Retrospective Study

Apolipoprotein E variants correlate with the clinical presentation of paediatric inflammatory bowel disease: A cross-sectional study

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Abstract

BACKGROUND

It has been suggested that apolipoprotein E (APOE) polymorphisms are associated with the risk of developing inflammatory bowel disease (IBD) and the early age of disease onset. However, there are no reports regarding the relationship with clinical characteristics and disease severity.
Apolipoprotein E polymorphisms are associated with the risk of developing IBD and the early age of disease onset.

METHODS
In total, 406 patients aged 3-18 with IBD (192 had ulcerative colitis and 214 had Crohn’s disease) were genotyped using the TaqMan hydrolysis probe assay. Clinical expression was described at diagnosis and the worst flare by disease activity scales, albumin and C-reactive protein levels, localisation and behaviour (Paris classification). Systemic steroid intake with the total number of courses, immunosuppressive, biological, and surgical treatment with the time and age of the first intervention were determined. The total number of exacerbation-caused hospitalisations, the number of days spent in hospital due to exacerbation, the number of relapses, and severe relapses were also estimated.

RESULTS
Ulcerative colitis patients with the APOEε4 allele had lower C-reactive protein values at diagnosis ($P = 0.0435$) and the worst flare ($P = 0.0013$) compared to patients with the APOEε2 allele and genotype APOEε3/ε3. Crohn’s disease patients with the APOEε2 allele scored lower on the Pediatric Crohn’s Disease Activity Index at diagnosis ($P = 0.0204$). IBD patients with APOEε2 allele spent fewer days in the hospital due to relapse ($P = 0.0440$).

CONCLUSION
Apolipoprotein E polymorphisms are associated with the risk of developing IBD and the clinical expression of IBD. However, the clinical relevance of the differences identified is rather modest.

Key Words: Apolipoprotein E polymorphism; Crohn’s disease; Ulcerative colitis; Immunosuppression; Surgery; Disease severity

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Core Tip: Apolipoprotein E polymorphisms are associated with the risk of developing inflammatory bowel disease and seem to be associated with the disease expression and treatment. However, the clinical relevance of the differences is relatively modest.

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INTRODUCTION
Heritability and disease risk can only be partly explained by genetic factors alone. Inflammatory bowel disease (IBD) has a strong genetic makeup. To date, 240 risk loci have been associated with the disease. Several genetic variations are linked to specific IBD phenotypes. For instance, NOD2, IRGM, ATG16L1, and NCF4/NCF2 are related to segmental, structuring, or early-onset disease. Genetic testing for these and other variants may prove useful in predicting the disease course for future clinical use.

One of the well-known genetic determinants of some diseases other than IBD is apolipoprotein E (APOE), most commonly known for its role in Alzheimer’s disease. Although first recognised for its role in lipoprotein metabolism, APOE is involved in several biological processes not directly related to lipid transport function. Importantly, APOE is a key player in immunoregulation and...
MATERIALS AND METHODS

Patients

Patients recruited to the study belonged to the Polish Paediatric Crohn’s and Colitis cohort and involved 406 paediatric IBD patients: 214 with Crohn’s disease (CD; 86 females, 128 males) and 192 with ulcerative colitis (UC; 87 females, 105 males) (Table 1). Patients were recruited in the course of hospital treatment or during scheduled visits at outpatient clinics (Department of Pediatric Gastroenterology and Metabolic Diseases, Poznań University of Medical Sciences; The Department of Gastroenterology, Hepatology, Feeding Disorders and Paediatrics; The Children’s Memorial Health Institute, Warsaw; Department of Pediatric Gastroenterology and Nutrition, Medical University of Warsaw; Department and Clinic of Pediatrics, Gastroenterology and Nutrition, Wroclaw Medical University; Department of Pediatrics, Faculty of Medical Sciences in Zabrze, Medical University of Silesia, Katowice; Department of Pediatrics, Faculty of Medical Sciences, Medical University of Silesia in Katowice and Department of Pediatric Endoscopy and Gastrointestinal Function Testing, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń, Bydgoszcz, Poland). The diagnosis of IBD was confirmed by experienced gastroenterologists using standard diagnostic criteria[36,37]. The inclusion criteria were a diagnosis of CD or UC and aged 3-18. Patients in life-threatening, severe general condition were excluded from the study. The study obtained the approval of the Bioethical Committee at Poznań University of Medical Sciences (960/15 with the associated amendments).

Disease severity evaluation

Disease activity was assessed using appropriate scales at diagnosis and the worst flare [Pediatric Ulcerative Colitis Activity Index and Pediatric Crohn’s Disease Activity Index (PCDAI)][38], which was defined by the highest Pediatric Ulcerative Colitis Activity Index and PCDAI scales in their medical history. Albumin (g/dL) and C-reactive protein (CRP; mg/L) concentrations at diagnosis and the worst flare were obtained from medical records (CRP reference range 0-5 mg/L). The treatment domain included data regarding systemic steroid intake with the total number of courses, immunosuppressive treatment with the time and age of the first intake, biological therapy with time and age of first admission, and operative treatment with time and age of first surgery. The localisation and behaviour of the disease were defined by the Paris Classification at the diagnosis and worst flare[39]. Most CD patients presented with an ileocolonic location and nonstricturing behaviour of the disease (Supplementary Table 1), while most UC patients presented with pancolitis and were never severe (S0: > 65 on the Pediatric Ulcerative Colitis Activity Index scale;
### Table 1 Demographic and clinical expression of Crohn’s disease and ulcerative colitis

| Variables                          | Median (IQR) or n (%) | Crohn’s disease | Ulcerative colitis | P value |
|------------------------------------|-----------------------|----------------|-------------------|---------|
| Age in yr                          |                       |                |                   |         |
| At inclusion                       | 397                   | 15.18 (13.32-17.05) | 15.11 (11.70-16.75) | 0.044   |
| At diagnosis                       | 404                   | 12.58 (10.02-14.32) | 12.14 (7.89-14.94)  | 0.365   |
| At worst flare                     | 355                   | 13.63 (11.54-15.85) | 13.76 (10.13-15.84) | 0.244   |
| Duration of the disease (yr)       | 390                   | 2.23 (0.82-4.25)  | 1.88 (0.36-3.77)   | 0.239   |
| Female                             | 173                   | 86 (40.2)       | 87 (45.3)          | 0.297   |
| Nutritional status                 |                       |                |                   |         |
| Weight at diagnosis in kg          | 387                   | 38.0 (27.0-49.8) | 40.0 (27.8-53.9)   | 0.490   |
| Weight at diagnosis, z score       | 383                   | -0.82 [-1.39,-0.04] | -0.51 [-1.12,-0.22] | 0.003   |
| Height at diagnosis in cm          | 382                   | 151.0 (137.0-164.5) | 152.0 (130.5-168.5) | 0.718   |
| Height at diagnosis, z score       | 378                   | -0.37 [-1.29,-0.47] | 0.06 [-0.67,-0.81]  | 0.001   |
| Body mass index at diagnosis in kg/m² | 382       | 16.6 (14.5-18.4) | 17.4 (15.5-19.3)   | 0.019   |
| Body mass index at diagnosis, z score | 378       | -0.79 [-1.47,-0.04] | -0.49 [-1.00,-0.16] | 0.006   |
| Albumin level at diagnosis in g/dL  | 345                   | 3.90 (3.51-4.25) | 4.10 (3.70-4.40)   | < 0.003 |
| Parameter of inflammation          |                       |                |                   |         |
| CRP at diagnosis in mg/L¹          | 386                   | 12.94 (2.10-29.25) | 2.24 (0.50-10.80)  | < 0.001 |
| CRP at worst flare in mg/L         | 347                   | 13.95 (3.03-32.43) | 2.70 (0.63-13.44)  | < 0.001 |
| Disease activity scales            |                       |                |                   |         |
| PCDAI/PUCAI at diagnosis           | 190/166               | 32 (23-48)      | 45 (28-60)         |         |
| PCDAI/PUCAI at worst flare         | 170/155               | 40 (30-53)      | 50 (35-65)         |         |
| Treatment                          |                       |                |                   |         |
| Systemic steroids²                 | 406                   | 115 (53.7)      | 138 (71.9)         | < 0.001 |
| Immunosuppressive treatment³       | 405                   | 168 (78.5)      | 112 (58.6)         | < 0.001 |
| Biological therapy⁴                | 406                   | 107 (50.0)      | 49 (25.5)          | < 0.001 |
| Operative treatment⁵               | 406                   | 29 (13.6)       | 4 (2.1)            | < 0.001 |

¹ C-reactive protein reference range 0-5 mg/L.
² Systemic steroid therapy included: methylprednisolone, prednisone, hydrocortisone.
³ Immunosuppressive and anti-inflammatory agents included: Azathioprine, methotrexate, mercaptopurine, cyclosporine, mycophenolate mofetil, tacrolimus, sulfasalazine.
⁴ Biological agents included: infliximab, adalimumab, golimumab, vedolizumab.
⁵ Only surgery related to inflammatory bowel disease-specific problems (e.g., colectomy, resection, fistula, perforation, abscess) was included. CRP: C-reactive protein; IBD: Inflammatory bowel disease; IQR: Interquartile range; PCDAI: Pediatric Crohn’s Disease Activity Index; PUCAI: Pediatric Ulcerative Colitis Activity Index.

### Supplementary Table 2

Based on medical records, the total number of exacerbation hospitalisations, the number of days spent in hospital due to exacerbation, the number of relapses, and severe relapses from diagnosis were estimated and calculated per year of the disease duration. The associated extraintestinal symptoms and concomitant diseases were collected from the medical history.

### Genotyping

DNA was isolated from whole blood using the Blood Mini (A and A Biotechnology). A hydrolysis probe assay (TaqMan assay) was used with the following probes, C_904973_10 and C_3084793_20, to genotype patients (Life Technologies Corp. Carlsbad. California, United States). The genotyping was performed on the CFX-96 thermocycler system with allele discrimination plots provided by CFX Manager Software (Bio-Rad, Hercules, CA, United States).
**Statistical analysis**

Differences in categorical variables were compared with two-tailed Fisher’s exact test. Differences in continuous variables were evaluated by the Mann Whitney U test and Kruskal-Wallis test. Post hoc comparisons were performed with Dunn’s test, and the significance level for the time-to-treatment analysis was evaluated by Gehan’s test. The explanatory factor analysis was used to analyse the underlying factors in the questionnaire. The significance level was set at \( P < 0.05 \), and statistical analyses were performed using Statistica 13.1 software (StatSoft Inc, Tulsa, OK, United States), JASP 0.10.2 (University of Amsterdam, Amsterdam, the Netherlands), and G*Power (Dusseldorf University, Germany). Comparisons between groups with less than ten patients were not included.

**RESULTS**

**Genotyping**

The most prevalent genotype in UC and CD was APOEε3ε3 (Table 2). No differences in the distribution of alleles and genotypes between UC and CD were documented. The distribution of the APOE genotypes was compared to previous studies in the Polish population (Supplementary Table 3). Pooling available data\(^{[40-42]} \) to obtain a similar sample size \((n = 425)\) showed a significantly lower frequency of APOEε3ε3 genotype in IBD patients compared to controls \((62.3\% \text{ vs } 71.5\%); \ P = 0.0051; \text{ odds ratio } = 0.66; 95\% \text{ confidence interval: 0.49-0.88}) and simultaneously higher frequency of APOEε4/ε4 genotype \((21.7\% \text{ vs } 15.1\%); \ P = 0.0153; \text{ odds ratio } = 1.56; 95\% \text{ confidence interval: 1.09-2.23}) with no difference in other genotypes or for the APOEε3 allele \((P = 0.8625)\). However, in the study of Bojar et al.\(^{[43]} \) (postmenopausal women; \(n = 402\)), the distribution of APOEε3ε3 genotype was similar to the present study \((62.9\% \text{ vs } 62.3\%; \ P = 0.8555; \text{ odds ratio } = 0.97; 95\% \text{ confidence interval: 0.73-1.30})

UC patients with APOEε3ε3 had higher CRP values, and the APOEε2ε3 genotype were predisposed to left-sided colitis (E2) at diagnosis (Table 2). Concomitant diseases in CD patients occurred at different frequencies in major APOE genotypes, and children with APOEε2ε3 genotype had significantly lower PCDAI scores at diagnosis than patients with the remaining genotypes (Table 4). UC patients with the APOEε4 allele had significantly lower CRP levels than the patients with APOEε3ε3 genotype and APOEε2-positive, both at diagnosis and at the worst flare (Table 5). There were also differences in age at first biological treatment. Additionally, APOEε2-positive patients with IBD spent significantly fewer days in the hospital due to relapse per year of disease duration than APOEε4-positive patients and with the APOEε3ε3 genotype (Table 5). Patients with CD and APOEε3ε3 genotype had lower values of standardised body height at diagnosis (Table 5). No difference was observed in the frequency of systemic steroids, immunosuppressive, and biological treatment between APOE genotypes in UC and CD patients. Supplementary Table 4 shows the results for the whole group of IBD patients.

**DISCUSSION**

The present study investigated the relationship between APOE genotype and disease severity in IBD, suggesting that the APOE genotype might be associated with some indices of disease course such as CRP and albumin levels at the worst flare, age at surgery and numbers of hospitalisation days. UC patients with the APOEε4 allele had the lowest values of CRP, both at diagnosis and the worst flare. The median age at first biological therapy in UC was lowest in patients with the APOEε4 allele, whereas left-sided colitis was more frequent among patients with the APOEε2 allele. In CD patients, the APOEε4 allele was associated with higher albumin at worst flare and higher standardised body height at diagnosis. Moreover, patients with the APOEε2 allele scored lower on the PCDAI. This study is the largest to show the genetic distribution of APOE polymorphisms in IBD to date.

APOE is known to be associated with inflammation indicators\(^{[31]} \). The findings of the present study confirm this relationship as the CRP levels differed between APOE genotypes. Patients with the APOEε4 allele and APOEε3ε4 genotype had lower CRP values at diagnosis and the worst flare, while patients with the APOEε3ε3 genotype had higher levels of CRP at the worst flare. These results are similar to those obtained in healthy adults, which showed that subjects with APOEε3ε3 had the highest plasma
levels of CRP and individuals with \( APOE\epsilon 4\epsilon 4 \) and \( APOE\epsilon 2\epsilon 4 \) had the lowest levels\(^{13}\). A similar pattern has also been observed in other diseases such as coronary artery disease\(^{44-46}\). März et al\(^{47}\) proved that in coronary artery disease, both white cell count and fibrinogen were not related to the \( APOE \) genotype, suggesting that the underlying mechanism is not associated with inflammation\(^{48}\) but rather to the mevalonate/cholesterol synthetic pathway, which may be downregulated in patients with \( APOE\epsilon 4 \) in response to altered lipoprotein metabolism and hepatic uptake\(^{49}\). In another study, the \( APOE\epsilon 4 \) allele was also associated with lower CRP but not white blood cell count\(^{45}\). Further mechanistic studies are needed to explain the link.

Our study is the first to report that in CD patients, the \( APOE\epsilon 4 \) allele is associated with higher median levels of albumins at the worst flare. Albumin level is negatively correlated with the extent of the inflammatory response, which is caused by a hypercatabolic state and a decrease of albumin synthesis in the liver\(^{50}\). Tumour necrosis factor-\( \alpha \) inhibits albumin expression causing hypoalbuminemia\(^{51}\), a state associated with IBD activity, unresponsiveness to treatment, and increased risk of colectomy in UC. Patients with hypoalbuminemia had a higher likelihood of having more than two courses of corticosteroids, thiopurine, or anti-tumour necrosis factor treatment\(^{52}\). In CD, albumin levels were reported as a marker of postoperative complications\(^{50}\) and active clinical disease\(^{53}\). Low albumin level together with high CRP may correlate with an increased inflammatory response\(^{54}\). In the study of Sayar et al\(^{55}\), the area under the curve values for severe UC were 0.883 for albumin levels (cut-off 3.6 g/dL) and 0.941 for CRP/albumin ratio (cut-off 0.6)\(^{55}\). Given these data, the results of our study may suggest that the \( APOE\epsilon 4 \) allele is associated with a milder disease course of CD. The association of the \( APOE\epsilon 2 \) allele with lower PCDAI scores and fewer days of hospitalisation due to relapse might suggest a protective role of this allele on disease severity. However, this relationship is more complicated as we found that the \( APOE\epsilon 2 \) allele is also associated with a younger age at first surgery. This finding should be verified, preferably in adults patients with a longer disease course and higher surgery rates.

The biology of \( APOE \) in IBD has not been fully elucidated, but recent studies have shown that the \( APOE \) transcript is overexpressed in paediatric IBD patients\(^{56}\). Studies in colonic epithelial cells in a mouse model showed that the apoE-mimetic peptide (COG112) inhibited the inflammatory response to \( Citrobacter rodentium \)\(^{57}\), a bacterium known to cause colitis in mice\(^{58}\). The authors suggested this occurred by preventing the activation of nuclear factor \( \kappa B \)\(^{58}\). Therefore, further mechanistic studies of \( APOE \) action are warranted.

A previous study on \( APOE \) in IBD in a group with a different genetic background (Saudi Arabia) did not focus on disease severity. Therefore, any comparisons are difficult\(^{59}\). In that study, the \( APOE\epsilon 4 \) allele was associated with the risk of developing IBD and early onset, whereas our study did not identify significant differences between \( APOE \) genotypes and age at diagnosis. The frequencies of \( APOE\epsilon 3\epsilon 3 \) genotype were lower in IBD patients in comparison to controls, which is consistent with the above-mentioned report\(^{60}\).

The present study involved a large multicentre paediatric cohort, including a comprehensive clinical description, which allowed a detailed genotype-phenotype analysis. However, defining the global severity of the disease course remains challenging, especially in diseases with such a differentiated clinical presentation. The major limitation of this study is related to the retrospective character of the data collection regarding diagnosis and the worst flare. Need for surgery, which is one of

### Table 2 Apolipoprotein E genotype and allele distribution compared between ulcerative colitis and Crohn’s disease

| Genotype/allele | UC, \( n = 192 \) | CD, \( n = 214 \) | \( P \) value, two-tailed Fisher exact | Odds ratio (95%CI) |
|-----------------|-----------------|-----------------|-------------------------------------|-------------------|
| \( \epsilon 3/\epsilon 3 \) | 118             | 135             | 0.7590                             | 0.93 (0.62-1.40)   |
| \( \epsilon 3/\epsilon 4 \) | 47              | 41              | 0.2278                             | 1.37 (0.85-2.20)   |
| \( \epsilon 2/\epsilon 3 \) | 18              | 35              | 0.0397                             | 0.53 (0.29-0.97)   |
| \( \epsilon 3^+ \) | 183             | 211             | 0.0757                             | 0.29 (0.08-1.08)   |
| \( \epsilon 4^+ \) | 54              | 43              | 0.0062                             | 1.56 (0.98-2.46)   |
| \( \epsilon 2^+ \) | 24              | 37              | 0.2108                             | 0.68 (0.39-1.19)   |

CD: Crohn’s disease; CI: Confidence interval; UC: Ulcerative colitis.
### Table 3 Clinical characteristics in patients with ulcerative colitis depending on major apolipoprotein E genotypes

| Variables median (IQR) or n (%) | n  | ε2/ε3 | ε3/ε3 | ε3/ε4 | P value |
|----------------------------------|----|-------|-------|-------|---------|
| **Age in yr**                    |    |       |       |       |         |
| At inclusion                     | 184| 15.7 (12.5-16.9) | 15.3 (11.9-16.9) | 14.3 (11.5-16.3) | 0.2464 |
| At diagnosis                     | 191| 11.4 (7.9-14.6) | 12.4 (7.9-15.0) | 12.4 (8.2-14.9)  | 0.9070 |
| At worst flare                   | 171| 14.6 (9.9-16.4) | 13.7 (10.4-16.0) | 13.7 (10.0-15.7) | 0.7255 |
| Duration of the disease in yr    | 179| 3.0 (1.4-6.2) | 1.9 (0.4-3.5) | 1.2 (0.0-3.5) | 0.0868 |
| **Nutritional status**           |    |       |       |       |         |
| Weight at diagnosis in kg        | 180| 40.0 (28.8-59.5) | 39.0 (27.8-54.0) | 43.8 (29.5-53.4) | 0.9704 |
| Weight at diagnosis, z score     | 179| -0.20 [-0.86]-0.43 | -0.5 [-1.1]-0.1 | -0.24 [-0.95]-0.63 | 0.3037 |
| Height at diagnosis in cm        | 175| 146.5 (129.0-169.0) | 153.0 (131.0-168.5) | 156.0 (131.5-169.0) | 0.9175 |
| Height at diagnosis, z score     | 174| 0.12 [-0.62]-0.75 | 0.09 [-0.69]-0.79 | 0.22 [-0.44]-1.06 | 0.5823 |
| Body mass index at diagnosis in kg/m² | 175| 17.61 (16.02-19.74) | 17.0 (15.4-19.1) | 17.9 (15.4-20.3) | 0.5121 |
| Body mass index at diagnosis, z score | 174| -0.11 [-0.70]-0.29 | -0.56 [-0.99]-0.11 | -0.30 [-1.12]-0.56 | 0.2293 |
| Weight at worst flare in kg      | 164| 46.1 (31.6-62.0) | 46.2 (31.9-55.6) | 50.0 (28.0-61.0) | 0.9600 |
| Weight at worst flare, z score   | 161| -0.33 [-1.00]-0.56 | -0.58 [-0.95]-0.16 | -0.52 [-0.90]-0.40 | 0.6599 |
| Height at worst flare in cm      | 162| 162.5 (138.5-173.5) | 159.0 (140.9-171.0) | 160.0 (135.0-172.0) | 0.9688 |
| Height at worst flare, z score   | 161| 0.11 [-0.72]-1.16 | -0.09 [-0.62]-0.78 | 0.06 [-0.62]-0.89 | 0.8376 |
| Body mass index at worst flare in kg/m² | 160| 18.20 (16.47-19.74) | 17.36 (15.75-19.71) | 17.93 (15.89-20.96) | 0.6013 |
| Body mass index at worst flare, z score | 159| -0.22 [-1.16]-0.14 | -0.68 [-1.10]-0.16 | -0.43 [-1.12]-0.63 | 0.6789 |
| **Albumin level**                |    |       |       |       |         |
| At diagnosis in g/dL             | 159| 4.2 (4.0-4.6) | 4.1 (3.7-4.4) | 4.1 (3.6-4.4) | 0.2569 |
| At worst flare in g/ dL          | 148| 4.3 (4.0-4.7) | 4.1 (3.6-4.4) | 4.2 (4.0-4.4) | 0.3488 |
| **Parameter of inflammation**    |    |       |       |       |         |
| CRP at diagnosis in mg/L         | 178| 3.8 (0.7-6.6) | 2.5 (0.7-12.2) | 1.1 (0.2-8.0) | 0.0515 |
| CRP at worst flare in mg/L       | 162| 2.1 (1.1-23.3) | 3.7 (1.1-19.0) | 0.8 (0.3-2.9) | 0.0012 |
| **Disease activity scales**      |    |       |       |       |         |
| PUCAI at diagnosis               | 166| 40 (18-55) | 45 (30-60) | 50 (25-60) | 0.5144 |
| PUCAI at worst flare             | 155| 48 (20-65) | 55 (40-65) | 50 (30-65) | 0.3766 |
| **Disease localisation and behaviour** | | | | | |
| E1 at diagnosis                   | 19/192| 3 (16.7) | 10 (8.5) | 6 (12.8) | 0.4694 |
| E2 at diagnosis                   | 33/192| 8 (44.4) | 16 (13.6) | 9 (19.1) | 0.0063 |
| E3 at diagnosis                   | 28/192| 1 (5.6) | 18 (15.3) | 9 (19.1) | 0.3953 |
| E4 at diagnosis                   | 83/192| 5 (27.8) | 60 (50.8) | 18 (38.3) | 0.0990 |
| S0 at diagnosis                   | 110/192| 13 (72.2) | 69 (58.5) | 28 (59.6) | 0.5383 |
| S1 at diagnosis                   | 37/192| 3 (16.7) | 23 (19.5) | 11 (23.4) | 0.7885 |
| E1 at worst flare                 | 9/192| 1 (5.6) | 4 (3.4) | 4 (8.5) | 0.3863 |
| E2 at worst flare                 | 27/192| 3 (16.7) | 18 (15.3) | 6 (12.8) | 0.8943 |
| E3 at worst flare                 | 23/192| 3 (16.7) | 16 (13.6) | 4 (8.5) | 0.5814 |
| E4 at worst flare                 | 75/192| 7 (38.9) | 50 (42.4) | 18 (38.3) | 0.8750 |
| S0 at worst flare                 | 83/192| 9 (50.0) | 52 (44.1) | 22 (46.8) | 0.8713 |
| S1 at worst flare                 | 49/192| 5 (27.8) | 34 (28.8) | 10 (21.3) | 0.6114 |

**Treatment**
Systemic steroids 1 | 192 | 11 (61.1) | 92 (78.0) | 29 (61.7) | 0.0599
Number of courses of steroid treatment | 190 | 1 (0-2) | 1 (1-2) | 1 (0-2) | 0.0672
Immunosuppressive treatment 2 | 191 | 9 (50.0) | 74 (63.2) | 25 (53.2) | 0.3451
Number of immunosuppressants | 191 | 1 (0-1) | 1 (0-1) | 1 (0-1) | 0.2572
Time-to-first dose of immunosuppressive treatment in mo | 109 | 3.0 (2.0-17.0) | 4.0 (0.0-10.0) | 2.8 (0.0-8.0) | 0.4356
Age at first intake of immunosuppressive treatment in yr | 109 | 14.7 (10.4-16.1) | 12.3 (7.8-14.1) | 11.0 (7.3-15.5) | 0.2381
Biological therapy 3 | 192 | 4 (22.2) | 29 (24.8) | 13 (27.7) | 0.8781
Total number of biologics | 192 | 0 (0-0) | 0 (0-0) | 0 (0-1) | 0.8164
Time-to-first dose of biological treatment in mo | 48 | 19.9 (12.8-50.3) | 16.4 (9.1-28.1) | 10.8 (4.0-27.7) | 0.3152
Age at first biological treatment | 49 | 15.7 (14.7-15.9) | 11.5 (7.9-14.6) | 10.7 (4.5-15.5) | 0.0852
Operative treatment 4 | 192 | 0 (0.0) | 3 (2.5) | 1 (2.1) | 0.7893
Age at first surgery in yr | 6 | 7.7 (5.9-9.6) | 14.8 (6.8-17.1) | 13.0 (10.4-15.6) | 0.2969
Time-to-first surgery in mo | 4 | 16.7 (5.0-28.7) | 19.1 (9.0-37.4) | 1.0000 | 
Hospitalisations, if duration ≥ 1 yr
Hospitalisations for relapse, per 1 yr of the disease | 98 | 0.3 (0.3-0.8) | 0.6 (0.3-1.6) | 0.9 (0.5-1.3) | 0.2518
Days of hospitalisation for relapse, per 1 yr of the disease | 98 | 2.5 (0.6-4.5) | 4.8 (1.8-9.3) | 7.3 (3.8-8.7) | 0.1362
Relapses from diagnosis, per 1 yr of the disease | 98 | 0.3 (0.1-0.8) | 0.6 (0.3-1.2) | 0.8 (0.3-1.3) | 0.3491
Severe relapses from diagnosis, per 1 yr of the disease | 100 | 0.0 (0.0-0.3) | 0.1 (0.0-0.6) | 0.2 (0.0-0.4) | 0.7150
Concomitant diseases 5 | 192 | 9 (50.0) | 41 (34.7) | 15 (31.9) | 0.3781
Extraintestinal manifestations | 192 | 3 (16.7) | 23 (19.5) | 10 (21.3) | 0.9131

1Systemic steroid therapy included: methylprednisolone, prednisone, hydrocortisone.
2Immunosuppressive and anti-inflammatory agents included: azathioprine, methotrexate, mercaptopurine, cyclosporine, mycophenolate mofetil, tacrolimus, sulfasalazine.
3Biological agents included: Infliximab, adalimumab, golimumab, vedolizumab.
4Only surgery related to inflammatory bowel disease-specific problems (e.g., colectomy, resection, fistula, perforation, abscess) was included.
5e.g., celiac disease, bronchial asthma, obesity, gastroesophageal reflux disease, epilepsy, hypothyroidism. CRP: C-reactive protein; IBD: Inflammatory bowel disease; IQR: Interquartile range; PUCAI: Pediatric Ulcerative Colitis Activity Index.

the most crucial measures of disease course, would require longer follow-up in order to describe disease severity. Although we did not include a control group, APOE polymorphisms in healthy subjects have been studied in the Polish population[^40^-^42],[^56] which allowed us to estimate whether there was any frequency distribution difference.

**CONCLUSION**

APOE polymorphisms are associated with the risk of developing IBD and seem to be associated with the clinical expression of the disease and applied treatment (with inflammatory markers and nutritional status, disease activity and localisation, hospitalisations). However, the clinical relevance of the differences identified is relatively modest.
### Table 4 Clinical characteristics in patients with Crohn's disease depending on major apolipoprotein E genotypes

| Variables median (IQR) or n (%) | ε2/ε3 | ε3/ε3 | ε3/ε4 | P value |
|---------------------------------|-------|-------|-------|---------|
| Age in yr | | | | |
| At inclusion | 213 | 15.5 (13.2-16.8) | 15.2 (13.3-17.2) | 15.2 (13.4-16.2) | 0.8055 |
| At diagnosis | 213 | 11.8 (10.1-14.6) | 12.7 (9.9-14.5) | 12.6 (10.0-13.9) | 0.8796 |
| At worst flare | 184 | 13.5 (11.6-15.2) | 13.6 (11.3-15.8) | 14.3 (12.8-15.9) | 0.5121 |
| Duration of the disease in yr | 211 | 2.8 (0.6-5.4) | 2.0 (0.8-4.0) | 2.3 (0.8-4.1) | 0.7843 |
| Nutritional status | | | | |
| Weight at diagnosis in kg | 207 | 38.3 (27.6-48.0) | 37.3 (25.3-49.5) | 38.4 (28.3-57.6) | 0.5360 |
| Weight at diagnosis, z score | 204 | -0.53 [-1.02,-0.02] | -0.91 [-1.46,-0.12] | -0.73 [-1.34,-0.38] | 0.2062 |
| Height at diagnosis in cm | 207 | 148.3 (141.0-164.0) | 151.5 (134.0-164.0) | 151.3 (141.0-170.0) | 0.6757 |
| Height at diagnosis, z score | 204 | -0.17 [-0.85,-0.51] | -0.47 [-1.43,-0.32] | 0.05 [-1.10,0.96] | 0.0617 |
| Body mass index at diagnosis in kg/m² | 207 | 16.73 (14.28-18.42) | 16.59 (14.41-18.22) | 16.40 (14.78-20.78) | 0.8397 |
| Body mass index at diagnosis, z score | 204 | -0.72 [-1.33,-0.16] | -0.79 [-1.53,-0.08] | -0.88 [-1.29,-0.49] | 0.7878 |
| Weight at worst flare in kg | 181 | 41.8 (34.8-50.3) | 41.9 (29.6-52.6) | 46.8 (36.2-58.9) | 0.2294 |
| Weight at worst flare, z score | 178 | -0.67 [-1.16,-0.10] | -1.14 [-1.64,-0.25] | -0.60 [-1.22,-0.02] | 0.0756 |
| Height at worst flare in cm | 183 | 153.0 (148.5-166.0) | 158.0 (141.5-167.0) | 162.0 (148.5-171.5) | 0.3088 |
| Height at worst flare, z score | 180 | -0.15 [-1.09,-0.61] | -0.52 [-1.41,-0.21] | -0.24 [-1.10,-0.43] | 0.1234 |
| Body mass index at worst flare in kg/m² | 181 | 17.29 (15.33-18.60) | 16.89 (14.87-19.03) | 17.09 (15.56-21.74) | 0.4172 |
| Body mass index at worst flare, z score | 178 | -0.87 [-1.38,-0.01] | -1.03 [-1.55,-0.19] | -0.53 [-1.46,-0.49] | 0.3913 |
| Albumin level | | | | |
| At diagnosis in g/dL | 186 | 3.9 (3.7-4.3) | 3.8 (3.4-4.4) | 3.9 (3.4-4.3) | 0.5796 |
| At worst flare in g/dL | 179 | 3.9 (3.8-4.3) | 3.9 (3.4-4.1) | 3.9 (3.6-4.3) | 0.0611 |
| Parameter of inflammation | | | | |
| CRP at diagnosis in mg/L | 208 | 13.8 (0.8-40.0) | 13.0 (2.1-29.6) | 12.0 (3.4-24.9) | 0.8818 |
| CRP at worst flare in mg/L | 185 | 18.3 (1.7-31.5) | 14.0 (3.3-38.5) | 13.6 (3.2-26.8) | 0.7672 |
| Disease activity scales | | | | |
| PCDAI at diagnosis | 190 | 25 (20-35) | 35 (25-50) | 30 (25-43) | 0.0282 |
| PCDAI at worst flare | 170 | 35 (23-50) | 45 (30-53) | 38 (30-53) | 0.1898 |
| Disease localisation and behaviour | | | | |
| L1 at diagnosis | 53/213 | 9 (25.7) | 35 (26.1) | 8 (19.5) | 0.6852 |
| L2 at diagnosis | 40/213 | 9 (25.7) | 19 (42.4) | 11 (28.6) | 0.0935 |
| L3 at diagnosis | 99/213 | 13 (37.1) | 65 (50.0) | 16 (39.0) | 0.2507 |
| L4 at diagnosis | 23/213 | 4 (11.4) | 14 (10.4) | 4 (9.8) | 0.9721 |
| L4b at diagnosis | 8/213 | 1 (2.9) | 7 (5.2) | 0 (0.0) | 0.2950 |
| B1 at diagnosis | 146/213 | 24 (68.6) | 89 (66.4) | 33 (80.5) | 0.2287 |
| B2 at diagnosis | 15/213 | 3 (8.6) | 11 (8.2) | 1 (2.4) | 0.4263 |
| B3 at diagnosis | 19/213 | 3 (8.6) | 15 (11.2) | 1 (2.4) | 0.2304 |
| B2B3 at diagnosis | 4/213 | 1 (2.9) | 3 (2.2) | 0 (0.0) | 0.5927 |
| G0 at diagnosis | 145/213 | 24 (68.6) | 92 (68.7) | 29 (70.7) | 0.9667 |
| G1 at diagnosis | 33/213 | 3 (8.6) | 24 (17.9) | 6 (14.6) | 0.3921 |
| F at diagnosis | 19/213 | 0 (0.0) | 16 (11.9) | 3 (7.3) | 0.0824 |
| L1 at worst flare | 40/213 | 5 (14.3) | 26 (19.4) | 9 (22.0) | 0.6873 |
L2 at worst flare  & 27/213 & 7 (20.0) & 14 (10.4) & 6 (14.6) & 0.3007  
L3 at worst flare  & 92/213 & 10 (28.6) & 66 (49.3) & 16 (39.0) & 0.0708  
L4a at worst flare  & 18/213 & 3 (8.6) & 12 (9.0) & 3 (7.3) & 0.9477  
L4b at worst flare  & 9/213 & 1 (2.9) & 5 (3.7) & 3 (7.3) & 0.5507  
B1 at worst flare  & 114/213 & 17 (48.6) & 74 (55.2) & 23 (56.1) & 0.7549  
B2 at worst flare  & 19/213 & 2 (5.7) & 12 (9.0) & 5 (12.2) & 0.6165  
B3 at worst flare  & 21/213 & 1 (2.9) & 16 (11.9) & 4 (9.8) & 0.2798  
B2B3 at worst flare  & 5/213 & 1 (2.9) & 4 (9.8) & 0 (0.0) & 0.5367  
G0 at worst flare  & 121/213 & 18 (51.4) & 79 (59.0) & 24 (58.5) & 0.7184  
G1 at worst flare  & 34/213 & 2 (5.7) & 24 (17.9) & 8 (19.5) & 0.1776  
P at worst flare  & 20/213 & 0 (0.0) & 17 (12.7) & 3 (7.3) & 0.0649  

**Treatment**

| Systemic steroids¹  | 214 | 19 (34.3) | 73 (54.1) | 21 (51.2) | 0.9455  
| Number of courses of steroid treatment  | 212 | 1 (0.2) | 1 (0.2) | 1 (0.1) | 0.5535  
| Immunosuppressive treatment²  | 214 | 25 (71.4) | 110 (81.5) | 31 (75.6) | 0.3756  
| Number of immunosuppressants  | 214 | 1 (0.1) | 1 (1.1) | 1 (1.1) | 0.2632  
| Time-to-first dose of immunosuppressive treatment in mo  | 166 | 1.3 (0.0-13.0) | 2.0 (0.0-7.0) | 1.0 (0.0-9.0) | 0.8866  
| Age at first intake of immunosuppressive treatment in yr  | 166 | 12.9 (10.3-13.9) | 13.0 (10.7-14.9) | 12.7 (9.6-14.3) | 0.6668  
| Biological therapy³  | 214 | 15 (42.9) | 73 (54.1) | 18 (43.9) | 0.3303  
| Total number of biologics  | 214 | 0 (0.1) | 1 (0.1) | 0 (0.1) | 0.2243  
| Time-to-first dose of biological treatment in mo  | 102 | 17.8 (6.3-44.0) | 12.6 (5.6-25.9) | 13.3 (6.1-26.7) | 0.6313  
| Age at first biological treatment  | 102 | 13.8 (12.7-14.8) | 13.6 (11.3-15.3) | 14.0 (10.7-15.6) | 0.8880  
| Operative treatment⁴  | 214 | 2 (5.7) | 19 (14.1) | 8 (19.5) | 0.2158  
| Age at first surgery in yr  | 30 | 11.3 (9.4-13.1) | 14.5 (12.5-16.5) | 14.9 (14.0-15.7) | 0.1698  
| Time-to-first surgery in mo  | 26 | 12.0 | 19.4 (0.0-41.1) | 25.1 (7.9-43.5) | 0.7807  

| Hospitalisations, if duration ≥ 1 yr  |
| Hospitalisations for relapse, per 1 yr of the disease  | 133 | 0.4 (0.2-0.7) | 0.5 (0.3-0.8) | 0.4 (0.2-1.3) | 0.6615  
| Days of hospitalisation for relapse, per 1 yr of the disease  | 132 | 2.7 (0.7-5.6) | 4.7 (1.6-7.5) | 4.0 (1.1-7.6) | 0.4001  
| Relapses from diagnosis, per 1 yr of the disease  | 132 | 0.4 (0.2-0.9) | 0.5 (0.2-0.9) | 0.4 (0.2-1.4) | 0.8664  
| Severe relapses from diagnosis, per 1 yr of the disease  | 129 | 0.0 (0.0-0.3) | 0.2 (0.0-0.5) | 0.2 (0.0-0.5) | 0.1996  
| Concomitant diseases⁵  | 214 | 16 (45.7) | 40 (29.6) | 8 (19.5) | 0.0446  
| Extraintestinal manifestations  | 214 | 7 (20.0) | 34 (25.2) | 11 (26.8) | 0.7660  

¹Systemic steroid therapy included: methylprednisolone, prednisone, hydrocortisone.

²Immunosuppressive and anti-inflammatory agents included: azathioprine, methotrexate, mercaptopurine, cyclosporine, mycophenolate mofetil, tacrolimus, sulfasalazine.

³Biological agents included: infliximab, adalimumab, golimumab, vedolizumab.

⁴Only surgery related to inflammatory bowel disease-specific problems (e.g. colectomy, resection, fistula, perforation, abscess) was included.

⁵e.g., celiac disease, bronchial asthma, obesity, gastroesophageal reflux disease, epilepsy, hypothyroidism. CRP: C-reactive protein; IQR: Interquartile range; PCDAI: Pediatric Crohn’s Disease Activity Index.
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Table 5 Summary of relevant findings depending on apolipoprotein E genotypes and alleles

| Variables                              | Median (IQR) or n (%) | ε3/ε3 | APOEε2-positive | APOEε4-positive | P value |
|----------------------------------------|-----------------------|-------|----------------|----------------|--------|
| IBD                                    |                       |       |                |                |        |
| Albumin level at worst flare in g/dL   | 327                   | 3.9 (3.4-4.3) | 4.0 (3.9-4.5) | 4.1 (3.8-4.4) | 0.0176 |
| CRP at worst flare in mg/L             | 347                   | 7.7 (1.9-31.3) | 4.3 (1.1-28.3) | 3.2 (0.5-16.7) | 0.0146 |
| Age at first surgery in yr             | 36                    | 14.5 (11.7-16.7) | 9.5 (7.7-11.4) | 14.9 (14.0-15.6) | 0.0378 |
| Days of hospitalisation for relapse, per 1 yr of the disease | 230                   | 4.7 (1.6-8.3) | 2.2 (0.7-4.8) | 6.1 (1.7-8.7) | 0.0440 |
| CD                                     |                       |       |                |                |        |
| Albumin level at worst flare in g/dL   | 327                   | 3.9 (3.4-4.1) | 3.9 (3.8-4.4) | 4.4 (3.6-4.3) | 0.0363 |
| PCDAI at diagnosis                     | 190                   | 35 (25-50) | 25 (20-35) | 30 (25-45) | 0.0204 |
| Height at diagnosis, z score           | 378                   | -0.47 [-1.43-0.32] | -0.16 [-0.85-0.61] | 0.00 [-1.10-0.96] | 0.0482 |
| UC                                     |                       |       |                |                |        |
| CRP at diagnosis in mg/L               | 386                   | 2.5 (0.7-12.2) | 3.8 (0.8-7.3) | 1.1 (0.2-8.2) | 0.0435 |
| CRP at worst flare in mg/L             | 347                   | 3.7 (1.1-19.0) | 2.1 (1.8-7.3) | 0.9 (0.3-3.6) | 0.0013 |
| Age at first biological treatment      | 151                   | 11.5 (7.9-14.6) | 15.7 (15.3-15.7) | 10.7 (4.8-15.5) | 0.0432 |
| E2 at diagnosis                        | 192                   | 16 (13.6) | 8 (40.0) | 9 (18.0) | 0.0160 |

*Post hoc APOEε3ε3 vs APOEε2-positive: P = 0.0383 (Bonferroni and Holm); APOEε3ε3 vs APOEε4-positive: P = 0.0417 (Bonferroni) and P = 0.0383 (Holm).
*Post hoc APOEε3ε3 vs APOEε4-positive: P = 0.0556 (Bonferroni and Holm).
*APOEε3ε3 vs APOEε2-positive: P = 0.0534 (Bonferroni) and P = 0.0356 (Holm); APOEε2-positive vs APOEε4-positive: P = 0.0216 (Bonferroni and Holm).

CD: Crohn’s disease; CRP: C-reactive protein; IBD: Inflammatory bowel disease; PCDAI: Pediatric Crohn’s Disease Activity Index; UC: Ulcerative colitis.

ARTICLE HIGHLIGHTS

Research background
Apolipoprotein E (APOE) polymorphisms were previously reported to be linked with the risk of developing inflammatory bowel diseases (IBD).

Research motivation
No data on the relationship between APOE polymorphisms and disease severity are available.

Research objectives
This study aimed to investigate the link between APOE variants and disease severity in IBD.

Research methods
The TaqMan hydrolysis probe assay was used to genotype 406 patients with IBD (192 had ulcerative colitis and 214 had Crohn’s disease). Clinical expression involved disease activity scales, albumin and C-reactive protein levels, disease localisation and behaviour, and treatment with the time and age of the first intervention. The number of hospitalisations and days spent in hospital due to exacerbation as well as the number of relapses and severe relapses were also estimated.

Research results
Ulcerative colitis patients with the APOEε4 allele had the lowest C-reactive protein values both at diagnosis (P = 0.0435) and the worst flare (P = 0.0013) compared to patients with the APOEε2 allele and genotype APOEε3ε3. Crohn’s disease patients with the APOEε2 allele scored lower on the Pediatric Crohn’s Disease Activity Index at diagnosis (P = 0.0204). All IBD patients with the APOEε2 allele spent fewer days in the hospital due to relapse (P = 0.0440).

Research conclusions
The APOE genotype seems to be associated with some indices of disease course such
as inflammatory markers, disease activity, and applied treatment. However, the clinical significance of the differences identified remains modest.

Research perspectives
Further mechanistic studies of APOE action in IBD are warranted.

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