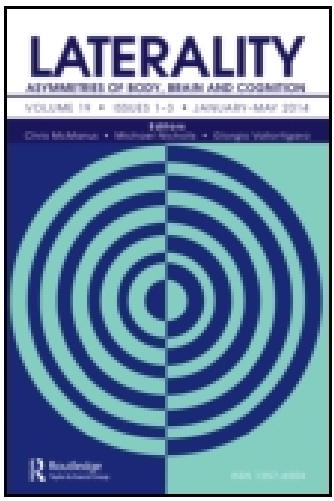

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Lack of an association between left-handedness and APOE polymorphism in a large sample of adults: Results of the Czech HAPIEE study

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Lack of an association between left-handedness and *APOE* polymorphism in a large sample of adults: Results of the Czech HAPIEE study

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An association between *APOE* genotype and left-handedness has been previously reported. We examined whether such association exists in a population sample of 4438 unrelated Caucasian adults aged 45–69 years (2022 males and 2416 females). Left-handedness was based on self-reported left-hand dominance for writing (prevalence 4.9%) and on consistently higher left-hand grip strength in two repeated measurements (prevalence 12.2%). Individuals with higher left hand grip strength were seven times more likely to be self-reported left handers ($p < .0001$, χ^2 159.7, 2 *df*). There were no differences in the proportion of self-reported left-handedness ($p = .828$, χ^2 2.1, 5 *df*) or higher grip strength in left hand ($p = .557$, χ^2 3.9, 5 *df*) between *APOE* genotypes. The lack of association was similar in both genders and did not differ by age group. The results suggest that left-handedness in adults is not related to *APOE* genotype.

Keywords: Apolipoprotein E; Handedness; Polymorphism.

It remains unclear why in most populations around 10% of individuals (with significant geographical differences) are left-handed and why left-handedness

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is more frequent among males than females (for review, see Llaurens, Raymond, & Faurie, 2009) but left- and right-handedness appear to have existed since the stone age (Steele & Uomini, 2005). Hand preference is clearly heritable, as the highest proportions of left-handed offspring come from families where both parents are left handers (about 40%) (McKeever, 2000). The proportion of variation in left-/right-handedness that can be explained by genetic predisposition is estimated to be about 20–60% (Llaurens et al., 2009).

Left-handedness may be medically and psychologically significant; a higher proportion of left-handed persons have been reported among patients with epilepsy, schizophrenia, and developmental impairment (Gutwinski et al., 2011). Probably because of this moderate heritability and unclear medical or psychosocial significance of this phenomenon, the evidence on the genetic variants associated with left hand preferences remains sparse.

The gene for apolipoprotein E (*APOE*, gene ID 348, OMIM acc. no. 107741) is one of candidate genes with the potential to affect left-handedness. There are many variants within the *APOE* gene; among them the three allelic polymorphisms (*APOE2*, *APOE3*, and *APOE4*) are among the most widely analysed human genetic markers. The ancestral *APOE4* allele (Hanlon & Rubinsztein, 1995) is deleterious for number of diseases, including Alzheimer disease (Corder et al. 1993) and cardiovascular disease (Angelopoulos, & Lowndes, 2008; Jofre-Monseny, Minihane, & Rimbach, 2008). Recently Bloss, Delis, Salmon, and Bondi, (2010) found significantly higher prevalence (3.6-fold) of left hand dominance among children carrying the *APOE2* allele. As this finding was based on a small paediatric sample (only 147 individuals), which negatively affects the statistical power, and since there are no other reports on this important question, we used a large Slavonic population cohort of adults to investigate whether the association between the *APOE* polymorphism and left hand dominance exists in adults.

METHOD AND MATERIALS

We analysed data from the Czech part of the HAPIEE project (Peasey et al. 2006). The study recruited over 8000 Caucasian men and women aged 45–69 years at baseline (2002–2005), randomly sampled from population registers of seven Czech towns. Of these, 6681 provided blood sample for DNA preparation during the baseline examination. DNA was extracted from venous blood samples and *APOE* genotypes were determined using the conventional PCR-RFLP method (Hixson & Vernier, 1990).

Two criteria were adopted to define hand dominance, both using data collected during the re-examination of the cohort in 2006–2008 (total of 5362 participants). First, participants reported their left/right hand dominance for writing. Second, we used grip strength data and classified as left-handed

those who recorded higher grip strength on their left hand on both successive tests. Both hand dominance and *APOE* genotype were available for 4438 participants (2022 males and 2416 females), mean age 58.0 (*SD* 7.1) years. Differences in the proportion of left-handed individuals between *APOE* subgroups, both in the full sample and when stratified by age and sex, were assessed by a chi-square test. In addition we tested the association between left-handedness and the presence of the *APOE2* allele vs either *APOE33* or *43/44*, using logistic regression. We also assessed the association separately by 5-year age group, and we tested for potential interaction between age group and *APOE* genotype. All analyses were conducted using the STATA version 12 statistical software (Station College, TX, USA).

The study was approved by the local ethics committees at both Czech National Institute of Public Health and at University College London. Written informed consent was obtained from each participant.

RESULTS

A total of 217 (4.9%) individuals reported having a dominant left hand for writing and 543 (12.2%) persons had consistently higher grip strength on their left hand. These two measures were strongly correlated; individuals with higher left hand grip strength were five times more likely to be self-reported left-handers (odds ratio 5.2, 95% confidence interval 4.0–6.7, $p < .0001$). The frequency of the most common *APOE3* allele was 81.1%, followed by the *APOE4* allele (11.3%), and the least common was the *APOE2* allele (7.5%).

The distribution of left-handers based on either self-report or grip strength did not differ between carriers of different *APOE* genotypes; the *p*-values were 0.828 (χ^2 2.1, 5 *df*) and 0.557 (χ^2 3.9, 5 *df*) (Table 1). Similarly,

TABLE 1
Distribution of left-handers among the different *APOE* genotypes

	Self-reported hand preference for writing		*Higher grip strength*	
	Right-handers	*Left-handers*	*Right hand*	*Left hand*
APOE	*N* (%)	*N* (%)	*N* (%)	*N* (%)
E2E2	28 (93.3)	2 (6.7)	26 (86.7)	4 (13.3)
E2E3	495 (95.4)	24 (4.6)	456 (87.9)	63 (12.1)
E3E3	2,780 (94.9)	151 (5.1)	2,573 (87.8)	358 (12.2)
E4E3	794 (95.8)	35 (4.2)	730 (88.1)	99 (11.9)
E4E2	85 (95.5)	4 (4.5)	73 (82.0)	16 (18.0)
E4E4	42 (97.7)	1 (2.3)	40 (93.0)	3 (7.0)
	$p = .828$		$p = .557$	

there were no statistically significant differences when carriers of *APOE2E2* and *APOE2E3* were combined, and compared with *APOE3E3* homozygotes and with *APOE4* (*APOE4E3* and *APOE4E4*) carriers, with no odds ratio being anywhere close of statistical significance (Table 2).

Further analyses, stratified by 5-year age group, did not reveal any significant association between left-handedness and *APOE* genotype in any age group, nor any interactions between *APOE* and age group (Table 2). Similar analyses, stratified for sex, also produced negative results (Table 2).

DISCUSSION

While many studies have suggested a genetic contribution to handedness (see Annet, 1994), very few studies investigated specific genetic markers in relation to left-/right-handedness (Scerri et al. 2011) and only one previous study assessed such an association with *APOE* specifically. This study, a study of children, did find an association between *APOE* and left handedness (Bloss et al., 2010). Our study, much larger than the previous investigation but in adults, did not find any association between *APOE* genotype and hand dominance.

The *APOE* genotype frequencies in our study were similar to the frequencies detected in neighbouring populations (Bazrgar et al. 2008; Gerdes, Klausen, Sihn, & Faergeman, 1992); they also did not differ significantly from the study by Bloss et al. (2010)—the *p*-value for differences between these two studies was 0.3. The genotype frequencies were also similar to a study conducted in neighbouring Slavonic/Polish population in which the *APOE4* allele was associated with elevated risk of Alzheimer disease (Klimkowicz-Mrowiec et al., 2010).

There are two main limitations of our study: the measurement of handedness and the restricted age range of the examined individuals. Both these factors limited our ability to analyse life-long handedness and possible redirection of handedness in childhood. Hand preference is more a continuous rather than binary trait, and ambidexterity may be more common than strict left-handedness (Llaurens et al., 2009). The assessment of handedness in our study was based on subjective self-report and on measurement of grip strength, not allowing to us to detect the potential ambidextrous individuals. None of our two outcome classifications is ideal, especially because the age groups included in our study might have been forced to use their right hand when they were children. This fact may also explain the discrepancy between self-report and grip strength results, although in both methods the proportions of left-handers were reasonably close to the expected range of 5 to 10% (Llaurens et al., 2009).

On the other hand one might argue that the degree of enforcement might have differed between sexes or between birth cohorts; the absence of any

TABLE 2
Odds ratios

	Grip stronger in left hand				*Grip stronger in left hand*			
	APOE2 vs APOE33 ($N = 3447$)		*APOE2 vs APOE43/44* ($N = 1411$)		*APOE2 vs APOE33* ($N = 3447$)		*APOE2 vs APOE43/44* ($N = 1411$)	
	OR (95%CI)	*p-value*	*OR (95%CI)*	*p*-value	*OR (95%CI)*	*p*-value	*OR (95%CI)*	*p*-value
All age groups*	0.92 (0.60–1.41)	0.691	1.16 (0.69–1.95)	0.995	0.96 (0.72–1.27)	0.771	1.01 (0.72–1.41)	0.966
45–49 years	0.78 (0.29–2.04)	0.608	1.07 (0.33–3.49)	0.909	0.91 (0.44–1.85)	0.789	0.86 (0.38–1.98)	0.731
50–54 years	0.80 (0.28–2.33)	0.685	1.10 (0.30–4.00)	0.884	1.08 (0.58–2.00)	0.808	1.06 (0.51–2.18)	0.885
55–59 years	1.16 (0.43–3.12)	0.770	1.57 (0.44–5.55)	0.485	0.91 (0.48–1.75)	0.781	0.82 (0.39–1.74)	0.606
60–64 years	1.48 (0.66–3.31)	0.340	1.63 (0.59–4.44)	0.343	0.91 (0.51–1.62)	0.742	1.45 (0.70–3.02)	0.317
65–69 years	0.55 (0.19–1.57)	0.264	0.68 (0.21–2.22)	0.521	1.00 (0.53–1.86)	0.991	0.93 (0.45–1.40)	0.834
p for heterogeneity	*0.615*		*0.825*		*0.994*		*0.837*	
Men	0.79 (0.40–1.54)	0.484	0.75 (0.35–1.62)	0.472	0.97 (0.65–1.48)	0.915	0.95 (0.59–1.53)	0.882
Women	1.03 (0.59–1.79)	0.915	1.78 (0.86–3.70)	0.122	1.00 (0.68–1.47)	0.992	1.13 (0.72–1.79)	0.587
p for heterogeneity	*0.540*		*0.108*		*0.932*		*0.591*	

Age-sex-adjusted and age-specific odds ratios of left-handedness by presence of *APOE2* allele, with confidence intervals and *p*-values. Left-handedness was the dependent variables coded as 0 (non-left-handed) and 1 (left-handed); the presence of *APOE2* allele was coded as 0 (no *APOE2* allele present) and 1 (at least one *APOE2* allele present). *Adjusted for age and sex

confounding or effect modification by age or sex contradicts the presence of a major bias. The observations that the proportion of left-handed persons based on grip strength was close to prevalence of 12% reported in an earlier study in the Czech population (Dvorakova, & Zvolsky, 1989), and the expected higher prevalence in males than females, further suggest that the grip strength based measure may be the more reliable of the two measures.

Our study had sufficient power to detect relatively modest differences in the prevalence of left-handedness between *APOE2* carriers and carriers of others genotypes, and the three-fold difference reported by Bloss et al. (2010) would be comfortably detected. However, we cannot completely exclude the possibility that small differences exist in left-handedness and *APOE* genotypes. Given the low prevalence of *APOE2E2* and *APOE4E4* homozygosity (less than 1%), a much larger study would be needed to demonstrate such a small effect for these rare genotypes.

Notwithstanding these limitations, there was no suggestion of an association between *APOE* genotype and left-handedness. This is consistent with a recent meta-analysis by Piper et al. (in press). We therefore conclude that common polymorphism within the *APOE* gene is likely not a major genetic determinant of left-handedness in adults.

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