polymorphism.

Two research groups have attempted to replicate these findings. Tsai, Yu and Hong [3] found no associations between temperament and *apoE*. However, the study lacked statistical power due to a small sample that included a total of 135 subjects of whom only 32 were $\epsilon 4$ -carriers. Jorm and colleagues [4] examined activity in a sample of 681 participants and found no significant associations after controlling for multiple testing. The contradictory results may reflect differences in temperamental phenotypes, because different assessments were used in different studies. Jorm and colleagues [4] used, for instance, such methods in assessing activity and hyperactivity as

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the Rutter Problem Behavior Questionnaire [5], and Tsai and colleagues [3] used Cloninger's Tridimensional Personality Questionnaire [6]. Neither study used the same temperament dimensions as in our original study [2]. Furthermore, there might be temperamental differences between populations.

The purpose of this study is to confirm the original finding of the Young Finns Study in a sample that consists of the participants in the original article [2] supplemented with over 1200 new participants who were part of the same Young Finns Study, but not included in the original article. New and more reliable techniques in genotyping were used in the new sample, which remarkably reduce the risk of human error which might account for even as much as over 90% of the errors in genotyping [7]. Confirmation of the association between temperament and *apoE* is of importance because childhood temperament has been associated with somatic CHD risk factors in both childhood [8] and in adulthood [9,10] and $\epsilon 4$ -variants of the *apoE* gene constitute a well-known risk for CHD [1,11]. There might be some shared biological basis underlying both CHD and temperament, and *apoE* might be one part of this shared background.

2. Methods

2.1. Participants

The participants were drawn from an ongoing population-based prospective Young Finns Study which began in 1980. The original sample at the baseline comprised 3596 participants from six age cohorts, 3, 6, 9, 12, 15 and 18-year-olds, with different geographical and socioeconomic backgrounds. An equal number of urban and rural boys and girls were randomly chosen from the national population register to ensure national representativeness of the Finns, as comprehensively detailed previously [12]. The study had the approval of the local ethics committees and the participants gave written informed consent.

All the 3596 participants were invited to participate in genotype and temperament assessments. *ApoE* genotyping was conducted on 2946 persons who agreed to participate, of whom 2643 were genotyped by new methods and 303 had been genotyped earlier with an older method. The participants whose genotypes differed between the two measurement times were excluded from the analyses ($n = 27$) and thus *apoE* genotypes were available altogether on 2919 participants. Sufficient information on temperament was received from 2808 genotyped participants at the baseline in 1980 and from 2367 genotyped participants (52.6% women, 47.4% men) at the first follow-up in 1983. All the participants who had been successfully genotyped and had sufficient temperament data on any of the assessed temperament scales comprised the present study sample. The participants were divided into two age groups: the three youngest age cohorts (3 - 9

years at the baseline and 6 - 12 years at the follow-up) were combined as a *children's* group. Similarly, the three oldest age cohorts (12 - 18 years at the baseline and 15 - 21 years at the follow-up) were combined as an *adolescent's* group.

2.2. ApoE Genotyping

New *apoE* genotyping was conducted by analyzing two SNPs (rs429358 and rs7412). Genomic DNA was extracted from peripheral blood leukocytes by using the QIAampÖDNA Blood Minikit and automated biorobot M48 extraction (Qiagen, Hilden, Germany). Genotyping was performed by using TaqmanÖSNP Genotyping Assays (rs429358 assay C 3084793_20; rs7412 assay C_904973_10) and the ABI Prism 7900HT Sequence Detection System (Applied Biosystems, Foster City, CA, USA). Discrepancies did not emerge in the genotyping results of duplicate samples. The old method for genotyping *apoE* was based on isoelectric focusing, cysteamine treatment and immunoblotting from delipidated plasma and has been documented in detail elsewhere [13]. The frequencies of the *apoE* genotypes in the present sample were 5, 173, 53, 1631, 849 and 97 in the genotype groups of $\epsilon 2/2$, $\epsilon 3/2$, $\epsilon 4/2$, $\epsilon 3/3$, $\epsilon 4/3$ and $\epsilon 4/4$, respectively. Group $\epsilon 2/2$ was excluded from the analyses due to its small sample size ($n = 5$).

2.3. Temperament

The same methods in assessing temperament were used as in our original study [2]. First, mothers assessed the participants' temperament at the baseline in 1980 (participants aged 3 - 18) and at the follow-up in 1983 (participants aged 6 - 21) on scales derived from the Health Examination Survey [14]. *Motor activity* was evaluated on a four-point continuum: 1) always controlled; 2) overactive or restless only occasionally, for instance, when tired; 3) continuously more active than the average child or youth, and 4) always extremely active and energetic, even restless. *Low cooperativeness* was evaluated on a three-point continuum: 1) always very cooperative and responsive to others; 2) sometimes problems with peers, but mostly cooperative, and 3) continuous problems in cooperating with peers. *Negative emotionality* was assessed with eight items (e.g., "Other children's parents often complain about the child's behavior") on 2-, 3- and 5-point Likert-type scales. Because of different scaling, standardized scores were used. A mean score (for negative emotionality) was computed if the participant's mother had answered at least 50% of the items. Reliabilities (Cronbach's alphas) for negative emotionality were 0.62 at the baseline and 0.80 at the follow-up.

Second, in 1983 mothers also assessed their children's temperament with the semantic differential measure that was based on the Operation Family Study [15]. The meas-

ure consisted of seven items that each had two opposite attributes and were ranked on 5-point scales. *Mental vitality* was evaluated by three items (passive-active, listless-full of energy, unresponsive-alert); *sociability* was evaluated by two items (alone-sociable, quiet-talkative), and *positive emotionality* was evaluated by two items (depressed-happy, hostile-friendly). Sum scores were used to calculate each scale and due to the low number of items on the scales no missing answers were allowed. Reliabilities (Cronbach's alphas) in the present sample were 0.47 for mental vitality, 0.54 for sociability and 0.41 for positive emotionality.

In addition to mother-ratings, self-ratings on temperament were also made in 1983 by adolescent participants (aged 15 - 21) with the semantic differential measure. The scales mental vitality, sociability and positive emotionality were calculated similarly as described above. Reliabilities (Cronbach's alphas) in the present sample for self-rated temperament were 0.48 for mental vitality, 0.54 for sociability and 0.38 for positive emotionality.

2.4. Statistical Methods

Analyses were conducted separately for children and adolescents. The analysis of covariance was carried out between five genotype groups of *apoE* and each tem-

perament dimension separately. First, all possible sex \times *apoE* interactions predicting temperament were tested. As all interactions were non-significant, sexes were analyzed together with sex as a covariate.

3. Results

The means of the temperament dimensions of motor activity, cooperativeness and negative emotionality did not differ between the *apoE* groups. All associations were non-significant at the baseline and at the follow-up among both children and adolescents (all p-values > 0.10). This replicates our original results on absence of association of *apoE* with cooperativeness, negative emotionality and adolescents' motor activity. The original significant finding (p < 0.05) of children's motor activity did not replicate, as children's motor activity was now unrelated to the *apoE* polymorphisms (p = 0.145).

Table 1 presents the means of temperament dimensions of mental vitality, sociability and positive emotionality. Children's temperament was unrelated to the *apoE* polymorphisms (all p-values > 0.60) replicating our previous finding. In adolescence, mental vitality, F(4,983) = 5.05, p < 0.001, sociability, F(4,1002) = 4.02, p = 0.003, and positive emotionality, F(4,996) = 3.76, p = 0.005,

Table 1. Sex-adjusted temperament means and sex-adjusted differences between *apoE* genotypes. The original 1993 reported means and significances are shown below [2].

	Age	n	ϵ 3/2	n	ϵ 4/2	n	ϵ 3/3	n	ϵ 4/3	n	ϵ 4/4	p-Value
<i>Mothers' assessment</i>												
Mental vitality												
	6 - 12	90	11.2	20	11.6	740	11.3	394	11.3	49	11.3	ns
1993 reported:	6 - 12		11.0		11.7		11.4		11.4		11.2	ns
	15 - 21	56	10.3 ^{abc}	25	10.1 ^{def}	574	11.1 ^{ad}	305	11.2 ^{be}	29	11.7 ^{ef}	<0.001
1993 reported:	15 - 21		10.1		9.2		11.0		11.4		12.0	<0.001
Sociability												
	6 - 12	92	7.6	20	7.6	757	7.7	403	7.7	50	7.5	ns
1993 reported:	6 - 12		7.7		8.1		7.7		7.8		7.4	ns
	15 - 21	56	7.1 ^a	25	6.5 ^{bc}	587	7.3 ^{bd}	310	7.6 ^{acde}	30	6.9 ^e	<0.01
1993 reported:	15 - 21		6.9		5.8		7.3		7.5		7.4	<0.01
Positive emotionality												
	6 - 12	92	7.9	20	8.0	744	7.9	397	8.0	50	7.8	ns
1993 reported:	6 - 12		7.9		8.1		7.9		8.1		7.9	ns
	15 - 21	56	7.7 ^a	24	7.3 ^{bc}	582	7.7 ^d	310	7.9 ^{be}	30	8.5 ^{acde}	<0.01
1993 reported:	15 - 21		7.3		7.5		7.7		7.9		8.8	<0.01
<i>Self-assessment</i>												
Mental vitality												
	15 - 21	57	10.2 ^a	25	10.2	621	10.5 ^b	325	10.8 ^{ab}	31	10.8	0.05
1993 reported:	15 - 21		9.9		9.8		10.4		10.9		11.0	<0.01
Sociability												
	15 - 21	57	6.7	25	6.7	625	7.2	323	7.2	31	7.0	ns
1993 reported:	15 - 21		6.5		6.8		7.2		7.2		7.3	ns
Positive emotionality												
	15 - 21	57	7.5	24	7.2 ^a	628	7.5 ^{bc}	325	7.7 ^b	30	7.9 ^{ac}	<0.01
1993 reported:	15 - 21		7.1		7.3		7.4		7.7		8.1	<0.01

^{a-f}Pair-wise comparisons, groups that are marked with the same letter, differ statistically significantly from each other (p < 0.05); Note: The 1993 reported means and differences were first published in Psychosomatic Medicine, Vol. 55, No. 2, 1993, pp. 155-163.

were all associated with *apoE* polymorphisms when assessed by mothers. Similarly as in our previous study, the highest mental vitality and positive emotionality were found in the $\epsilon 4/4$ group, whereas the highest sociability was found in the $\epsilon 4/3$ group. Thus, the results on mental vitality, sociability and positive emotionality assessed by mothers replicate our original findings. When temperament was self-rated by adolescents, positive emotionality, $F(4,1058) = 3.44$, $p = 0.008$, differed between the *apoE* groups. The association between mental vitality and *apoE*, which was significant in our previous study ($p < 0.01$), was only of borderline significance, $F(4,1053) = 2.35$, $p = 0.052$. As in our previous study, the highest positive emotionality was found in the $\epsilon 4/4$ group and the highest mental vitality in the $\epsilon 4/3$ and $\epsilon 4/4$ groups, although the means of mental vitality did not differ significantly in the pair-wise comparisons for $\epsilon 4/4$. Furthermore, as previously, sociability was not associated with the *apoE* polymorphisms ($p = 0.095$). Thus, only the results on mental vitality differed from our original findings conducted with self-ratings.

4. Discussion

The present findings confirm an association between temperament and *apoE* in a larger and more reliably genotyped sample, using the same temperament dimensions as in our original study [2]. Adolescents scoring high on mental vitality, positive emotionality and sociability carried $\epsilon 4/4$ or $\epsilon 4/3$ variants of the *apoE* gene. The weakest association of our original article [2], that between motor activity and *apoE*, was no longer found. In accordance with our previous findings, associations were found in adolescents, but not children, which might reflect instability of personality in childhood compared to adolescence or adulthood [16].

The studies mentioned in the introduction [3,4] did not replicate our original findings [2]. The contradictory findings might result from differences in temperament assessments leading to different phenotypes. All the above-mentioned studies used measures different from our original study; therefore, they may have examined slightly different phenomena.

A great variance of phenotypes belongs to the core problems of behavioral genetics. In spite of high expectancy the studies of behavioral genetics have not provided satisfactory results in personality psychology. This is, at least partly, caused by a wide collection of measures used in different studies. Perhaps more importantly, even the same measures do not assess the same personality traits in different cultures.

The original finding was from a study among Finns [2] while the other studies were conducted in Australian [4] and Chinese [3] cultures. Cross-cultural personality differences have been found. For example, Finns report

more temperamental positive affectivity [17] and less reward dependence and persistence [18] than Americans. Cross-cultural differences may reflect real personality distinctions between cultures that are due to differences in child-rearing practices, attitudes, values and expectations. In addition, the same personality traits are variously perceived, valued and accepted in different cultures. Reference-group effect is one regulating factor of personality self-assessments. People tend to assess themselves compared to others and the others to whom they compare themselves may differ from population to population [19,20]. Thus, cross-cultural personality differences might reflect true personality distinctions or they may reflect differences in culture-related attitudes and values, even culture-related response styles.

When a genetic background of a personality trait is found in one culture, replicating the results requires finding a proper measure that captures the same personality trait phenotype and phenomenon in another culture. It has been meta-analytically shown that the trait dimensions that are thought to reflect similar latent traits are not all associated with same gene polymorphisms in different cultures [21]. Furthermore, in a genome-wide association study that used exactly the same methods in assessing temperament, weak support for similar genetic associations between Finnish and Australian populations was found for only some of the traits [22], implying that some trait phenotypes are more culture-specific than others. Thus, it seems likely that the discrepancies between temperament and *apoE* findings might be affected by cultural differences.

In addition to cultural differences in personality assessment, there are also biological differences between populations. Finns have an overrepresentation of the *apoE* $\epsilon 4$ -allele [13] and a larger representation of an allele increases power to detect phenotypic differences related to different genotypes [23]. Thus, it is possible that the previous replication studies [3,4] lacked statistical power to detect differences between the different genotypes and the temperamental phenotypes. Our larger representation of the $\epsilon 4$ -allele might enable us to detect quite small but still significant temperament differences between different *apoE* groups.

It has been shown that $\epsilon 4/3$ and $\epsilon 4/4$ variants of the *apoE* gene constitute an evident risk for CHD [1,11]. In our studies, high mental vitality, positive emotionality and sociability—*i.e.*, a tendency to enjoy another's company—were associated with the risk genotypes of the *apoE* gene. At first, this may seem contradictory, because all those traits are considered “positive” characteristics and rather socially protective than harmful personally traits. Sociability is especially highly appreciated in the Western cultures and has several positive outcomes [24,25]. However, we have previously shown that high

sociability might be linked with an increased risk for CHD. For instance, high sociability has been associated with high serum insulin and low high-density lipoprotein cholesterol levels in childhood, adolescence and young adulthood [8,26] and with high intima-media thickness in adulthood [27]. Supporting our findings, high sociability has also been associated with a higher risk for mental stress-induced ischemia among cardiac patients [28]. It might be that high sociability becomes a stressful characteristic when it leads to excessive eagerness to help and please others and to overachieve at work. Thus, function and health outcomes of sociability need further examination.

Other temperament dimensions that were now associated with the CHD risk genotypes of *apoE*, that is, high mental vitality and high positive emotionality, have previously been associated with low somatic risk factors of CHD in childhood and adolescence [8]. This suggests that genetic and behavioral risk factors may function in different directions, *i.e.*, temperament might be genetically associated with CHD risk, but at the same time protect from illness through tendencies in behavior. The present study confirms our previous finding that there is an association between temperament and *apoE* [2]. Temperament characteristics might contribute to the pathogenesis of CHD, even though their specific roles need further examination.

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