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Apolipoprotein E genotype, lifestyle and coronary artery disease: Gene-environment interaction analyses in the UK Biobank population

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ABSTRACT

Background and aims: The *APOE ε4* genotype has a higher risk for developing coronary artery disease (CAD), but there is preliminary evidence that antioxidative lifestyle factors interact with *APOE* genotype on CAD risk. Here, we assessed the effect modification of physical activity, oily fish and polyunsaturated fatty acid (PUFA) intake with *APOE* genotype on risk of incident CAD.

Methods: The present study comprised 345,659 white European participants from UK Biobank (mean age: 56.5 years, 45.7% men) without a history of CAD. Information regarding physical activity, oily fish intake and PUFA intake was collected through questionnaires, and information on incident CAD through linkage with hospital admission records. Analyses were performed using Cox proportional hazard models adjusted for age and sex.

Results: Higher physical activity level and oily fish intake were both associated with a lower incidence of CAD. However, these associations were similar across the different *APOE* genotypes (p-values for interaction > 0.05). Most notable, higher PUFA intake was associated with a lower CAD risk in *APOE ε4* genotype carriers (hazard ratio: 0.76, 95% confidence interval: 0.63–0.92), and not in *APOE ε3/ε3* genotype carriers (0.90; 0.79, 1.02), but without statistical evidence for effect modification ($p\text{-value}_{\text{interaction}} = 0.137$).

Conclusions: While higher physical activity and high fish and PUFA intake were associated with a lower risk of incident CAD, no evidence for interaction of these lifestyle factors with *APOE* genotype was observed in UK Biobank participants. Interventions intended to reduce cardiovascular risk might therefore be similarly effective across the *APOE* genotype carriers.

1. Introduction

Coronary artery disease (CAD) is one of the most common causes of morbidity and mortality in the general population [1]. Large initiatives have been undertaken to investigate the genetics of CAD pathogenesis [2]. Genetic variation in the *APOE* gene has been widely recognized to increase the risk of CAD, which has also been confirmed by genome-wide association studies [2–4]. There is a standing notion that interactions between lifestyle and genetics may affect the response to cholesterol lowering medication and the susceptibility to CAD [5].

In order to explore the biological mechanisms via which lifestyle may modify disease traits, gene-environment interactions have been investigated [6–10]. We recently reviewed the current evidence on the existence of *APOE*-lifestyle interactions in the development of age-related diseases, including CAD, and argued that the beneficial effect of high physical activity and a high intake of oily fish might be largest for *APOE* ε4 genotype carriers [11]. From a biological perspective, such effect modification make sense given that it has previously been shown that *APOE* ε4 is associated with poor antioxidant capacity [12], which is generally considered to increase the risk of developing age-related diseases [13]. In line, a population-based cross-sectional survey performed in 1,708 randomly selected participants aged 35–74 years, showed that a high intensity level of physical activity was associated with an increase of high-density lipoprotein

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(HDL) cholesterol and a decrease of triglyceride levels, specifically in *APOE* ε4 genotype carriers [14]. Furthermore, it has been hypothesized that specifically PUFA intake may have a beneficial effect in *APOE* ε4 genotype carriers. Small-scale intervention studies indeed indicate that polyunsaturated fatty acid (PUFA) intake and physical activity may have specific beneficial effects on CAD (risk factors) in *APOE* ε4 genotype carriers [15–17]. However, the effect of smoking on the risk of CAD was not shown to be different in different *APOE* genotype carriers in a study of 130,000 individuals [18]. Nevertheless, evidence for physical activity and oily fish, as a source of PUFA, from large perspective cohort studies, to modify the risk of *APOE*--genotype-associated risk of CAD is lacking.

In the present study, we assessed whether the association between *APOE* genotype and incident CAD risk is modified by oily fish and PUFA intake and physical activity levels in middle-aged individuals without a history of CAD from the UK Biobank cohort.

2. Patients and methods

2.1. Study setting and population

The UK Biobank cohort is a prospective general population cohort. Baseline assessments took place between 2006 and 2010 in 22 different assessment centers across the United Kingdom [19]. A total of 502,628 participants between the age of 40 and 70 years were recruited from the general population. Invitation letters were sent to eligible adults registered to the National Health Services (NHS) and living within a 25 miles distances from one of the study assessment centers. At the study assessment center, participants completed a questionnaire through touchscreen that included topics as sociodemographic characteristics, physical and mental health, lifestyle and habitual food intake. All participants from the UK Biobank cohort provided written informed consent, and the study was approved by the medical ethics committee. The project was completed under project number 32292.

In the present study, genotyped European-ancestry participants without a history of cardiovascular disease were followed till the development of the study outcome, death or the end of the study period (March 31, 2017; N = 363,745). Participants with missing data on questionnaire-based oily fish intake (N = 1,654) and physical activity frequency per week (N = 16,432) were excluded from the study. In total, the present study was conducted in 345,659 participants. Additionally, we performed analyses in a subsample of the study population with data on polyunsaturated fatty acids (PUFA) intake (N = 52,478).

2.2. APOE genotyping

UK Biobank genotyping was conducted by Affymetrix using a bespoke BiLEVE Axium array for approximately 50,000 participants; the remaining participants were genotyped using the Affymetrix UK Biobank Axiom array. All genetic data were quality controlled centrally by UK Biobank resources. More information on the genotyping processes can be found online (https://www.ukbiobank.ac.uk). SNPs in *APOE* determining the *APOE* genotype (notably rs7412 and rs429358) were directly genotyped. Both genetic variants were in Hardy-Weinberg equilibrium (p-value > 0.05). As a reference group, we used participants who are homozygous for the *APOE* ε3 allele (ε3/ε3 genotype). The *APOE* ε4 group consisted of individuals with the genotype ε3/ε4 and ε4/ε4. The *APOE* ε2 group consisted of individuals with the genotype ε2/ε3 and ε2/ε2. In addition, we looked at the individual *APOE* genotypes, notably ε2/ε2, ε2/ε3, ε2/ε4, ε3/ε3, ε3/ε4, ε4/ε4, with ε3/ε3 as reference. We acknowledge, however that some of the genotype groups contained a low number of cases.

2.3. Lifestyle exposures

Via touchscreen questionnaires, information on the frequency of oily fish intake and physical activity per week was collected [20]. Via the same questionnaires, we determined the number of days per week at which participants had more than 10 min of vigorous physical activity [21], which was defined as "doing physical activity that made you sweat or breathe hard". Groups for oily fish intake and physical activity were divided based on whether individuals reported oily fish intake of at least once per week or were active for at least one day per week. In order to assess whether there is a dose-response relationship for oily fish intake and physical activity on a lower CAD incidence, we formed groups based on whether individuals had oily fish intake or physical activity only once, twice, or three or more times per week. As a reference group we used those individuals who reported to not have any intake of oily fish or were not active for any day of the week.

In a subset of the population, the frequency of intake of 200 consumed food items and drinks over the previous 24 h was collected with a 24-h dietary recall questionnaire (25) based on which the average intake of macro- and micronutrients was calculated. Information regarding polyunsaturated fatty acid (PUFA) intake was obtained via this questionnaire. The groups for PUFA intake were based on the median PUFA intake in which a higher than median PUFA intake was considered high and a lower than the median intake was considered as low and used as a reference group in our analyses.

2.4. Cardiovascular disease outcomes

Information on incident cardiovascular disease was collected through information from the data provided by the NHS record systems. Diagnoses were coded according to the International Classification of Diseases (ICD) [19]. Here, the study outcome was CAD which we defined as: angina pectoris (I20), acute myocardial infarction (I21), and acute and chronic ischemic heart disease (I24 and I25). In addition, we analyzed acute myocardial infarction and chronic ischemic heart disease as separate outcomes.

2.5. Covariates

Body Mass Index (BMI) was calculated by dividing the weight in kilograms by the height in meters squared, which were measured objectively at the study center. Participants were asked to remove shoes and heavy outer clothing before weighting. During the visit of the assessment center, participants completed touchscreen questionnaires regarding smoking status (never, previous or current), frequency of alcohol consumption, disease status (e.g. diabetes mellitus) and medication usage (lipid lowering medication and blood pressure lowering medication).

2.6. Statistical analyses

Characteristics of the study population were examined at baseline and expressed as means (standard deviations), medians (interquartile ranges; for non-normally distributed variables only), and proportions.

We examined the association between physical activity, oily fish intake and PUFA intake on incident CAD in a population without a history of CAD using cox proportional hazard models adjusted for age at recruitment and sex in R (version 3.6.1) using the survival package (version 2.44–1.1) [22, 23]. Time of follow-up, starting at the date of recruitment till the day of the event, loss-to-follow-up, death or the end of the study (March 31, 2017), whichever came first, was included as the time variable, presented in years, in the statistical analyses. We visualized the validity of the analyses presented in our study (e.g., proportionality assumption) by examining the Kaplan Meier curves. Results were visualized using the R-based packages ggplot2, survminer and the metafor package [24–26] and were presented as the hazard ratios with the accompanying 95% confidence intervals. Since individuals who are at high-risk for development of CAD may alter their lifestyle, we excluded participants who used lipid lowering medication, blood pressure lowering medication or had a clinical diagnosis of diabetes mellitus

at the date of recruitment in a sensitivity analysis. In order to formally test for an interaction, we added an interaction term (on a multiplicative scale) between the (individual) *APOE* genotypes and the lifestyle factor to the cox proportional hazard model adjusted for the confounders. We acknowledge that lifestyle factors as well as the risk to develop CAD differs between men and women [27], and therefore we additionally stratified the analyses by sex.

3. Results

3.1. Characteristics of the study population

A total of 345,659 white European participants were included in the present study. In Table 1, the population characteristics for the study population are presented stratified by *APOE* genotype. In general, study characteristics are comparable between subgroups. However, statin use, total cholesterol levels and LDL-cholesterol are lower in individuals with the *APOE* ε2 genotype as compared to *APOE* ε3 carriers and higher for *APOE* ε4 carriers. In Supplementary Table 1, the population characteristics are presented when stratified based on lifestyle factors. Individuals with a low fish intake are slightly younger than those with a high fish intake. Moreover, individuals with a high physical activity level are more often males, have a lower statin use, a lower use of blood pressure lowering medication and have less diabetes as compared to individuals with a low physical activity level.

3.2. Incident cardiovascular disease per APOE genotype

A total of 12,806 participants had an incident event of coronary artery disease (CAD) during a median follow-up period of 8.11 years. Fig. 1 depicts the event-free survival probability per *APOE* genotype. The highest event-free survival probability was observed in *APOE* ε2 carriers and the lowest probability in *APOE* ε4 carriers with accompanying hazard ratios of 0.93 (95% confidence interval (CI) 0.88–0.98) and 1.10 (95%CI: 1.06–1.14). No evidence for a statistical interaction with sex was observed (p for interaction = 0.58).

3.3. Incident cardiovascular disease per lifestyle group

As shown in Fig. 2 and Supplementary Table 2, oily fish intake was associated with a lower incidence of CAD in carriers of the ε2 genotype (hazard ratio (HR): 0.78 [95% confidence interval (CI): 0.67–0.92]), in carriers of the ε3 genotype (HR: 0.76 [95%CI: 0.71–0.82]), and in carriers of the ε4 genotype (HR: 0.83 [95%CI: 0.75–0.93]). Physical activity was associated with a lower CAD incidence in *APOE* ε2 carriers (HR: 0.81 [95%CI: 0.73–0.90]), in *APOE* ε3 carriers (HR: 0.77 [95%CI: 0.74–0.81]) as well as in ApoE ε4 carriers (HR: 0.76 [95%CI: 0.71–0.81]). Here, we did not find evidence for a statistical interaction with fish intake or physical activity with *APOE* genotype on the incidence of CAD (p for interactions>0.10). A high PUFA intake was associated with a lower incidence of CAD (HR: 0.76 [95%CI: 0.63–0.92], only in ε4 carriers, however no statistical interaction was observed (Fig. 2; p for interaction = 0.137).

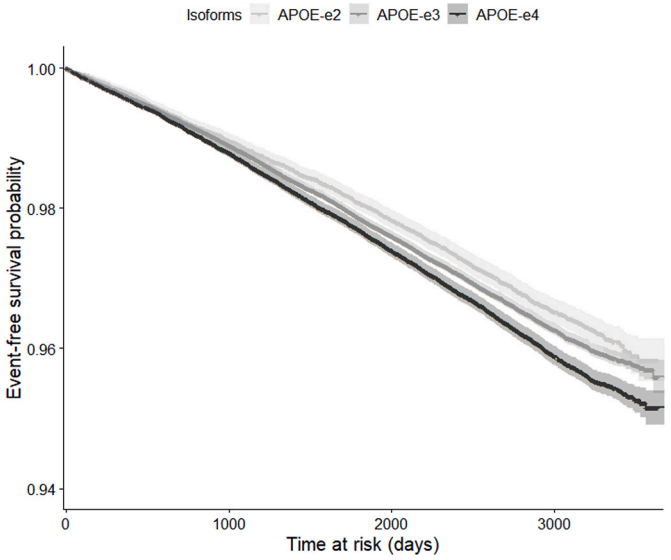

Fig. 1. Cardiovascular disease-free survival per *APOE* genotype.

Results were similar when we restricted the case definition to chronic ischemic heart disease (Supplementary Table 3) or acute myocardial infarction (Supplementary Table 4). Moreover, no clear dose-response relationship was observed for either fish intake or physical activity and CAD risk (Supplementary Table 5). However, when the frequency of fish intake or physical activity is taken into account, an interaction for once a week of physical activity in the group with *APOE* ε2 and *APOE* ε3 and an interaction for once a week of fish intake in the group with *APOE* ε3 and *APOE* ε4 was observed (Supplementary Fig. 1).

As a sensitivity analysis, we excluded participants who used lipid-lowering medication, blood pressure-lowering medication or with self-reported diabetes mellitus. Results were comparable to those obtained in our previous analyses (Supplementary Figs. 2 and 3). We observed similar results when we specifically investigated homozygous *APOE* ε2/ε2 and ε4/ε4 carriers (Supplementary Tables 6 and 7), and we did not observe large difference between men and women in all analyses (Supplementary Tables 2–7).

Table 1
Baseline characteristics of the participants in the UK Biobank, stratified by *APOE* genotype.

	*APOE ε2*N = 45,570	*APOE ε3*N = 207,909	*APOE ε4*N = 92,180
Demographics			
Age in years, mean (SD)	56.5 (8.0)	56.4 (8.0)	56.3 (8.0)
Sex, N (%male)	20,445 (44.9)	92,612 (44.5)	40,930 (44.4)
Lifestyle variables			
BMI, mean (SD)	27.3 (4.7)	27.2 (4.7)	27.1 (4.7)
Smoking status, N (%current)	4,199 (9.2)	19,221 (9.2)	8,236 (8.9)
Oily fish intake in days per week, median (IQR)	2 [1–2]	2 [1–2]	2 [1–2]
10 min of vigorous PA in days per week, median (IQR)	1 [0–3]	1 [0–3]	1 [0–3]
Cardiovascular risk factors			
Statin use, N (%yes)	4,613 (10.1)	29,120 (14.0)	15,394 (16.7)
Blood pressure lowering medicines use, N (%yes)	8,039 (17.6)	37,763 (18.2)	16,823 (18.3)
Diabetes, N (%yes)	1,955 (4.3)	8,613 (4.1)	3,492 (3.8)
Cholesterol in mmol/L, mean (SD)	5.4 (1.0)	5.8 (1.1)	5.9 (1.2)
HDL-cholesterol in mmol/L, mean (SD)	1.5 (0.4)	1.5 (0.4)	1.4 (0.4)
LDL-cholesterol in mmol/L, median (IQR)	3.2 [2.7–3.7]	3.6 [3.0–4.2]	3.7 [3.2–4.3]
Triglycerides in mmol/L, median (IQR)	1.5 [1.1–2.3]	1.4 [1.0–2.1]	1.5 [1.1–2.2]

BMI, body mass index; IQR, interquartile range; N, number; PA, physical activity; SD, standard deviation.

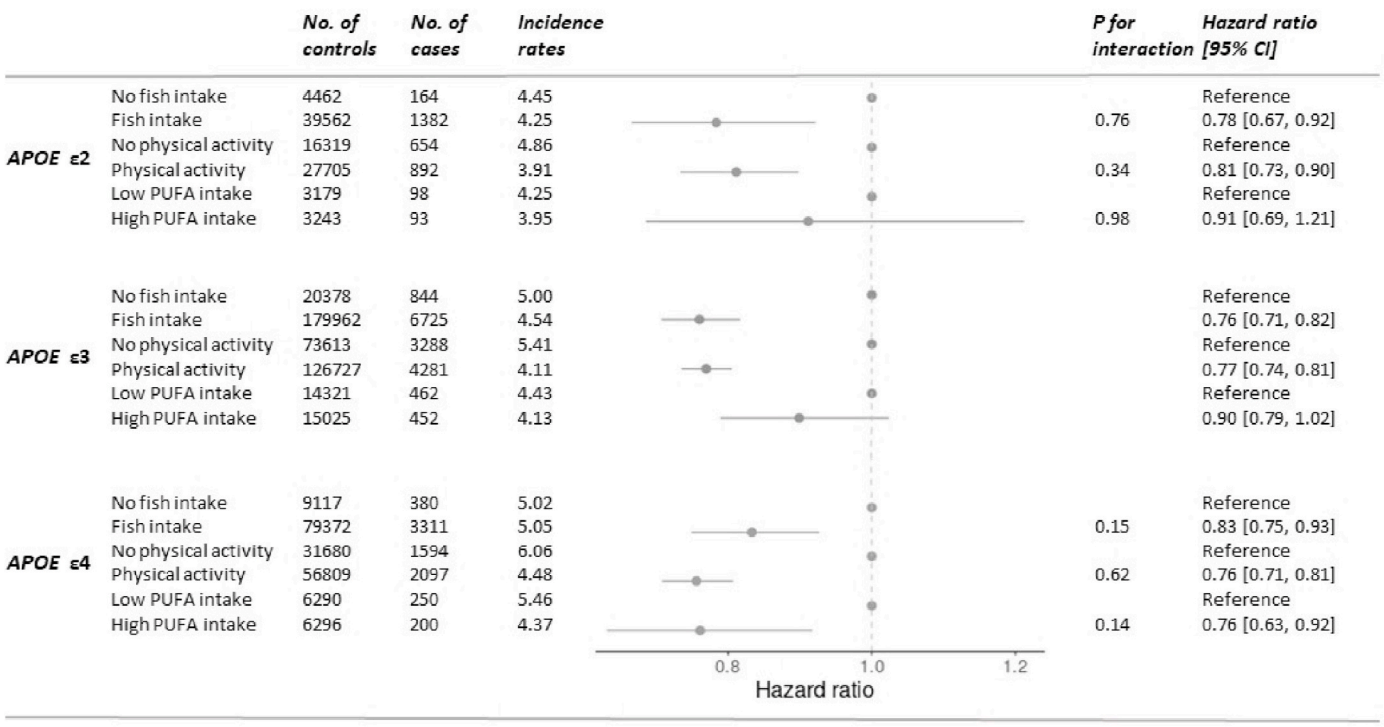

Fig. 2. Hazard ratios for CAD incidence for fish intake, physical activity and polyunsaturated fatty acid (PUFA) intake, stratified by *APOE* genotype. Cox-proportional hazard models were adjusted for age and sex.

4. Discussion

In the present study, we assessed whether there is evidence for lifestyle-*APOE* interactions on incident CAD in middle-aged individuals of the UK Biobank. Here, we showed that, independent of *APOE* genotype, a higher intake of fish and a higher physical activity level both associated with a lower CAD risk. However, we reported no evidence for a statistical interaction between fish intake, physical activity and polyunsaturated fatty acid (PUFA) intake with *APOE* genotype on incident CAD. A higher PUFA intake was only associated with a lower CAD risk in *APOE* ε4 carriers, however, no formal statistical interaction was observed.

In APOE ε4 carriers, the apolipoprotein has a different binding affinity for lipoprotein particles or the LDL-receptor than in carriers of the other genotypes [28]. Apolipoprotein ε4 has a higher binding ability for triglyceride-rich lipoproteins, such as chylomicron remnants and very-low-density-lipoprotein (VLDL) particles, than for LDL particles [29]. This results in a diminished clearance of LDL-cholesterol, resulting in higher LDL-cholesterol levels as compared to carriers of *APOE* ε2 and ε3 [30]. We hypothesized that carriers of the ε4 allele may benefit differently from a higher physical activity and a higher intake of oily fish, however, we did not find evidence supporting this hypothesis. In the present study, for individuals with a high physical activity level, the incidence rate for CAD was lower than for those with a low physical activity level. These lower incidence rates were similar across the different *APOE* carrier groups. Therefore, a higher physical activity is likely to be beneficial irrespective of *APOE* genotype. Moreover, in our study the incidence rate of CAD decreased with a higher oily fish intake, in carriers of all *APOE* genotypes and was not higher in carriers of the ε4 allele. Interestingly, a higher intake of PUFA associated with a lower CAD incidence only in *APOE* ε4 carriers points towards a possible lifestyle-*APOE* interaction on incident CAD. One possible explanation is that intake of PUFA may result in a lower concentration of VLDL and thereby may increase the uptake of LDL by the liver, resulting in lower LDL levels [11]. However, these observations likely have no clear benefit at a clinical level. Since the group with information regarding PUFA intake was relatively small, this may have resulted in limited statistical power and, therefore, further research to investigate the effect on a larger population level is warranted.

Although *APOE*-lifestyle interactions on cognitive function have been hypothesized as well [11], no significant interaction with cognitive function was observed in the UK Biobank population previously [31]. The lack of an *APOE*-lifestyle interactions in this population may be a reflection of some sort of selection bias where the current study population includes general healthier *APOE* ε4 carriers. Indeed, there is evidence of a 'healthy volunteer' bias in the UK Biobank sample [32]. Moreover, a genome-wide association study on habitual physical activity in the UK Biobank identified *APOE* to be one of the strongest associations with physical activity [21]. The association was markedly stronger among older participants; therefore, it may be that the older *APOE* risk allele carriers are particularly enriched for healthy lifestyle. One explanation could be that individuals with a known familial history of dementia and cardiovascular disease purposefully increase their physical activity levels and intake of oily fish. This bias may have resulted in an underestimation of the effect of exercise and fish intake. Alternatively, participants of the UK Biobank are still in good health or are slightly too young to show significant effects of the *APOE* genotype on CAD incidence. Moreover, additional lifestyle interactions, not covered in the present study, with *APOE* genotype may be possible. However, it should be noted that recent large-scale genome-wide interaction efforts were not able to identify interactions between physical activity, sleep duration, alcohol intake or smoking on blood lipid levels, limiting the potential of APOE-lifestyle interactions in the pathogenesis of CAD [6–10].

A strength of this study is that we used data from the UK Biobank and therefore, to the best of our knowledge, this is the largest study to test for an interaction of lifestyle factors and *APOE* on incident CAD. However, the current analyses have only been performed in participants of European descent, thereby hampering the translation to individuals with a different ancestry. This is of particular importance since variability exists in *APOE*-related disease prevalence in different ancestry groups.

Based on our results, a higher intake of fish and a higher physical activity level both associated with a lower CAD risk independent of *APOE* genotype. However, it is unlikely that there is a significant interaction between genetic variation in *APOE* and various lifestyle factors on the development of incident CAD in a population of middle-aged and older

individuals. Therefore, it seems likely that interventions intended to reduce cardiovascular risk via increased physical activity and increased intake of oily fish will be equally effective in carriers of the *APOE* ε4 genotype as in the other *APOE* genotype carriers and may thus have considerable health benefits irrespective of *APOE* genotype.

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CRediT authorship contribution statement

Maxime M. Bos: Study design, Statistical analyses, Writing – original draft, Critical commenting and final approval of the manuscript. **Lina de Vries:** Study design, Statistical analyses, Writing – original draft, Critical commenting and final approval of the manuscript. **Gerard Jan Blauw:** Supervision, Results interpretation, Critical commenting and final approval of the manuscript. **Diana van Heemst:** Study design, Supervision, Results interpretation, Critical commenting and final approval of the manuscript. **Raymond Noordam:** Study design, Statistical analyses, Supervision, Results interpretation, Critical commenting and final approval of the manuscript.

Author contributions

MMB, LdV, DvH, RN: study design. MMB, LdV, RN: statistical analyses. MMB, LdV: drafting of the manuscript. GJB, DvH, RN: project supervision. Results interpretation: all co-authors. Critical commenting and final approval of the manuscript: all co-authors.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2021.05.014.

References

[1] C. Andersson, R.S. Vasan, Epidemiology of cardiovascular disease in young individuals, Nat. Rev. Cardiol. 15 (2018) 230–240.
[2] M. Nikpay, A. Goel, H.H. Won, et al., A comprehensive 1,000 Genomes-based genome-wide association meta-analysis of coronary artery disease, Nat. Genet. 47 (2015) 1121–1130.
[3] CARDIoGRAMplusC4D Consortium, P. Deloukas, S. Kanoni, et al., Large-scale association analysis identifies new risk loci for coronary artery disease, Nat. Genet. 45 (2013) 25–33.
[4] Y. Song, M.J. Stampfer, S. Liu, Meta-analysis: apolipoprotein E genotypes and risk for coronary heart disease, Ann. Intern. Med. 141 (2004) 137–147.
[5] J.M. Hagberg, K.R. Wilund, R.E. Ferrell, APO E gene and gene-environment effects on plasma lipoprotein-lipid levels, Physiol. Genom. 4 (2000) 101–108.
[6] A.R. Bentley, Y.J. Sung, M.R. Brown, et al., Multi-ancestry genome-wide gene-smoking interaction study of 387,272 individuals identifies new loci associated with serum lipids, Nat. Genet. 51 (2019) 636–648.
[7] P.S. de Vries, M.R. Brown, A.R. Bentley, et al., Multiancestry genome-wide association study of lipid levels incorporating gene-alcohol interactions, Am. J. Epidemiol. 188 (2019) 1033–1054.
[8] T.O. Kilpelainen, A.R. Bentley, R. Noordam, et al., Multi-ancestry study of blood lipid levels identifies four loci interacting with physical activity, Nat. Commun. 10 (2019) 376.
[9] D.C. Rao, Y.J. Sung, T.W. Winkler, et al., Multiancestry Study of Gene-Lifestyle Interactions for Cardiovascular Traits in 610 475 Individuals from 124 Cohorts: Design and Rationale, Circ Cardiovasc Genet 10 (2017).
[10] R. Noordam, M.M. Bos, H. Wang, et al., Multi-ancestry sleep-by-SNP interaction analysis in 126,926 individuals reveals lipid loci stratified by sleep duration, Nat. Commun. 10 (2019) 5121.
[11] M.M. Bos, R. Noordam, G.J. Blauw, et al., The ApoE epsilon4 isoform: can the risk of diseases be reduced by environmental factors? J Gerontol A Biol Sci Med Sci 74 (2019) 99–107.
[12] C. Jolivalt, B. Leininger-Muller, P. Bertrand, et al., Differential oxidation of apolipoprotein E isoforms and interaction with phospholipids, Free Radic. Biol. Med. 28 (2000) 129–140.
[13] J. Luo, K. Mills, S. le Cessie, et al., Ageing, age-related diseases and oxidative stress: what to do next? Ageing Res. Rev. 57 (2020) 100982.
[14] M.S. Bernstein, M.C. Costanza, R.W. James, et al., Physical activity may modulate effects of ApoE genotype on lipid profile, Arterioscler. Thromb. Vasc. Biol. 22 (2002) 133–140.
[15] A.M. Minihane, S. Khan, E.C. Leigh-Firbank, et al., ApoE polymorphism and fish oil supplementation in subjects with an atherogenic lipoprotein phenotype, Arterioscler. Thromb. Vasc. Biol. 20 (2000) 1990–1997.
[16] E. Olano-Martin, E. Anil, M.J. Caslake, et al., Contribution of apolipoprotein E genotype and docosahexaenoic acid to the LDL-cholesterol response to fish oil, Atherosclerosis 209 (2010) 104–110.
[17] J.H. Lee, S.M. Hong, Y.A. Shin, Effects of exercise training on stroke risk factors, homocysteine concentration, and cognitive function according the APOE genotype in stroke patients, J Exerc Rehabil 14 (2018) 267–274.
[18] M.V. Holmes, R. Frikke-Schmidt, D. Melis, et al., A systematic review and meta-analysis of 130,000 individuals shows smoking does not modify the association of APOE genotype on risk of coronary heart disease, Atherosclerosis 237 (2014) 5–12.
[19] C. Sudlow, J. Gallacher, N. Allen, et al., UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age, PLoS Med. 12 (2015), e1001779.
[20] K.E. Bradbury, H.J. Young, W. Guo, et al., Dietary assessment in UK Biobank: an evaluation of the performance of the touchscreen dietary questionnaire, J. Nutr. Sci. 7 (2018) e6.
[21] Y.C. Klimentidis, D.A. Raichlen, J. Bea, et al., Genome-wide association study of habitual physical activity in over 377,000 UK Biobank participants identifies multiple variants including CADM2 and APOE, Int. J. Obes. 42 (2018) 1161–1176.
[22] R.C.R. Team, A Language and Environment for Statistical Computing, R Foundation for Statistical Computing, Vienna, Austria, 2019.
[23] T.M. Therneau, A Package for Survival Analysis in S, Mayo Clinic, 2015.
[24] H. Wickham, ggplot2: Elegant Graphics for Data Analysis, Springer-Verlag, New York, 2009.
[25] AKaM. Kosinski, survminer, Drawing Survival Curves Using, ggplot2, 2019.
[26] W. Viechtbauer, Conducting meta-analyses in (R) with the (metafor) package, J. Stat. Software 36 (2010) 1–48.
[27] J.E. van der Toorn, O.L. Rueda-Ochoa, N. van der Schaft, et al., Arterial calcification at multiple sites: sex-specific cardiovascular risk profiles and mortality risk-the Rotterdam Study, BMC Med. 18 (2020) 263.
[28] D.Y. Hui, T.L. Innerarity, R.W. Mahley, Defective hepatic lipoprotein receptor binding of beta-very low density lipoproteins from type III hyperlipoproteinemic patients. Importance of apolipoprotein E, J. Biol. Chem. 259 (1984) 860–869.
[29] K.H. Weisgraber, Apolipoprotein E distribution among human plasma lipoproteins: role of the cysteine-arginine interchange at residue 112, J. Lipid Res. 31 (1990) 1503–1511.
[30] R.W. Mahley, S.C. Rall Jr., E. Apolipoprotein, Far more than a lipid transport protein, Annu. Rev. Genom. Hum. Genet. 1 (2000) 507–537.
[31] D.M. Lyall, C. Celis-Morales, L.M. Lyall, et al., Assessing for interaction between APOE epsilon4, sex, and lifestyle on cognitive abilities, Neurology 92 (2019) e2691–e2698.
[32] A. Fry, T.J. Littlejohns, C. Sudlow, et al., Comparison of sociodemographic and health-related characteristics of UK biobank participants with those of the general population, Am. J. Epidemiol. 186 (2017) 1026–1034.