Review paper

Can "deleterious genes variants" be beneficial? Antagonistic pleiotropy on the example of the *ApoE* gene

Paula B. Bartecka[1,2], Andrzej Galbarczyk[1]

[1]Department of Environmental Health, Institute of Public Health, Faculty of Health Sciences, Jagiellonian University Medical College, Krakow, Poland
[2]Doctoral School of Medical and Health Sciences, Jagiellonian University Medical College, Krakow, Poland

Medical Studies
DOI: https://doi.org/10.5114/ms.2026.159848

Key words: antagonistic pleiotropy, APOE, polymorphism, fertility.

Abstract

Antagonistic pleiotropy is a phenomenon where one gene has both beneficial and detrimental effects. Apolipoprotein E is of particular interest due to its pleiotropic effects. It is encoded by the *ApoE* gene, which has three variants: *ApoE2*, *ApoE3*, and *ApoE4*. The *ApoE4* allele is a classic example of antagonistic pleiotropy. On the one hand, its presence increases the risk of diseases related to cholesterol metabolism, such as ischemic heart disease and Alzheimer's disease. On the other hand, *ApoE4* can increase fertility, indicating potential reproductive benefits. This article provides an overview of the established detrimental effects of the A*poE4* allele and a comprehensive analysis of eight studies (1996–2023) on the effects of APOE polymorphism on fertility. Antagonistic pleiotropy plays a crucial role in the evolution of the human genome, explaining why some deleterious gene variants persist in populations. Understanding these mechanisms is key to explaining the complexity of human evolution and health.

What is antagonistic pleiotropy?

Human genes can exist in several variants called alleles. Different alleles can encode different protein variants or affect their expression [1]. Some alleles may be associated with a higher risk of disease, while others may have a more beneficial effect on health [2]. There are also alleles that have pleiotropic effects on health; that is, they affect many different traits [3]. There are also cases when this influence is both positive and negative. This phenomenon is what we call antagonistic pleiotropy, or pleiotropy with opposite effects. If an allele has a positive effect on physical fitness early in life and a detrimental effect later in life, it is often the case that the former compensates for the latter, as it increases the power of selection in the early years of life, when genes are still being passed on to the next generation. Alleles that increase the risk of disease later in life have already been passed on to the next generation before they show their deleterious effects. Therefore, such pleiotropic genes are not removed by mechanisms of natural selection and will persist in the population [3–5].

The activity of the gene encoding apolipoprotein E (APOE) is an example of antagonistic pleiotropy. This article is structured into two parts. The first section provides an overview of the well-established detrimental effects of the *ApoE4* allele. The second section presents a comprehensive review of all studies (eight papers published between 1996 and 2023) investigating the effects of APOE polymorphism on reproductive functions, a topic that remains less thoroughly explored.

Apolipoprotein E

APOE is a major component of plasma lipoproteins – the protein-fat molecules responsible for lipid transport in the human body. Most plasma APOE is derived from hepatocytes in the liver, but it can also be synthesized by brain cells, adipocytes, myeloid immune cells, kidney cells, vascular smooth muscle cells, and adrenal cells [6]. APOE plays a significant role in lipid metabolism that includes being responsible for lipid mobilization, transport, and removal [7–9]. An important role of APOE is also to maintain cholesterol homeostasis in the body [7, 10].

APOE is encoded by the gene of the same name (*ApoE).* It is a polymorphic gene located on chromosome 19, and it encodes a protein composed of 299 amino acids [11]. There are 3 versions (alleles) of the *ApoE* gene. Depending on the allele present (*ApoE2*, *ApoE3*, *ApoE4)*, the corresponding protein isoforms are encoded as follows: APOE2, APOE3, APOE4 [12] (Table 1). The differences between these isoforms are the changes in the position of arginine and cysteine at positions 112 and 158 of the protein in question [13]. This polymorphism can result in 6 different genotypes: *ApoE2*/*ApoE2*, *ApoE3*/*ApoE3*, *ApoE4*/*ApoE4* (homozygotes) and

Table 1. APOE isoforms and their general biological characteristics

Isoform	Amino acid change	Frequency in populations	Populations with highest frequency	Time of emergence (evolution)	Effect on lipid metabolism
APOE4	Arg112, Arg158	10–15%* (more common among indigenous groups in Asia-Pacific countries)	Pygmies, Aborigines of Malaysia and Australia, Papuans	Oldest allele; ancestral form	Alters lipid metabolism significantly; higher LDL level; less efficient lipid transport
APOE3	Cys112, Arg158	~70–80% (most common worldwide)	European populations, including Poland	Emerged ~220,000 years ago from ApoE4	Neutral effect on lipid metabolism; reference isoform
APOE2	Cys112, Cys158	5–10% (rare; absent in some groups, e.g. Native Americans)	Rare in Europe, absent in Native Americans, low/rare in most populations	Last to emerge, after ApoE3	Reduced binding to LDL receptor; lower LDL level

**Applies only to Europe.*

ApoE2/ApoE3, *ApoE3/ApoE4*, *ApoE2/ApoE4* (heterozygotes) [14]. The *ApoE4* allele, unlike *ApoE2* and *ApoE3*, significantly alters lipid metabolism [10].

ApoE4 is considered to be the oldest allele evolutionary-wise. The *ApoE3* allele appeared about 220,000 years ago, and only then it gave rise to the last allele, *ApoE2* [15]. Studies by several independent researchers show that the most common allele in Poland is the *ApoE3* allele. This score is followed by a much less frequent *ApoE4*, and the rarest is *ApoE2* [16–18]. A similar distribution of alleles has also been observed in other neighbouring European countries [17]. In the Native American group, the *ApoE2* allele was observed to be absent, and the *ApoE3* allele appeared more frequently compared to *ApoE4* [19]. The *ApoE4* allele is most common for indigenous peoples such as Pygmies, Aborigines of Malaysia and Australia, and Papuans [20].

Detrimental effect of the *ApoE4* allele

Many studies have shown that the presence of the *ApoE4* allele in the genome can be detrimental to health. As early as in 1985, it was shown that people with the *ApoE4* allele (*ApoE4/ApoE2*, *ApoE4/ApoE3*, *ApoE4/ApoE4*) had 11.5 mg/dl higher total cholesterol and 9.6 mg/dl higher low density lipoprotein (LDL) cholesterol than those without the *ApoE4* allele [21]. *ApoE4* holders on a diet rich in saturated fats have elevated cholesterol levels when compared to non-holders on a similar diet [22]. A meta-analysis of the 82 studies on lipid levels in relation to the *ApoE* gene polymorphism confirmed that, on average, holders of the *ApoE4/ApoE4* genotype have 31% higher LDL levels than the holders of the genotype encoding the lowest levels, *ApoE2/ApoE2* [23]. Cholesterol is a precursor to steroid hormones, which in turn are precursors to bile acids that play an important role in the intestinal absorption of lipids from food. Excessive or reduced levels of cholesterol in tissues result in diseases, both at the embryonic stage and in adult life [24]. Thus, having *ApoE4* increases the risk of diseases for which elevated cholesterol is an important risk factor. These include diseases that are one of most common causes of death worldwide, i.e. cardiovascular disease and cancer [25].

An example of a disease associated with high cholesterol concentrations is an ischemic heart disease. It is caused by atherosclerosis, in the development of which *ApoE* may play a key role in terms of, among other things, receiving lipoproteins from the circulation, and controlling the transport of cholesterol to and from the cell [26]. Having at least one *ApoE4* allele increases the risk of ischemic heart disease by 42% in comparison to the *ApoE3/ApoE3* genotype holders [27]. For the individuals with the *ApoE4* allele who have had a myocardial infarction, the risk of death is almost twice as high compared to the others [28]. A strong association between having the *ApoE4* allele and hypertension has also been shown. For the individuals with *ApoE3/ApoE4* genotypes or *ApoE4* homozygotes, the risk of developing hypertension was twice as high compared to other genotypes [29]. A study summarizing 121 articles on the relationship between *ApoE* gene polymorphisms and the risk of coronary heart disease showed that it increases linearly in the following order: *ApoE2/ApoE2*, *ApoE2/ApoE3*, *ApoE2/ApoE4*, *ApoE3/ApoE3*, *ApoE3/ApoE4*, *ApoE4/ApoE4* [23].

Another disease the risk of which is carried by the presence of the *ApoE4* allele is Alzheimer's disease [7]. Alzheimer's disease is responsible for about 60–80% of cases of dementia, which is a debilitating type of abnormal cognitive aging. In addition to its adverse effects on cognitive decline and quality of life, Alzheimer's disease is one of the leading causes of death among 65-year-olds and older [30]. The *ApoE4* gene expresses itself at lower brain levels, and cerebrospinal fluid in other neurodegenerative diseases as well [10]. Several studies have shown that the *ApoE4* allele plays a role in the pathophysiology of Alzheimer's disease. A meta-analysis showed that patients with *ApoE4* have smaller hippocampal volume because of the be-

Table 2. Studies of the effects of APOE polymorphism on reproductive functions

Population studied [reference no.]	Participants, *n*	Main finding
Southern Poland – rural [18]	Women, *n* = 118, aged 24–37	*ApoE4* carriers produced ~20% more progesterone during the menstrual cycle.
Bolivia – pre-industrial [34]	Women, *n* = 795, aged 13–90	*ApoE4* carriers had 0.3 to 0.5 more children than *ApoE3/3* homozygotes; *ApoE4/4* homozygotes had 1.4 to 2.1 more children than *ApoE3/3* homozygotes.
Ghana – rural [35]	Women, *n* = 197, aged 44–64	*ApoE4* carriers had 1 child more; *ApoE4/4* homozygotes had 3.5 more children than non-carriers.
Ecuador – pre-industrial [20]	Women, *n* = 164 aged 15–82	*ApoE3/4* heterozygotes had 1.5 more children than other genotypes (not *ApoE4/4*).
Italy – rural [37]	Women and men, *n* = 160, aged 70–100	*ApoE3/3* homozygotes had 1.5 more children, more pregnancies than other genotypes.
Denmark – urban [28]	Men, *n* = 379, aged 40	*ApoE3/3* homozygotes had 1.22 more children than *ApoE3/4* heterozygotes, *ApoE4/4* homozygotes and *ApoE2* carriers. No semen quality difference [38].
Puerto Rico – urban [36]	Women, *n* = 616, aged 16–50	*ApoE4* carriers reported 2 times fewer spontaneous miscarriages.

ta-amyloid deposition. This results in the brain hypometabolism, which is a biomarker of Alzheimer's disease [31]. The risk of developing the disease increases two to three times in the heterozygous system and five to ten times in the homozygous system compared to the general population [14].

Beneficial effects of the *ApoE4* allele

All of the examples above clearly indicate that the *ApoE4* allele has greater negative effects compared to its isoforms. However, having the *ApoE4* allele may also be related to potential benefits. Based on the knowledge that *ApoE4* is responsible for elevated cholesterol, researchers have hypothesized that *ApoE* may also be involved in the regulation of sex hormones. Cholesterol is a precursor to the synthesis of steroid hormones such as oestrogens and testosterone. This fact may suggest that the gene may play some role in reproduction processes [32] (Table 2).

A study conducted in a rural community in southern Poland found that young women carrying at least one *ApoE4* allele produce 20% more progesterone during their menstrual cycle compared to women with other genotypes [18]. Progesterone plays a key role during embryo implantation in the uterus and maintenance of pregnancy [33]. Therefore, women with at least one *ApoE4* allele may have higher potential fertility.

The effect of *ApoE4* on fertility has also been demonstrated by the works examining the relationship between *APOE* polymorphisms and the number of children. A study conducted in a rural community in South America found that women with at least one *ApoE4* allele gave birth to 0.3 to 0.5 more children than women with *ApoE3/ApoE3* homozygotes, while those with two *ApoE4* alleles gave birth to 1.4 to 2.1 more children in similar comparison [34]. The association between the *ApoE4* allele and having more children was also confirmed by another study. In a rural setting in Ghana, women carrying one *ApoE4* allele gave birth to, on average, one more child, and women carrying two *ApoE4* alleles had, on average, 3.5 times more children than women who did not carry the *ApoE4* allele [35]. Another study indicated that *ApoE4* holders started reproduction on average 0.8 years earlier, had interbirth intervals shorter by 0.23 years [34], and were pregnant on average 1.5 times more often than women with other alleles [20]. All of these results suggest that the *ApoE4* allele may be associated with higher fertility rates; and in consequence with a higher reproductive success.

The *ApoE4* allele may have a positive effect not only on the number of children and potential fertility, but also on pregnancy maintenance. High concentrations of progesterone are essential for the maintenance and proper course of pregnancy [33]. A study from Puerto Rico found that endometriosis patients with the *ApoE4* allele reported spontaneous miscarriage twice less often as women with other alleles [36].

However, the research results are inconsistent. A study conducted in a pre-industrial population in Ecuador found that women with the *ApoE3/ApoE4* genotype had, on average, 1.5 times more children than women with the *ApoE3/ApoE3*, *ApoE3/ApoE2*, *ApoE4/ApoE4*, and *ApoE4/ApoE2* genotypes [20]. Thus, it was not the *ApoE4/ApoE4* genotype that was the most favourable fertility-wise. Another study from Italy found that it was those with the *ApoE3/ApoE3* genotype that had an average of/on average 1.5 times more children compared to the *ApoE2/ApoE2*,

ApoE3/ApoE2, and *ApoE4/ApoE3* genotypes, and were pregnant an average of 1.4 times/pregnant on average 1.4 times more often than those with the *ApoE3/ApoE2* and *ApoE4/ApoE3* genotypes [37]. The study examining the effect of the APOE polymorphism on the male fertility only showed that it was also the *ApoE3* allele that was associated with having the highest number of children among the participants. Men with the *ApoE3/ApoE3* genotype had an average of/had on average 1.22 more children compared to men with genotypes such as *ApoE3/ApoE4*, *ApoE4/ApoE4*, *ApoE3/ApoE2*, and *ApoE2/ApoE2* [28]. It is worth noting that the men studied were 40 years old, so their reproduction was, as the authors suggest themselves, not yet complete. The *APOE* polymorphism is also not associated with semen quality [38]. The studies above suggest that in pre-industrial populations, the allele responsible for more children is *ApoE4*, while in industrial ones it is *ApoE3*.

In addition to the advantage of the *ApoE4* allele in terms of higher fertility, a number of other benefits of having this gene variant have also been demonstrated. In regions with a high load of pathogens and parasites, women with the *ApoE4* allele had a higher survival rate. For the researchers, this fact constitutes yet another reason to consider this allele to be evolutionarily adaptive [35]. It has been also shown that *ApoE4* holders may have a less severe course of hepatitis B [39].

The allele in question may also positively affect cognitive abilities in early years of life. Young individuals with the *ApoE4* allele from a tribe living in the pathogen-rich Amazonian equatorial forest were observed to have better cognitive performance [40]. In a slum area in Brazil, children carrying the allele in question had a lower predisposition to diarrhoea compared to children with the *ApoE2* allele, who in turn showed a high predisposition to diarrhoea [41]. Individuals with the *ApoE4* allele, before the onset of Alzheimer's disease, have been shown to have an advantage in cognitive function, memory and concentration compared to those without the allele [42].

Conclusions

ApoE4 is the second most common allele of the *ApoE* gene worldwide, despite the fact that it increases the risk of death at a later stage of life. This non-random distribution of alleles in populations may suggest that, on the one hand, it may give an advantage in early life that counteracts deleterious effects in later life, the phenomenon of which is called antagonistic pleiotropy.

The most popular theory, however, in the context of defective alleles being preserved in a population is the life history theory. It claims that their relationship results from the trade-offs between competing biological functions – human reproduction and the concomitant high risk of diseases in old age. The latter include cardiovascular disease, coronary heart disease, and myocardial infarction. This trade-off between enhanced body adaptation and higher disease risk is often caused by a single gene or allele. An example of such a relationship is the *ApoE4* allele, the presence of which can boost fertility at reproductive age, but at the same time can increase the risk of developing diseases, such as Alzheimer's disease, later in life.

The mechanism of antagonistic pleiotropy is still largely underestimated and underutilized in research on disease aetiology, despite the fact that there are a lot of studies suggesting that antagonistic pleiotropy can affect many human diseases. This issue is very important, as it may help explain why certain genetic diseases are more common in the population than expected. With gene modification and gene therapies becoming increasingly feasible, the phenomenon of antagonistic pleiotropy and its evolutionary mechanism must be thoroughly understood and studied. Removing a potentially deleterious allele may be harmful, as it also has some beneficial functions.

It is important to remember that although having the *ApoE4* allele carries a higher risk of Alzheimer's disease, among other things, contracting any disease is not guaranteed. It all depends on the lifestyle of the *ApoE4* holders. If it is rich in physical activity and healthy habits such as avoiding high-fat foods, the cholesterol levels are significantly lower, and so is the risk of dangerous diseases related to lipid metabolism.

Acknowledgments

The authors would like to thank Natalia Kwaśniak for linguistic revision.

Funding

No external funding.

Ethical approval

Not applicable.

Conflict of interest

The authors declare no conflict of interest.

References

1. Buckland PR. Allele-specific gene expression differences in humans. Hum Mol Genet. 2004; 13(suppl_2): R255-R2–60.
2. Carter AJR, Nguyen AQ. Antagonistic pleiotropy as a widespread mechanism for the maintenance of polymorphic disease alleles. BMC Med Genet. 2011; 12: 160.
3. Medawar PB. Old age and natural death. Mod Quart. 1946; 2: 30-49.
4. Hamilton WD. The moulding of senescence by natural selection. J Theor Biol. 1966; 12(1): 12-45.

5. Williams GC. Pleiotropy, Natural Selection, and the Evolution of Senescence. Sci Aging Knowl Environ. 2001; 2001(1): cp13.
6. McMaster MW, Shah A, Kangarlu J, Cheikhali R, Frishman WH, Aronow WS. The impact of the apolipoprotein E genotype on cardiovascular disease and cognitive disorders. Cardiol Rev. 2024; doi: 10.1097/CRD.0000000000000703.
7. Farrer LA, Cupples LA, Haines JL, Hyman B, Kukull WA, Mayeux R, Myers RH, Pericak-Vance MA, Risch N, van Duijn CM. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease: a meta-analysis. JAMA. 1997; 278(16): 1349-1356.
8. Niu W, Qi Y, Qian Y, Gao P, Zhu D. The relationship between apolipoprotein E ε2/ε3/ε4 polymorphisms and hypertension: a meta-analysis of six studies comprising 1812 cases and 1762 controls. Hypertens Res. 2009; 32(12): 1060-1066.
9. Corbo RM, Ulizzi L, Piombo L, Scacchi R. Study on a possible effect of four longevity candidate genes (ACE, PON1, PPAR-γ, and APOE) on human fertility. Biogerontology. 2008; 9: 317-323.
10. Mahley RW. Central nervous system lipoproteins: ApoE and regulation of cholesterol metabolism. Arterioscler Thromb Vasc Biol. 2016; 36(7): 1305-1315.
11. Davignon J, Gregg RE, Sing CF. Apolipoprotein E polymorphism and atherosclerosis. Arteriosclerosis. 1988; 8(1): 1-21.
12. Wenham P, Price W, Blundell G. Apolipoprotein E genotyping by one-stage PCR. Lancet. 1991; i: 1158-1159.
13. Harerimana NV, Goate AM, Bowles KR. The influence of 17q21. 31 and APOE genetic ancestry on neurodegenerative disease risk. Front Aging Neurosci. 2022; 14: 1021918.
14. Mahley RW, Nathan BP, Pitas RE. Apolipoprotein E. Structure, function, and possible roles in Alzheimer’s disease. Ann N Y Acad Sci. 1996; 777(1): 139-145.
15. Fullerton SM, Clark AG, Weiss KM, Nickerson DA, Taylor SL, Stengård JH, Salomaa V, Vartiainen E, Perola M, Boerwinkle E, Sing CF. Apolipoprotein E variation at the sequence haplotype level: implications for the origin and maintenance of a major human polymorphism. Am J Hum Genet. 2000; 67(4): 881-900.
16. Kowalska A, Wiechmann I, Walter H. Genetic variability of apolipoprotein E in a Polish population. Hum Biol. 1998; 70: 1093-1099.
17. Bednarska-Makaruk M, Broda G, Kurjata P, Rodo M, Roszczynko M, Rywik S, Wehr H. Apolipoprotein E genotype, lipid levels and coronary heart disease in a Polish population group. Eur J Epidemiol. 2001; 17: 789-792.
18. Jasienska G, Ellison PT, Galbarczyk A, Jasienski M, Kalemba-Drozdz M, Kapiszewska M, Nenko I, Thune I, Ziomkiewicz A. Apolipoprotein E (ApoE) polymorphism is related to differences in potential fertility in women: a case of antagonistic pleiotropy? Proc Biol Sci. 2015; 282(1803): 20142395.
19. Gamboa R, Hernandez-Pacheco G, Hesiquio R, Zuniga J, Masso F, Montaño LF, Ramos-Kuri M, Estrada J, Granados J, Vargas-Alarcón G. Apolipoprotein E polymorphism in the Indian and Mestizo populations of Mexico. Hum Biol. 2000; 72: 975-981.
20. Corbo RM, Ulizzi L, Scacchi R, Martinez-Labarga C, De Stefano GF. Apolipoprotein E polymorphism and fertility: a study in pre-industrial populations. Mol Hum Reprod. 2004; 10(8): 617-620.
21. Sing CF, Davignon J. Role of the apolipoprotein E polymorphism in determining normal plasma lipid and lipoprotein variation. Am J Hum Genet. 1985; 37(2): 268.
22. Eichner JE, Dunn ST, Perveen G, Thompson DM, Stewart KE, Stroehla BC. Apolipoprotein E polymorphism and cardiovascular disease: a HuGE review. Am J Epidemiol. 2002; 155(6): 487-495.
23. Bennet AM, Di Angelantonio E, Ye Z, Wensley F, Dahlin A, Ahlbom A, Keavney B, Collins R, Wiman B, de Faire U, Danesh J. Association of apolipoprotein E genotypes with lipid levels and coronary risk. JAMA. 2007; 298(11): 1300-1311.
24. Luo J, Yang H, Song BL. Mechanisms and regulation of cholesterol homeostasis. Nat Rev Mol Cell Biol. 2020; 21(4): 225-245.
25. Wilson PW, Schaefer EJ, Larson MG, Ordovas JM. Apolipoprotein E alleles and risk of coronary disease: a meta-analysis. Arterioscler Thromb Vasc Biol. 1996; 16: 1250-1255.
26. Davignon J, Cohn JS, Mabile L, Bernier L. Apolipoprotein E and atherosclerosis: insight from animal and human studies. Clin Chim Acta. 1999; 286(1–2): 115-143.
27. Song Y, Stampfer MJ, Liu S. Meta-analysis: apolipoprotein E genotypes and risk for coronary heart disease. Ann Intern Med. 2004; 141(2): 137-147.
28. Gerdes LU, Gerdes C, Hansen PS, Klausen IC, Færgeman O. Are men carrying the apolipoprotein ε4-or ε2 allele less fertile than ε3ε3 genotypes? Hum Genet. 1996; 98: 239-242.
29. Shi J, Liu Y, Liu Y, Li Y, Qiu S, Bai Y, Gu Y, Luo J, Cui H, Li Y, Zhao Q, Zhang K, Cheng Y. Association between ApoE polymorphism and hypertension: a meta-analysis of 28 studies including 5898 cases and 7518 controls. Gene. 2018; 675: 197-207.
30. Pirraglia E, Glodzik L, Shao Y. Lower mortality risk in APOE4 carriers with normal cognitive ageing. Sci Rep. 2023; 13(1): 15089.
31. Liu Y, Yu JT, Wang HF, Han PR, Tan CC, Wang C, Meng XF, Risacher SL, Saykin AJ, Tan L. APOE genotype and neuroimaging markers of Alzheimer’s disease: systematic review and meta-analysis. J Neurol Neurosurg Psychiatry. 2015; 86(2): 127-134.
32. Finch CE, Sapolsky RM. The evolution of Alzheimer disease, the reproductive schedule, and apoE isoforms. Neurobiol Aging. 1999; 20(4): 407-428.
33. Norwitz ER, Schust DJ, Fisher SJ. Implantation and the survival of early pregnancy. N Engl J Med. 2001; 345(19): 1400-1408.
34. Trumble BC, Charifson M, Kraft T, Garcia AR, Cummings DK, Hooper P, Lea AJ, Rodriguez DE, Koebele SV, Buetow K, Beheim B, Minocher R, Gutierrez M, Thomas GS, Gatz M, Stieglitz J, Finch CE, Kaplan H, Gurven M. Apolipoprotein-ε 4 is associated with higher fecundity in a natural fertility population. Sci Adv. 2023; 9(32): eade9797.
35. van Exel E, Koopman JJE, Bodegom D van, Meij JJ, Knijff P de, Ziem JB, Finch CE, Westendorp RGJ. Effect of APOE ε4 allele on survival and fertility in an adverse environment. PLoS One. 2017; 12(7): e0179497.
36. Collazo MS, Porrata-Doria T, Flores I, Acevedo SF. Apolipoprotein E polymorphisms and spontaneous pregnancy loss in patients with endometriosis. Mol Hum Reprod. 2012; 18(7): 372-377.
37. Corbo RM, Scacchi R, Cresta M. Differential reproductive efficiency associated with common apolipoprotein e alle-

les in postreproductive-aged subjects. Fertil Steril. 2004; 81(1): 104-107.
38. Paoli D, Zedda S, Grassetti D, Gallo M, Corbo RM, Lombardo F, Lenzi A, Gandini L. Are apolipoprotein E alleles correlated with semen quality? Int J Androl. 2012; 35(5): 714-719.
39. Toniutto P, Fattovich G, Fabris C, Minisini R, Burlone M, Pravadelli C, Peraro L, Falleti E, Caldera F, Bitetto D, Pirisi M. Genetic polymorphism at the apolipoprotein E locus affects the outcome of chronic hepatitis B. J Med Virol. 2010; 82(2): 224-331.
40. Trumble BC, Stieglitz J, Blackwell AD, Allayee H, Beheim B, Finch CE, Gurven M, Kaplan H. Apolipoprotein E4 is associated with improved cognitive function in Amazonian forager-horticulturalists with a high parasite burden. FASEB J. 2017; 31(4): 1508.
41. Oria RB, Patrick PD, Oriá MOB, Lorntz B, Thompson MR, Azevedo OGR, Lobo RNB, Pinkerton RF, Guerrant RL, Lima AAM. ApoE polymorphisms and diarrheal outcomes in Brazilian shanty town children. Brazil J Med Biol Res. 2010; 43: 249-256.
42. Marchant NL, King SL, Tabet N, Rusted JM. Positive effects of cholinergic stimulation favor young APOE ε4 carriers. Neuropsychopharmacology. 2010; 35(5): 1090-1096.

Address for correspondence

Paula B. Bartecka
Department of Environmental Health
Institute of Public Health
Faculty of Health Sciences
Jagiellonian University
Medical College
Krakow, Poland
E-mail: paula.bartecka@doctoral.uj.edu.pl

Received: 18.12.2024
Accepted: 28.08.2025
Online publication: 3.03.2026